Studying individual differences and emotion regulation effects on PTSD-like responding and recovery: A psychophysiological VR-trauma paradigm

Freya Rumball

Submitted by Freya Rumball, to the University of Exeter as a thesis for degree of Doctor of Philosophy by research in Psychology, September 2013

I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or other University.

.....

Abstract

Despite a high proportion of the population experiencing traumatic events within their lifetime, the number of individuals who go on to develop posttraumatic stress disorder (PTSD) is comparatively small; herein highlighting the importance of individual differences in imparting risk and resilience towards the development and maintenance of PTSD. Existing literature illustrates that biological and ecological factors are important in predicting PTSD development, with pathological vulnerabilities excepting their effects at pre- peri- and post trauma stages. Whilst cognitive and emotion based models of PTSD account for the role of a minority of known pre-trauma risk factors, individual differences in peri- and post trauma processes are held as critical to the development of PTSD. The broad range of risk factors implicated in the empirical literature, and necessity of traumatic exposure to PTSD, implicates the utility of a diathesis-stress conceptualisation of PTSD development. The current thesis employed an analogue VR-trauma paradigm to investigate the respective importance of vulnerability factors at each stage, in the prediction of analogue PTSD symptoms (memory problems, startle responses, re-exposure fear habituation), whilst measuring affective and electrophysiological concomitance. Findings supported the importance of peri-traumatic responses in the prediction of PTSD, where present, showing increased predictive capacities over pre- and post-trauma factors. Biological and ecological factors also illustrated important predictive associations, with genetic SNPs implicated in reflex startle and cardiac responses towards intrusive memories. Moreover, peri-traumatic HR decelerations and accelerations mediated the association between pre-trauma factors and cued recall inaccuracy and intrusion severity respectively. Results support existing cognitive and emotional models in their emphasis on peri-traumatic processes but suggest the added utility of a diathesis stress conceptualisation of the development of PTSD, in highlighting the importance of pre-trauma biological and ecological risk and resilience factors.

Acknowledgements

I would like to thank my supervisors for their encouragement throughout this thesis. Dr Anke Karl has been a great support and allowed me the opportunity to learn a fascinating range of psychophysiological methods that will hold me in good stead for my future career; I hope we will continue to collaborate for many years to come. Dr Aureliu Lavric fuelled my desire to learn more about neurological processes during my undergraduate project and I have learnt a lot from him during my time at the University.

I would like to thank my friends, my sister and Andy for always keeping a smile on my face and for sticking with me throughout- even when I have been a hermit on the other side of the country.

And finally I would like to thank my parents for first sparking my fascination in nature and psychology, and for their unwavering belief in me.

Table of contents

List of tables

List of figures

List of Appendices

Abbreviations

5-HTT	Serotonin Transporter
5-HTTLPR	5-HT Transporter-linked Polymorphic Region
α	Cronbach's alpha
ACC	Anterior cingulate cortex
ADORA2B	adenosine receptor A2b
ASI	Anxiety sensitiviy index
BDI	Beck depression inventory
BDNF	Brain derived neutropic factor
CAPS	Clinician administered PTSD scale
DNA	Deoxyribonucleic Acid
ECG	electrocardiography
EEG	Electroencephalography
EMG	electromyography
ER	Emotion regulation
ERP	Event related potential
ERQ	Emotion Regulation Questionnaire
HA	Tridimensional Personality Questionnaire- Harm avoidance scale
HWE	Hardy Weinberg Equilibrium
Hz	Hertz
IRET	Imaginal re-exposure therapy
κ	Cohens Kappa
MINI	Mini Mental State Examination
ms	milliseconds
N	Neutral startle trials
NICE	National Institute for Health and Care Excellence
NPS	Neuropeptide S
NPSR	Neuropeptide S Receptor
NYU	New York paragraph recall test
PCA	Princlipal components analysis
PHQ9	Patient Health Questionnaire
PTSD	posttraumatic stress disorder

s	seconds
SAM	situationally accessible memory
SAM mood	Self-assessment manikin
SC	skin conductance
SCL	skin conductance level
SCR	skin conductance response
SNP	Single-nucleotide polymorphism
SRRS	Social Readjustment Rating Scale
STAI-S	State trait anxiety inventory- state measure
STAI-T	State trait anxiety inventory- trait measure
TR	Trauma regulate startle trials (use manipulation strategy)
TV	Trauma no manipulation startle trials (view)
VAM	verbally accessible memory
VR	virtual reality
VRET	Virtual reality exposure therapy

1 INTRODUCTION

Posttraumatic stress disorder (PTSD) is an anxiety disorder which develops following trauma exposure and is characterised by intrusive recollections of the trauma, avoidance and numbing, and hyperarousal (DSM-IV TR: APA, 2000). Despite the fact that approximately 33% of the English population will be exposed to a traumatic event within their lifetime, prevalence rates of PTSD within this population are estimated to be around 3.5% (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009). Furthermore, research has illustrated that when the same trauma is experienced by a number of individuals, PTSD still only develops within a minority of those exposed (Galea, Tracey, Norris & Coffey, 2008; North et al., 2004). Evidence illustrating that PTSD is not the normative response to traumatic exposure illustrates that individual differences clearly play an important role in imparting risk and resilience to the development of PTSD following traumatic experiences. The major models of PTSD development provide a detailed account for the importance of peri- and post-trauma processes in producing PTSD symptomology, with emphasis on the neurobiological (Brewin, 2001,2010), cognitive (Ehlers & Clark, 2000; Brewin, 1996) and emotional components (Foa & Rothbaum, 1998; Lanius, 2010). However, despite the range of biological and ecological[1] pre-trauma factors that have been implicated in risk and resilience towards PTSD development (DiGangi et al., 2013; Nemeroff et al., 2006), no single model accounts for all known pre-trauma influences; with a particular lack of explicit mention of genetic and trait influences. Diathesis stress conceptualisations of PTSD seem a promising theory for highlighting the importance of a range of biological and ecological diatheses in promoting risk and resilience to PTSD development; as well as stressing the role of peri-traumatic experiences in acting as a catalyst to activate pre-trauma risk factors (McKeever & Huff, 2003; Elwood, Hahn, Olatunji, & Williams, 2009). This thesis sets out to explore the respective importance of pre- peri- and post-trauma individual difference factors in the development of PTSD-like symptomology and the habituation of arousal responses during analogue exposure treatment, and the role of peri-trauma responses in mediating the associations between pre-trauma vulnerabilities and symptom expression; investigating the utility of a diathesis stress conceptualisation of PTSD development.

[1] Within this thesis the term ecological will be used to describe both environmental (e.g. life events) and trait (e.g. personality and coping) styles. Although it is acknowledged by the author that traits are determined by both environmental and biological factors, the inclusion of trait factors within the term 'ecological' is in accordance with its use within current diathesis stress conceptualisations of PTSD (McKeeven & Huff, 2003).

The literature review in chapter 2 commences with an overview of empirical studies which illustrate the diverse range of biological (gender and geneotypes) and ecological (personality and life events) pre-trauma factors, peri-trauma responses and post-trauma factors which have been implicated in risk and resilience towards PTSD development. The major models of PTSD development are then outlined and their respective abilities to account for the range of pre-, peri- and post-trauma factors previously reviewed is critically analysed. The review highlights the need for more explicit incorporation of pre-trauma factors within current PTSD models – proposing the utility of integrating a diathesis stress conceptualisation of PTSD, and the call for further analogue research investigating physiological peri-traumatic responses (heart rate and skin conductance) within immersive virtual reality (VR) environments which are experienced from a first person perspective. Three main thesis questions and hypothesis are then derived in regards to the effectiveness of VR in analogue trauma designs and the respective role of pre- peri- and post-trauma factors in the prediction of PTSD-like outcomes. Chapter 3 addresses the choice of analogue outcome measures of symptomology (assessing memory distortions and startle responses) and analogue outcome measures of VR-exposure treatment related habituation in arousal responses (assessing arousal habituation towards virtual reality re-exposures). The chapter describes their independent predictive associations with pathological PTSD diagnosis and known association with individual difference factors; thus allowing for the formation of directional hypothesis for empirical chapters. The four empirical chapters which form this thesis are derived from two large scale experimental psychophysiological studies, which were carried out using a VR-trauma film to measure risk and resilience factors in the development and maintenance of PTSD within analogue samples (N=206 across both studies). Chapter 4 provides an outline of the psychometric, psychophysiological and computer based measures used across these studies and goes on to chart an overview of the 2 study protocols.

The empirical chapters begin with a study exploring the relationship between pre- and peri-trauma factors; investigating the profiles associated with startle response exaggeration and habituation, within Chapter 5, and memory distortions in free recall and thought suppression invoked intrusions, within Chapter 6. The subsequent empirical chapters outline the findings from a study which additionally incorporates post-trauma manipulations of emotion regulation (reappraisal and suppression compared to control), which have been previously illustrated to influence emotional affect, startle and physiological responses (for review see Gross, 2002). The influence of post-trauma emotion regulation strategies and the remaining predictive effects of pre- and peri-trauma factors are assessed, in relation to startle responses and

habituation within Chapter 7, and in relation to response habituation towards VR re-exposures (VR exposure treatment analogue) within Chapter 8. Each empirical chapter in turn will discuss the respective findings in relation to the chapter specific directional hypothesis, as well as briefly summarising the results in regards to the core thesis hypothesis derived within Chapter 2.

The general discussion in Chapter 9 concludes the thesis by providing a thorough overview of the findings of the empirical studies outlined within Chapters 5-8, in relation to their contribution to addressing the three main thesis hypotheses and the limitations of the work addressing each hypothesis, including suggestions for future research. In addition to the discussion of the main research questions a critical analysis will also be provided of the implication of these findings in relation to the new DSM-V diagnostic criteria, which was published following completion of the empirical work contained within the thesis; as well as the importance of the startle findings across Chapters 5 and 7 in regards to motivational priming hypothesis (Lang, Bradley & Cuthbert, 1998) and interrupt hypothesis (Graham, 1979; Miller et al.,2002) of startle response modulation.

2 VULNERABILITY FACTORS FOR THE DEVELOPMENT OF PTSD

2.1 WHAT IS PTSD: EVOLUTION OF DIAGNOSTIC CRITERIA

Posttraumatic stress disorder (PTSD) has only been officially recognised as a clinical disorder since the publication of the DSM-III manual in 1980 (American Psychiatric Association (APA), 1980) and the diagnostic criteria continue to evolve as more is understood about the condition. PTSD and acute stress disorder are differentiated from other clinical conditions by a pre-requisite environmental catalyst - exposure to a traumatic event. Within the DSM-IV-TR manual[2], to be classified as a traumatic event the situation must involve 'actual or threatened death or serious injury or a threat to the physical integrity of oneself or others'; whilst exposure constitutes either directly experiencing the event, witnessing the event or learning that the event has happened to someone close to you (Criterion A1, APA, 2000). Although adverse reactions are common in the immediate aftermath of traumatic events, longer term effects may constitute pathological responses which require clinical attention. Whilst acute stress disorder occurs within the first 4 weeks post-trauma exposure, PTSD involves more longstanding sequelae resulting in disturbances of more than one month. PTSD is characterized by re-experiencing (Criterion B), avoidance and numbing (Criterion C), and hyper-arousal (Criterion D) (APA, 2000) and is posited to develop as a result of an inability to adaptively process and integrate trauma memories within the existing autobiographical memory base (Ehlers & Clark, 2000; Brewin et al, 1996, 2001, 2010).

Over the course of DSM publications the specification of the feelings that should be evoked by the traumatic event (Criterion A2) has changed from a normative response towards a traumatic event that would 'evoke significant symptoms of distress in almost everyone' in DSM-III (APA, 1980), to a subjective response in which 'the person's response involved intense fear, helplessness, or horror' in the DSM-IV (APA, 1994) and DSM-IV-TR (APA, 2000). The changes in the trauma response criterion across the DSM manuals illustrates that as more is understood about the disorder, an emphasis has been placed on individual differences in subjective trauma responses.

[2] DSM-IV-TR was the current classification manual at the time of theoretical conceptualisation of the current thesis and remained so throughout the duration of study design and data collection; as such this classification will be used throughout the theoretical and empirical chapters. Within the integrated discussion chapter the changes to the recently published DSM-V criterion will be discussed in relation to the findings of this thesis.

2.2 IMPORTANCE OF INDIVIDUAL DIFFERENCES IN PTSD DEVELOPMENT

The realisation that PTSD is not a normative response to a traumatic event has stemmed from both anecdotal reports and empirical research illustrating that trauma exposure itself does not inherently predict PTSD development; in fact it is observed that PTSD is the minority response following trauma exposure. A recent English general population study has found that although 33% of individuals over the age of 16 have been exposed to a traumatic event, PTSD had a prevalence rate of 3.5% in adulthood (McManus et al.,2009). The conditional probability of developing PTSD, following adulthood trauma exposure, is therefore 8.9%. Moreover, these findings are even lower than previous estimates of lifetime trauma exposure of between 39.1%-89.6% (Breslau, Davis, Andreski, & Peterson, 1991; Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Norris, 1992) and comparable to previous estimates of conditional probability of PTSD development of between 3.5%-23.6% (Breslau et al., 1991 & 1998; Helzer et al., 1987). These findings show that exposure to a trauma is a necessary, though not a sufficient, factor in PTSD development; as such individual differences clearly play a role in predicting respective risk and resilience to PTSD development following trauma exposure (Foa, Steketee & Rothbaum, 1989; Jones & Barlow, 1990; Ehlers & Clark, 2000).

Individual difference vulnerabilities can constitute factors that are present pre- peri- and post-traumatically. The recognition of the importance of individual differences in PTSD has led to a multitude of research investigating risk and vulnerability factors and mechanisms; the findings of this research have increased our understanding of the development of PTSD. The existing research findings in regards to respective individual difference factors, which are believed to impart risk and resilience at pre-,peri- and post-trauma stages, will now be outlined.

2.3 PRE-TRAUMA VULNERABILITY: BIOLOGICAL AND ECOLOGICAL FACTORS

2.3.1 Biological Vulnerabilities

2.3.1.1 Gender

Research has suggested that gender differentially impacts upon vulnerability to traumatic exposure and on subsequent PTSD development. Whilst males are found to be at increased risk of exposure to traumatic events over their lifetime (Breslau, Davis & Andreski, 1995; Tolin & Foa, 2006), following a trauma females are more likely to develop PTSD (Breslau & Davis,

1992; Van Loey, Maas, Faber & Taal, 2003; Darves-Bornoz et al., 2008; Stein, Walker, & Forde, 2000; Tolin & Foa, 2006); with such sex differences shown not to be the result of differences in symptom reporting (Chung & Breslau, 2008). These findings have been supported by recent NHS statistics, gathered from a large scale national audit of mental health in England, showing that although a higher proportion of men (35.2%) than women (31.5%) experience a traumatic event in adulthood, the conditional probability of developing PTSD following exposure is greater in women (10.4%) than in men (7.5%) (McManus, Meltzer, Brugha, Bebbington & Jenkins, 2009). Interestingly however, meta-analysis of risk factors for PTSD development has shown that the strength of gender associations with PTSD development vary across research designs and populations (Brewin, Andrews & Valentine, 2000). Female gender was shown to be a significant predictor of PTSD development following civilian but not military trauma exposures, and to have stronger effects within studies using prospective compared to retrospective designs and studies using diagnostic categories compared to continuous symptom outcome measures. Nevertheless, some prospective research has shown female gender to be one of the strongest predictors of PTSD development (Perkonigg, Kessler, Storz & Wittchen, 2000).

An inherent problem in the investigation of gender as a risk factor for PTSD development is that the exposure to different types of traumatic events varies across genders, with males experiencing an excess in traumas relating to combat, accidents, non-sexual assaults or childhood abuse, natural disasters or fires and witnessing death or illness, and females experiencing an excess in sexual assault and childhood sexual abuse (Tolin & Foa, 2006; Edwards, Holden, Felitti, & Anda, 2003). Exposure to sexual assault and childhood abuse have been shown to be high risk factors for PTSD development (Bennice, Resick, Mechanic & Astin, 2003; Darves-Bornoz et al., 2008), as such it appeared to be possible that differential exposure to traumatic stressors were the primary factor explaining sex differences in PTSD. However, research has disputed this conclusion, showing that females also exhibit increased PTSD susceptibility and severity following non-sexual traumas, when compared to males experiencing the same trauma type (Tolin & Foa, 2006; Stein, Walker, & Forde, 2000). Furthermore, female gender has been found to remain a significant predictor of PTSD risk when the number of lifetime traumas and severity of the trauma exposure are controlled for (Stein et al., 2000).

A further complication is the presence of differential personality profiles and social support across the sexes. Andrews, Brewin & Rose, (2003) have found that when negative responses

from family and friends are accounted for in a regression model, gender no longer predicts PTSD development; suggesting that some of the apparent sex differences in PTSD development may be mediated by other correlated individual difference factors (Ozer et al., 2003). However, gender was also found to moderate the association between social support factors and PTSD symptom development, illustrating that gender still plays an important role in symptom development. Furthermore, a study carried out by O'Connor & Elklit (2008) has found that gender effects remain when risk variables which are known to be inflated in females, such as emotional coping and lack of social support, are controlled for in the analysis of PTSD severity; support the earlier findings of Ehlers et al. (1998) that gender makes a novel variance contribution to explaining PTSD vulnerability at 3 months post-trauma over other known risk factors.

In summary although female gender appears to be an important risk factor within specific contexts, findings are not consistent across paradigms and further research is warranted to assess the mechanisms by which gender may impart risk for PTSD development, within controlled experimental settings and accounting for the influences of other individual difference predictors.

2.3.1.2 Gene polymorphisms

Recent patient and animal research suggests that genes might also play a role in the development of PTSD. Specifically, is it believed that different genetic variants (polymorphisms: which represent the specific combination of alleles on homologous gene loci of a pair of chromosomes) are associated with observable characteristic (phenotypes) which influence risk and resilience to the development of PTSD (figure 2.1). A number of different study designs are used to assess the role of genes and specific polymorphisms in pathology. Animal studies allow for the manipulation of genes, by creating genetically engineered knock-out' or 'knock-in' mice via inactivation of a specific gene or targeted gene insertion at a particular location of the chromosome, and investigating the subsequent effects on phenotypic behaviours. Investigation of genes in human populations is facilitated by two main methodologies; genome-wide association studies (GWAS) and candidate gene studies. GWAS studies test scan the entire genome for genetic variants (alleles) across millions of single-nucleotide polymorphisms (SNP's), allowing for identification of specific gene polymorphism allele combinations which are present in the DNA of individuals with a certain pathological condition compared to those without such a condition, and as such may act a risk

polymorphisms in pathology. Candidate gene studies also analyse genetic polymorphisms and allele distributions of specific genes, however only a small number of pre-specified polymorphisms are extracted and analysed based on previous literature which has illustrated associations with pathology or phenotypic behavioural responses. Although GWAS allow for the best elucidation of genetic involvement in PTSD (Cornelis, Nugent, Amstadter & Koenen, 2010; DiGang, Guffanti, McLaughlin & Koenen, 2013), well powered studies are yet to be published and research to date has focused on candidate gene polymorphisms.

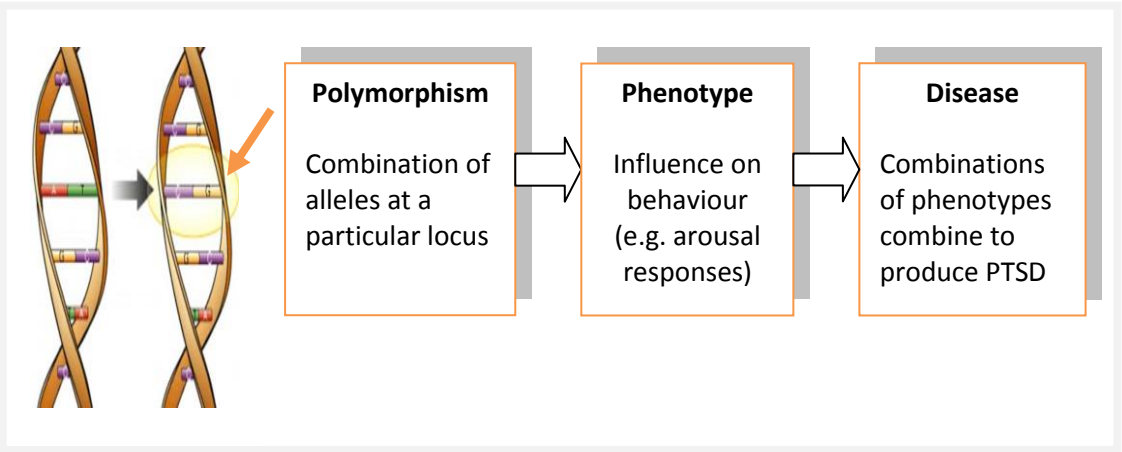


Figure 2.1: The stages through which gene polymorphisms can influence PTSD related pathology

The predominatly investigated and implicated gene polymorphisms in regards to PTSD include those pertaining to the dopaminergic system, serotonin system and brain derived neurotrophic factor; however, more recently investigations of genes relating to the adrenergic system and neuropeptides have begun. Although a number of genes have been implicated in PTSD pathology, the functional role of specific allelic expressions still remains unclear and further research is warranted.

2.3.1.2.1 Brain derived neurotrophic factor (BDNF)

Brain derived neurotrophic factor (BDNF) is a neurotrophin which plays a critical role in prenatal and post natal brain development (Croll et al., 1998) and is associated with alterations in learning and memory processes (Korte et al, 1995; Patterson et al, 1996). The receptors and promoters of the BDNF coding gene have been found to play a role in conditioned fear learning (Rattiner, Davis, French, Ressler, 2004; Rattiner, Davis & Ressler, 2004; Rattiner, Davis & Ressler, 2005) and extinction of fear-potentiated startle responses (Heldt, Stanek, Chhatwal & Ressler, 2007). Differential allele expression within a single nucleotide polymorphism (SNP)

at codon66 on chromosome 11 (Val66Met), on the BDNF gene, has been associated with alterations in neurology and contextual memory and has been implicated in a number of mood disorders (Rybakowski, 2008). The BDNF ValMet polymorphism consists of two allelic variants, valine (Val) and methionine (Met). The frequency of homozygote Met/Met carriers is rare, with only 4% of Caucasian populations carrying this genotype (Shimizu et al 2004, Gratacos et al, 2007), however comparable expression has been found between Met homozygote and heterozygote carriers leading to the conclusion that the Met allele has a dominant effect (Sen et al., 2003). As a result, smaller studies either exclude homozygote Met carriers from analysis or group them with heterozygote Val/Met carriers, to create a combined 'dominant' group.

The BDNF Met allele has been consistently implicated in human memory dysfunction and emotional responsivity. Compared to Val/Val homozygotes, heterozygote Met carriers exhibit poorer episodic memory (Egan et al., 2003), higher amygdala activation in response to emotional stimuli in a startle paradigm (Montag, Reuter, Newport, Elger & Weber, 2008) and decreased amygdala activation to attentional targets (Wang, Ashley-Koch, Steffens, Krishan, Taylor, 2012), smaller hippocampal volumes (Pezawas et al 2004, Szeszko et al, 2005, Bueller, Aftab, Sen, Gomez-Hassan, Burmeister & Zubieta, 2006; Frodl et al 2007) and reduced hippocampal functional activity during encoding and retrieval on hippocampal dependent memory task (Hariri et al, 2003). Similar neurological alterations have been previously reported in patients with PTSD (Karl, Schaefer, Malta, Dorfel, Rohleder & Werner, 2006), suggesting a role of BDNF Met in biological vulnerability to PTSD development. Genetic variant BDNF Met knock-in mice have been found to model the phenotypic hallmarks of the valine (Val) to methionine (Met) substitution (Met/Met polymorphism), showing reduced hippocampal volume and impaired contextual fear learning (Chen, Bath, McEwen, Hempstead & Lee, 2006) and fear extinction (Yu et al., 2009). BDNF Met/Met mice show increased anxiety behaviours in stressful environments (Chen et al, 2006; Hashimoto, 2007; Yu, Wang, Wang, Llu, Lee & Chen, 2012) and impaired synaptic transmission and a lack of neural plasticity (Pattewell, Bath, Perez-Castro, Lee, Chao, & Ninan, 2012), illustrating a possible neural mechanism in the association between the Met allele and anxiety related pathology.

The BDNF ValMet polymorphism has been associated with a number of anxiety-related traits; however across anxiety traits different allelic variants (i.e. Val or Met) have been implicated. Whilst the Met/Met genotype is associated with harm avoidance (Montag, Basten, Stelzael, Fiebach, & Reuter, 2010; Jiang et al., 2005), the Val/Val genotype has been associated with increased trait anxiety (Lang, Hellweg, Kalus, Bajbouj, Lenzen, Sander, Kunz & Galliant, 2005)

and neuroticism (Sen et al., 2003). Moreover, although BDNF has been related to a number of known PTSD-like symptoms, the relationship between BDNF and PTSD diagnosis remains unclear, with a recent study finding no differences in BDNF genotypic expression between PTSD, trauma control and non-trauma control groups (Valente et al, 2011) and a review of the literature showing no clear associations (Broekman, Olff & Boer, 2007). Inconsistencies across publications could be explained by a failure to take account of possible epistasis (gene by gene interaction) effects (Terracciano et al., 2010), epigenetic (gene by environment interaction) effects (Gatt et al., 2009) and mediators (Gatt et al, 2009), or be a result of the low expression of homozygote Met/Met polymorphisms within samples reducing the statistical power (Chen, Bath, McEwan, Hempstead & Lee, 2008).

In summary although BDNF Met allele appears to be implicated in emotional fear learning and memory structures, the role of BDNF in PTSD and associated anxiety traits still remains unclear. Further elucidation of the basic mechanisms by which genes influence the development of phenotypic symptoms will be of benefit to the field and may prove more fruitful than assessing associations with pathology, which may be too genetically complex to summarise in genetic association studies.

2.3.1.2.2 Serotonin transporter polymorphism (5HTTLPR)

The serotonin transporter polymorphism (5-HTTLPR) is a functional insertion-deletion polymorphism within the promoter region of the serotonin transporter (5-HTT) coding gene (SLC6A4). 5-HTT gene transcription is thought to be modulated by the long (l) or short (s) allele variants of 5-HTTLPR, for which the l allele is twice as transcriptionally effective (Hells, 1995; Lesch et al, 1996). Whilst s allele homozygote and heterozygote carriers show associated profiles, they have been found to differ from l allele homozygotes, suggesting an s allele dominance effect (Lesch et al, 1996). However, it has been found that there is an additional SNP within the 5HTTLPR polymorphism which creates an AP2 transcriptional factor binding site within its G allele that further affects 5HTT transcription (Nakamura, Ueno, Sano & Tanabe, 2000). This additional SNP affects the functional expression of the l allele and as such 5HTTLPR can be described as triallelic: s, l_A, l_G ; with the higher expressing allele being L_A and the lower expressing alleles being S and l_G (Hu, Oroszi, Chun, Smith, Goldman & Schuckit, 2005). To date many studies have not made this more subtle allelic discrimination, which may explain the discrepancy of findings across the literature to date.

Research into the effects of the 5-HTTLPR s and l alleles on anxiety traits has suggested a potential association between the s allele and neuroticism (Sen, Burmeister & Ghosh 2004; Lesch et al, 1996) harm avoidance (Lesch et al, 1996) and Cattell's trait anxiety measure (Lesch et al, 1996). However other studies have failed to find such associations (Munafo et al., 2009; Munafo, Clark & Flint., 2005), potentially due to epistasis (gene by gene interaction) effects influencing the associations between 5HTTL and anxiety traits (Szekely et al., 2004; Strobel et al., 2003). Furthermore, meta-analytic and large scale family based association studies across varied measurement instruments and populations have illustrated that 5HTTLPR and anxiety trait associations are inconsistent across study designs (Munafo et al., 2005; Middeldorp et al., 2007). Individuals homozygous or heterozygous for the s allele have also shown alterations in brain activation specifically towards emotional stimuli, with heightened amygdala activation when viewing of emotional faces specifically (Hagen, Passamonti, Nutland, Sambook, & Calder, 2011). Increased amygdala responding towards emotional and fearful stimuli has been found in s allele carriers compared to those homozygous for the l allele (Hariri et al, 2002; Wurtman, 2005; Munafo, Brown & Hariri, 2008).

The involvement of 5-HTTLPR with neurological, cognitive and psychological markers of anxiety disorders, and associations with depression (Kalia, 2005; Caspi et al., 2003), have spurred research investigating the serotonin transporter polymorphism as a biomarker of PTSD risk. The frequency of the s allele has been found to be significantly increased in PTSD patients, suggesting that a decrease in serotonin transporter expression in the brain may be a vulnerability factor in the development of PTSD (Lee et al., 2005). However when the additional A/G transcriptional binding alleles are accounted for, it has been found that when three or more traumas have been experienced it is in fact the L_A allele which increases PTSD risk three fold (Grabe et al., 2009). Moreover, epigenetic (gene by environment interactions) effects may play a role in the inconsistencies in findings. Increased amygdale activation has been associated with the L_A allele in patient populations, but with the L_G allele in healthy samples (Lau et al., 2005).

In summary, whilst the 5HTTLPS S allele is found to be associated with neural fear reactivity, associations with anxiety traits and PTSD development are less conclusive and the cognitive consequences of 5HTTLPR allelic expression are under investigated. Further research is needed to clarify potential mechanisms by which 5HTTLPR may differentially predict risk of PTSD related symptomology when the additional influences of the associated L/G SNP are accounted for.

2.3.1.2.3 α2β-adrenoreceptor (ADRA2B)

The importance of the noradrenergic system in emotional memory has been highlighted by findings of specifically enhanced recall of emotional material following pharmacological intervention with β-adrenergic receptor agonists (Cahill, Prins, Weber & McGaugh, 1994; O'Carroll, Drysdale, Cahill, Shajahan & Ebmeier, 1999). Furthermore, noradrenergic dysregulation has been associated with PTSD hyperarousal and re-experiencing symptoms (review see O'Donnell, Hegadoren & Coupland, 2004) and has been implicated in the creation of extinction resistant traumatic memories (Debiec, Bush & LeDoux, 2011). A functional insertion/deletion polymorphism within the ADRA2B gene, which encodes for the α2β-adrenoreceptor, has also been shown to be related to alterations in memory (Rasch et al., 2009; de Quervain et al., 2007). The deletion polymorphism (s), which is carried in around 30% of Caucasians, lacks three glutamic acid residues and results in reduced agonist promoted phosphorylation and receptor desensitization (Small, Brown, Forbes & Liggett, 2001). Homozygote and heterozygote carriers deletion variant carriers are often grouped together for analysis, due to the low number of carriers.

de Quervain et al. (2007) found that whilst the s deletion variant is functionally associated with enhanced recall of positive and negative emotional pictures, no effect was apparent on arousal ratings or recall of neutral material and the effects of the deletion variant on emotional memory did not differentially predict PTSD diagnosis. Functional imaging has shown that the s deletion variant is associated with enhanced amygdala activation during the encoding of negative images in deletion variant carriers (Rasch et al., 2009). Furthermore, war-exposed individuals carrying the ADRA2B deletion variant, experienced increased intrusive and distressing recollections of the traumatic event, however these symptom increases were independent of PTSD diagnosis (de Quervain et al., 2007). As such, ADRA2B appears to be implicated in the formation and retention of emotional memories irrespective of pathology. Pharmacological treatment studies have shown that adrenergic blockers (i.e. propranolol), administered soon after initial trauma exposure or during *in vivo* re-living of the trauma memory, reduce physiological responding (heart rate, skin conductance) in subsequent in vivo imaginal reliving (Pitman et al., 2002; Brunet, Orr, Tremblay, Robertson, Nader, & Pitman, 2008); implicating the adrenergic system as a promising target for the reduction of emotional reactivity and arousal associated with the re-experiencing symptom cluster in PTSD.

In summary, the ADRA2B deletion polymorphism is implicated in facilitated emotional memory, however its association with PTSD is less clear; with pharmacological evidence that the adrenergic system plays a role in symptom reductions but patient studies failing to find a genetic association with the ADRA2B SNP. Further investigation into the sequelae of functional genetic variation in the adrenergic system could aid in elucidating the role of emotional memory in PTSD development.

2.3.1.2.4 Neuropeptide S receptor (NPSR)

Neuropeptide S (NPS) is a newly discovered transmitter system which has been implicated in the behavioural expression of wakefulness and arousal, together with anxiolytic responses (Xu et al., 2004; Reinscheid & Xu, 2005; Okamura & Reinscheid, 2007). The neural mechanisms believed to produce the anxiolytic and arousal responses associated with NPS include increases in glutamatergic transmission to intercalculated GABAergic neurons in the amygdala (Jungling et al., 2008) and the release of dopamine within the medial prefrontal cortex (Si et al., 2010). The role of NPS in increasing arousal and reducing anxiety is consistent with Heller's model of emotional and brain organisation (Heller, 1990, 1993), which proposes that emotional arousal is dependent upon right parietotemporal activation and emotional valence is dependent upon left frontal activation; with frontal activation resulting in the inhibition of parietal activation, so as to differentially predict different subtypes of depressive and anxiety disorders (Heller & Nitschke, 1998). Findings illustrating that pleasure ratings and arousal ratings are uncorrelated to one another, with arousal increasing for both high pleasant and unpleasant affect, again implies that valence and arousal as different primary dimensions (Bradley & Lang, 1994).

In mice, central intra-cerebro-ventricular injection of NPS has been shown to increase anxiolytic behaviours across a series of behavioural tests and reduce physiological reactivity to stressors, whilst increasing locomotive activity and reducing sleep time (Leonard 2008; Rizzi et al., 2008). Administration of NPS directly to the amygdala complex shows comparable anxiolytic results, reducing startle responses during presentation of conditioned fear stimuli (Fendt, Imobersteg, Burki, McAllister & Sailer, 2010) and accelerating fear extinction (Jungling et al., 2008). These findings support the role of NPS in reduced anxiety and increasing arousal. Although the biphasic effect of NPS on anxiety and arousal are somewhat paradoxical in light of PTSD symptomology, findings highlight the need for further investigation into the potential role of NPS in anxiety traits and disorders such as PTSD, which is associated with arousal and

amygdala disregulation (Shin, Rauch & Pitman, 2006). Interestingly, several SNPs within the NPS and NPSR genes have already shown an association with panic disorder (Donner et al., 2010).

Recently research has focused on a functional SNP variant (rs324981) of the neuropeptide S receptor (NPSR) gene, leading to an amino acid Asn/Ile exchange, which has two allelic forms A and T. T allele carriers show substantially increased NPSR expression and NPS efficiency compared to homozygote A carriers (Brenier et al., 2006; Reinscheid et al., 2005). Presence of the T allele has been implicated as a gender specific female-dominant risk factor for the diagnosis of panic disorder (Domschke et al., 2010); with T carriers showing increased anxiety sensitivity scores, heart rate elevations during a behavioural avoidance task and reduced activation in the anterior cingulated cortex (ACC) towards presentation of fearful faces. Interestingly, decreased activation of the anterior cingulated cortex has been implicated in the engagement of arousal networks in PTSD (Felmingham et al., 2009; Shin et al., 2001) and successful PTSD exposure therapy has been associated with increased ACC activation (Felmingham et al., 2007), illustrating a potential link between the NPSR T allele and PTSD arousal responses. However, research has also shown that the NPSR A allele augments fear potentiated startle responses and impairs memory functioning (Okamura, et al., 2011;Lennertz et al, 2012), illustrating a potential link between the NPSR A allele and increased startle responses and memory impairments that are symptomatic of PTSD.

In summary NPSR is shown to reduce anxiety and increase arousal. As such, based on the current literature, whilst the NPSR T allele would appear to be implicated in PTSD arousal responses, the A allele would appear to be implicated in exaggerated startle responses and memory impairments in PTSD. This functional SNP warrants further investigation into potential biphasic effects on PTSD symptomology.

2.3.1.2.5 Dopamine receptor (D2 taq1)

The dopamine receptor gene (DRD2) contains a TaqA1/A2 SNP site with a C to T allelic substitution for the A1 polymorphism at the non-coding region of the DRD2 locus. Presence of the T substitution has been associated with a number of psychiatric disorders including alcoholism, schizophrenia and PTSD (Noble, 2000). Mixed evidence exists for a pathological association between PTSD diagnosis and expressing T allele. Whilst a minority of patient studies suggest a relationship between the T allele and current pathological status (Comings, Muhleman & Gysin, 1996) and increased risk of PTSD development (Rady et al., 2011), other

studies across war veterans (Bailey, Goenjian, Noble, Walling, Ritchie & Goenjian, 2010), earthquake survivors (Voisey et al., 2009) and mixed trauma subjects (Gelernter, Southwick, Goodson, Morgan, Nagy & Charney, 1999) have failed to find an increased frequency of the T substitution allele within PTSD populations. It has also been shown that the T allele predicts increased symptom reduction in response to pharmaceutical drug intervention with paroxetine, with particular improvements in social functioning (Lawford et al., 2003).

Although inconsistent evidence exists for the relationship between PTSD diagnosis and DRD2 allelic variation, research has implicated the T allele with vulnerability towards the development of PTSD associated phenotypes. Research has illustrated that the T allele imparts risk for co-morbid and pathologically associated psychological health problems, such as anxiety, insomnia, social dysfunction and depression in patients with current PTSD (Lawford, Young, Noble, Kann & Ritchie, 2006). Therefore rather than specifically imparting risk for full pathological PTSD development, the risk allele (C>T substitution) of the DRD2 polymorphism may instead predispose towards a endophenotypic vulnerability to express certain symptom subtypes and co-morbidities, which then mediate the relationship between DRD2 and pathological PTSD expression. Further investigation of the functional expression of the DRD2 alleles in relation to PTSD phenotypic symptoms could help to explain the inconsistent findings in regards to PTSD pathology.

2.3.2 Ecological[3] Vulnerabilities

2.3.2.1 Personality traits

A number of cognitive and affective traits have been implicated in PTSD, including neuroticism, anxiety sensitivity, trait anxiety, cognitive processing biases and harm avoidance. The harm avoidance sub-scale of the Tridimensional Personality Questionnaire has been found to be a consistent predictor of PTSD development both retrospectively (Richman & Frueh, 1997) and prospectively (Gill, 2005). Recent meta-analysis has shown that anxiety sensitivity (as measured by the Anxiety Sensitivity Index (ASI)) is associated with PTSD (Olatunji & Wolitzky-Taylor, 2009; Naragon-Gainey, 2010) and elevated levels of anxiety sensitivity have been

[3] As mentioned in the Chapter 1: within this thesis the term ecological will be used to describe both environmental (e.g. life events) and trait (e.g. personality and coping) styles. Although it is acknowledged by the author that traits are determined by both environmental and biological factors, the inclusion of trait factors within the term 'ecological' is in accordance with its use within current diathesis stress conceptualisations of PTSD (McKeeven & Huff, 2003).

shown to be a strong predictor of PTSD symptomology when the influences of other associated traits such as negative affectivity are accounted for (Leen-Feldner, Feldner, Reardon, Babson & Dixon, 2008; Feldner, Lewis, Leen-Feldner, Schnurr, Zvolensky, 2006; Feldner, Zvolensky, Schmidt & Smith, 2008). However, research has also suggested that in addition to predicting long term PTSD development, ASI scores appear to be malleable and increase in line with symptom development (Marshall, Miles & Stewart, 2010); prospective research is needed to clarify the role of ASI in PTSD development and symptomology.

Trait anxiety, most commonly assessed using the state-trait anxiety inventory (STAI), has had mixed evidence relating to its role in the etiology of PTSD. Trait anxiety (STAI-T) has been shown to be correlated with both PTSD and depression (Karakaya, Agaoglu, Coskun, Sismanlar & Yildiz, 2004), to be increased in PTSD veterans compared to veteran controls (Gregrek et al., 1996), and to interact with ASI to predict PTSD symptomology (Hensley & Varela, 2008). However, prospective analogue research in student populations has shown that state anxiety does not predict analogue symptomology, at a 4 week follow up (Carleton, Sikorski & Asmundson, 2010) or when controlling for the effects of processing styles (Davies & Clark, 1998b). Further prospective research controlling for associated pre-, peri- and post-trauma vulnerability factors, is needed to clarify the nature of the association between STAI and PTSD symptom development.

Individual differences in trait processing styles have also been implicated in PTSD symptom development. A perceptual (data-driven) processing bias, compared to a conceptual bias, has been associated with heightened intrusive thoughts, arousal and avoidance symptoms (Halligan, Clark & Ehlers, 2002). Trait factors associated with emotion regulation styles have been associated with PTSD; with increased PTSD symptom severity associated with an emotion focused trait coping style and a thought suppression trait coping style (Morgan, Matthews & Winton). A combined expression of different cognitive risk factors, including anger, rumination, thought suppression and dissociation have been shown to predict PTSD symptom trajectories (Ehlers, Mayou & Bryant, 2003). Individual differences in processing and emotion regulation styles clearly play a key role in the course of PTSD symptom development, however further research is needed to clarify the symptomology and mechanisms by which emotion regulation styles exert their effects.

One of the most consistent trait associations with PTSD has been that of neuroticism (e.g. Breslau, Davis, Andreski &Peterson, 1991; Morgan, Matthews & Winton, 1995; Holeva &

Tarrier, 2001; Lawrence & Fauerbach, 2003), although a link with symptom development in analogue studies is not always apparent (Davies & Clark, 1998). Neuroticism is a stable personality characteristic for which increased scores are indicative of generalised negative affect, emotional instability and nervousness (Eysenck & Eysenck, 1968; 1991). Importantly however, neuroticism scores are also a powerful risk factor for past and current depression (Duggan, Sham, Lee, Minne, & Murray, 1995; Enns & Cox, 1997). Depression is known to be highly co-morbid with PTSD (Keane & Wolfe, 1990), with comorbidity estimates of 44.5% at one month post-trauma, in PTSD patients recruited through emergency room admissions (Shalev et al., 1998) and 69.6% in PTSD patients who had developed PTSD following earthquake exposure (Başoglu, Kılıç, Şalcıoglu & Livanou, 2004). As neuroticism predicts both PTSD and depression, it is difficult to clearly separate the contribution of neuroticism to these two forms of pathology when carrying out analogue laboratory research. As such, research investigating the role of neuroticism in PTSD is best carried out in patient populations where PTSD diagnosis is explicit and co-morbid depression can be controlled for in analysis or screened out as exclusion criteria.

In summary, a number of anxiety and emotion related traits have been implicated in PTSD symptomology and diagnosis. Although the effects of neuroticism on PTSD may prove difficult to disentangle from its impacts upon depression, further research is warranted to explore the influences of harm avoidance, trait emotion regulation styles, anxiety sensitivity and state anxiety. Interestingly, research has indicated that personality traits may also exert their pathological effects by increasing the likelihood of trauma exposure, with individuals who score higher on neuroticism and extroversion traits found to experience increased exposure to traumatic events (Breslau, Davis & Andreski, 1995; Breslau, Davis, Andreski & Peterson, 1991). As such, controlled experimental research is required to determine if traits predict symptom development when trauma exposure is controlled across participants. By investigating the influence of pre-trauma traits in a controlled laboratory trauma design (typically investigated via exposure to a trauma-film; see section 2.8 for full outline of these paradigms), any influences that traits have on increasing susceptibility to trauma exposure would be accounted for. Furthermore this would allow for elucidation of the affective and physiological mechanisms by which personality factors increase PTSD symptomology; for example via the mediating effects of peri-traumatic responding on the association between traits and symptom outcomes (Laposa & Alden, 2008).

2.3.2.2 Previous life events: Traumatic and stressful events

Exposure to traumatic life events, which do not act as the primary catalyst for PTSD development, become a pre-trauma PTSD risk factor and can result in pathological reactions to subsequent stress or trauma exposure (Brewin et al., 2000; Ozer, Best, Lipsey, & Weiss, 2003). Traumatic events can be conceptualised as non-normative events which are often unanticipated, in contrast all individuals will experience a number of stressful events in their lifetime. Stress-inducing life events can be both positive (e.g. marriage) and negative (e.g. divorce) in character, as both types of life event can require stressful change and readjustment by the individual (Holmes & Rahe, 1967). Stressful life events, including changes in school or housing, examinations, marriage, childbirth or divorce, may have a cumulative negative effect on physiological and psychological well being. Both prior traumatic events (e.g. Brewin et al., 2000) and stressful life events (e.g. Joseph, Mynard & Mayhall, 2000) can act as pre-trauma risk factors and impart increased risk of PTSD development following exposure to a traumatic catalyst.

Meta-analysis elucidating the influence of prior traumatic events on PTSD development across varying study designs (Brewin et al., 2000),sub-dividing prior trauma history into childhood history of abuse, childhood adversity and other previous trauma, has shown that a history of childhood abuse is consistently predictive of increased PTSD risk across varied methodological designs and samples. However, although childhood adversity and other previous traumas (in childhood and adulthood) remained a significant predictor of PTSD across all of the study designs, the size of the association varied according to the study design. A similar meta-analysis by Ozer et al (2003) explored a smaller number of potential risk factors and hence evaluated a smaller number to studies. This meta-analysis differentially sub-divided prior trauma into childhood and adulthood trauma exposures, without independently looking at the effects of childhood abuse. Previous exposure to traumatic events in either childhood or adulthood was found to comparatively predict increased vulnerability to PTSD symptomology and diagnosis, although with a small effect size. The strength of association between prior trauma exposure and PTSD was not affected by study methodology or sample, although the relationship was weaker for combat traumas and accidents. The findings of both meta-analyses highlight lifetime prior exposure to traumatic events as an important pre-trauma risk factor in the development of PTSD, a conclusion which has been supported by subsequent prospective research (Berntsen, Johannessen, Thomsen, Bertelsen, Hoyle & Rubin, 2012).

In addition to the detrimental influences of prior traumatic events on PTSD, prior stressful life events have also been associated with an increased risk of PTSD development (Solomon, Mikulincer, Flum, 1988; Scott & Stradling, 1994; Joseph et al., 2000) and exaggerated startle responses (Joanovic, Blanding, Norrholm, Duncan, Bradley & Ressler, 2009). Interestingly, research has shown that the number of lifetime stressful events experienced is more predictive of PTSD symptomology than the number of traumatic events (Mol et al., 2005), implying a cumulative association between prior life stressors and PTSD vulnerability. The dose-response relationship between the number of stressful life events experienced and risk of PTSD development has also been supported by Brailey, Vasterling, Proctor, Constans and Friedman (2007), who also illustrated that social support factors attenuate this association thus suggesting that post-trauma psychological factors may play a role in moderating this relationship. Stressful life events have also been shown to detrimentally impact upon resting cortisol levels, with prior exposure to negative events associated with lower cortisol levels in police officers (Witteveen, Huizink, Slottje, Bramsen, Smid, & Ploeg, 2010). This finding is of particular interest in light of the fact that a dysregulation of the neuroendocrine stress response has been associated with PTSD symptom development (Heim, Ehlert, Hellammer, 2000) and pathology (Yehuda, Kahana, Binder-Brynes & Southwick, 1995). Research suggests that long lasting changes in cortisol levels induced by exposure to stressful life events may be a physiological mechanism by which stressful events predict PTSD development (Resnick, Yehuda, Pitman & Foy, 1995).

In summary, research clearly implicates a role of prior traumatic and stressful life events in imparting risk towards the development of PTSD following subsequent trauma exposures, with post-trauma factors potentially influencing this association. Further research is needed to clarify the specific mechanisms and symptom clusters on which prior life events exert their pathological effects.

2.4 PERI-TRAUMA VULNERABILITY: TRAUMA RESPONSE

The importance of the emotional reaction towards the traumatic event in PTSD development is highlighted by the DSM-IV-TR (APA, 2000) A2 criterion, which requires a reaction involving 'intense fear helplessness and horror' towards the traumatic stressor. Feelings of fear helplessness and horror during trauma exposure have indeed been associated with PTSD development; however PTSD diagnosis is not wholly synonymous with the intense presence of these emotions during the trauma itself (Brewin, Andrews & Rose, 2000). Since the publication

of DSM-IV there has been a large body of research suggesting that a peri-trauma dissociative response can be equally predictive of acute PTSD development and in order to account for such reactions the exclusion of the A2 criterion from DSM-V has been proposed (Brewin, Lanius, Novac, Schnyder & Galea, 2009).

2.4.1 Heightened emotional reaction

2.4.1.1 Affective response: self-report measures

By definition traumatic events will be inherently negative and anxiety provoking, however individual differences in the subjective experience of traumatic events have been posited to affect the risk of PTSD development. Negative emotional responses and appraisals during and immediately following traumatic events have been associated with heightened PTSD symptomology and diagnosis (Ozer et al, 2002; Laposa & Alden, 2003). Furthermore, state anxiety following a traumatic film, as well as directly predicting intrusion frequency (Laposa & Rector, 2012), has been shown to mediate the relationship between pre-trauma vulnerability factors and the frequency of traumatic intrusions (Laposa & Alden, 2008); illustrating a a dynamic relationship between peri-traumatic affect and pre-trauma PTSD vulnerability factors. Perceived trauma threat (i.e. self-reported trauma induced fear) assessed within 24 hours post- trauma has been associated with subsequent PTSD symptom expression at 1 year (Ehlers, Mayou & Bryant, 1998b) and 3 years post-trauma (Mayou et al., 2002); illustrating long term effects of subjective peri-trauma affect on PTSD symptom development. Fear and distress relating to the trauma, assessed in the first few weeks following rape, in a regression model with intrusive symptoms, can correctly classify 89.6% of PTSD diagnosis and 61.3% of non-PTSD cases at one year follow up (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992). These findings suggest a strong predictive relationship between peri-trauma self-report and PTSD development. However, in the aforementioned meta-analysis by Ozer et al. (2003), although perceived threat was a significant predictor of PTSD development, inconsistent associations were found across study designs and populations. As such, although research points to the importance of self-reported affective responses and subjective peri-traumatic characteristics in the PTSD development, further work is needed to clarify the exact conditions and mechanisms by which these responses influence PTSD symptomology and are influenced by pre-trauma characteristics.

2.4.1.2 Physiological response

Although clinical studies have indirectly explored the role of physiological arousal in the acute stages post trauma by collecting self-report measures of emotional responses towards the traumatic experience (Ozer et al, 2002; Laposa & Alden, 2003), the true investigation of peri-traumatic physiological responses would only be possible in prospective designs and would require 'at risk' participants (such as front line service men) to continuously wear wireless heart rate (HR) and skin conductance (SC) monitors during active deployment. As well as being an expensive and complicated methodological design, the required physiological equipment has the potential to unacceptably restrict individuals' movement and dexterity, as well as producing recordings that are likely to be highly contaminated by movement and other artifacts. As such, to the best of the author's knowledge, no clinical studies have achieved physiological peri-traumatic measurements. This form of research has relied on analogue laboratory studies in which participants are exposed to a traumatic film, with concurrent physiological responses recorded and individual differences in post-film PTSD-like symptoms measured.

Although much research has been carried out to illustrate the ability of the trauma-film paradigm to induce significant physiological arousal and thus to be a valid analogue measure of trauma exposure (Folkins, Lawson & Opton, 1968; Speisman, Lazarus, Mordkoff & Davidson, 1964; Lazarus, Opton, Nomikos & Rankin, 1965), far fewer have investigated the consequences of differential peri-trauma physiology on the development of PTSD symptomology. Research has suggested that it is possible for peri-traumatic physiological arousal to be adaptively manipulated by exposure to pre-film coping strategies such as cognitive rehearsal, relaxation and desensitisation (Speisman et al., 1964, Lazarus et al., 1965); illustrating malleability in peri-traumatic physiological responding, but not explicitly illustrating links with PTSD. Analogue research exploring the association between peri-traumatic physiological reactions and the development of PTSD-like symptoms, has of yet only employed HR as a peri-trauma measure and investigated the relationship with the frequency of subsequent intrusive memories (Holmes, Brewin & Hennessy, 2004; Weidmann, Conradi, Grogerm Fehm & Fydrich, 2009).

In a series of studies carried out by Holmes et al (2004) HR reductions (interpreted as fear bradycardia) during a road traffic accident related trauma-film, relative to a 6 minute pre-film baseline, were found to be correlated with an increased number of intrusions over the subsequent week. Evidence for reduced HR, or bradycardia, has been shown during attentional

orientation to threatening stimuli (Lang, Bradley & Cuthbert, 1997) and trauma-film scenes with the greatest traumatic content (Folkins et al 1968).Furthermore, when HR was analysed exclusively for intruding sections of the film, separately for each individual, increased bradycardia was found during intruding sequences compared to non-intruding sequences. This pattern of results was confirmed in two out of three of the experiments, however the third experiment showed no association for film HR relative to baseline and associations for intrusion specific sequences just fell short of significance, potentially explained by the comparatively smaller sample size in this analysis compared to that within the other two experiments. These findings appear to implicate peri-trauma HR changes in the maladaptive encoding of trauma memories. However, research comparing a number of different trauma-films has found opposite effects, with intrusive memories over three days post-film associated with increases in HR and self-reported disgust in response to the trauma film (Weidmann et al., 2009). HR responses are modulated by both sympathetic and parasympathetic divisions of the autonomic nervous system (For reviews see Levy & Martin, 1981; Levy, 1990) and as such research exploring purely sympathetic physiological measures such as SC (Lindberg & Wallin, 1981) may provide a clearer elucidation of the role of peri-traumatic physiological arousal responses in PTSD development. The small number of empirical studies which have investigated peri-traumatic physiological responses and associated PTSD symptomology, and the inconsistencies in results across existing studies, illustrates that further research is needed to explore the influences of a range of physiological arousal profiles (e.g. SC responses in addition to HR responses) on the development of a range of PTSD symptomology (e.g. hyperarousal profiles in addition to memory disturbances).

2.4.2 Dissociation and emotional numbing

Peri-traumatic dissociation refers to a process of detachment of self, place, time and meaning from the current environmental context, which can produce a sense of experiencing out of body experiences, alterations in time perception and an altered sense of reality (Marmar, Weiss, & Metzler, 1997). As such, dissociative responses to severe stressors result in a reduction of emotional affect and physiological responsiveness. Peri-traumatic dissociation towards a range of trauma experiences has been associated with PTSD development (Ozer et al., 2003; Shalev et al, 1996; Koopman, Classen & Spiegel, 1994; Ehlers et al., 1998; Epstein, Fullerton & Ursano, 1998; Dunmore, Clark & Ehlers, 1999), heightened avoidance (Griffin et al., 1997) and re-experiencing (Laposa & Alden, 2003) symptoms. Moreover, peri-traumatic dissociation has been found to be one the strongest predictors of PTSD diagnosis in meta-

analysis (Ozer et al., 2003), prospective studies (e.g. Shalev et al., 1996; Murray, Ehlers & Mayou, 2002; Marmar, Weiss, Metzler, Delucchi, Best & Wentworth, 1999) and retrospective studies (e.g. Griffin, Resick & Mechanic, 1997); uniquely predicting PTSD development over and above trait dissociation tendancies (Weiss, Metzler, Ronfeldt & Foreman, 1996) and emotional responses to the trauma (Roemer, Orsillo, Borkovec & Litz, 1998). Individuals who exhibit peri-traumatic dissociation are reported to be 4.12 times more at risk of developing acute PTSD and 4.86 times more likely to develop chronic PTSD following a motor vehicle accident (Ursano et al, 1999). Shalev et al (1996) showed that peri-trauma dissociation, reported at one week post trauma, predicted 29.4% of the variance in PTSD diagnosis 6 months post trauma. However a retrospective study carried out by Mayou et al (2002) showed that although traumatic dissociation was a predictor of PTSD symptom severity, no association was apparent with PTSD diagnosis at 3 years follow up. Interestingly, Ozer et al (2003) have found that studies assessing peri-trauma dissociation between 6 months to 3 years following the trauma show stronger associations with PTSD than those assessing peri-trauma dissociation at 1-6 months post trauma; suggesting that estimates of peri-trauma dissociation via retrospective reporting may be influenced and inflated during the course of PTSD development, highlighting importance of prospective research to confirm the predictive nature of peri-traumatic dissociative responses.

It has been suggested that the emotional content of the traumatic experience may impact upon the likelihood of dissociative responses, with directly threatening situations producing heighted dissociative responses peri-traumatically (Griffin et al., 1997; Marmar, Weiss, Metzler & Delucchi, 1996). These findings suggest that peri-traumatic dissociation may be employed as a coping strategy (such as suppression), which paradoxically leads to a reduced propensity to process and cope with the trauma subsequently. In support of this proposition, Griffin et al (1997) found that rape victims with high peri-traumatic dissociation scores showed inconsistencies in self report and physiological measures of arousal whilst talking about their traumatic experience. High dissociators showed significantly suppressed physiological (skin conductance and heart rate) responses compared to low dissociators, while self-report actually illustrated increased distress when talking about their trauma experience. It is unclear whether social desirability affected self-report measures in this study or if peri-traumatic dissociation leads only to subsequent physiological dissociation and not the entire loss of affective evaluations relating to the trauma experience, more research is needed to clarify this finding.

A recent review of analogue trauma film research has highlighted peri-trauma dissociation as an important mechanism in symptom development, though the exact mechanisms by which dissociation occurs still remain unclear (Holmes & Bourne, 2008). Studies have attempted to manipulate state dissociation in the laboratory by employing a concurrent task during trauma-film viewing, such as a visuospatial tapping task. However attempts to experimentally create an analogue of dissociation have not proved fruitful, with findings showing no group differences (Holmes et al., 2004) or even a reduced frequency of subsequent intrusions in the dual-task group (Brewin & Saunders, 2001). Naturally occurring peri-trauma dissociation, in which the individual has made the conscious or unconscious choice to detach themselves from the environment due to situational factors and personal evaluation, appears to operate in a different way to experimental analogues of such processes, in which detachment is not determined by the individual but imposed prior to any initial processing of the situation. Investigation of non-manipulated individual differences in peri-traumatic dissociation appears a better focus in investigating the mechanisms by which dissociative responses impart risk of PTSD symptomology and development.

2.5 POST-TRAUMA

2.5.1 Coping strategies: Emotion regulation

Individual differences in coping strategies in the aftermath of trauma exposure have been associated with risk and resilience towards PTSD development. Coping strategies, measured directly after trauma exposure, have been found to be highly predictive of PTSD symptom development (North et al., 2001; Silver et al, 2002). Active coping strategies, including positive reappraisal and actively addressing problems, have been associated with resilience; whilst passive coping strategies such as avoidance and suppression have been associated with risk (Olff, Langeland & Gerson, 2005). Across both active and passive coping strategies, emotion regulation strategies, including positive reappraisal and suppression, are specified as imparting resilience and risk respectively. Interestingly a large body of experimental work has been carried out illustrating the adaptive role of positive reappraisal and the maladaptive role of suppression in regulating emotional affect (See Gross, 2002 for a review article). This work follows from Gross's process model of emotion regulation differentiating between response focused and antecedent focused processes across five points of emotion generation; these include antecedent focused strategies of situation selection, modification of a situation, deployment of attention, change in cognitions and modulation of responses (Gross, 1998). Within this model reappraisal as an antecedent focused strategy, which alters cognitions, has

the ability to adaptively change emotional responses prior to elicitation and alter associated emotional feelings; however suppression as a response-focused strategy is attempting to reduce emotional responses which have already occurred and is therefore less effective at reducing emotional affect. The experimental work carried out by Gross and colleagues has illustrated that while reappraisal can effectively regulate negative affect, reducing negative emotional state; behavioural suppression (inhibiting facial responses relating to current emotional states) has no influence on negative affect reduction, and produces an augmentation in physiological arousal responses. Furthermore, reappraisal has been shown to have adaptive anxiety reducing influences on brain functioning (such as down-regulation of amygdala activation towards negative picture viewing: Walter et al., 2009; Erk et al., 2010; Ochsner, Bunge, Gross & Gabrieli, 2002), brain processing (reduced amplitudes of P3 ERP responses towards negative picture viewing: Gootjes, Fanken, & Van Strien, 2011) and reductions in startle responding (Jackson, Malmstadt, Larson, & Davidson, 2000) during emotionally adversive experiences.

In addition to the adaptive influences of positive reappraisal, acceptance and positively re-interpretive coping are shown to have on post-traumatic outcomes (for review see Linley & Joseph), research has shown that in turn negative appraisals can impart increased risk of PTSD development. Negative appraisals of PTSD symptoms have been associated with both the onset (Halligan, Michael, Clark & Ehlers, 2003) and maintenance (Halligan et al., 2003; Dunmore et al., 1999) of PTSD. Furthermore, the maladaptive role of suppression in PTSD has been supported by research illustrating that avoidant behavioural strategies are associated with PTSD development and maintenance (Halligan et al., 2003), with a recent meta-analysis carried out by Trickey et al., (2012) showing that of 25 risk factors for PTSD development, assessed within a child and adolescent population, post-trauma thought suppression showed the largest effect size. Despite evidence that both reappraisal and suppression are implicated in PTSD development and differential efficiency in emotion regulation, the majority of these research findings come from studies independently investigating one of these two strategies. Future research calls for the joint investigation of the respective resilience and risk afforded by positive based reappraisal and behavioural suppression in the prediction of PTSD symptomology; exploring the mechanisms by which these emotional coping strategies impart their influences on PTSD development within the same research paradigm.

2.5.2 Coping strategies: Social support

In addition to the aforementioned emotion and cognitive based coping strategies, social support forms another active coping strategy. Social support has been found to have a resilient effect on post-trauma PTSD development, whilst a lack of social support imparts risk of PTSD development. Meta-analytic studies of risk and resilience factors in PTSD development have illustrated that social support is an important factor in PTSD development with a medium effect size (Brewin et al,. 2000; Ozer et al., 2003; Trickey et al., 2012). As discussed previously social support may also mediate the effects of other risk factors, with the level of unit cohesion (i.e. social support) within a military population shown to moderate the risk of PTSD development afforded by prior stressful life events, with increased unit cohesion attenuating the association (Brailey et al., 2007). Interestingly however the influence of social support has been shown to be stronger within military populations, compared to civilian populations (Brewin et al., 2000); suggesting that the role of social support may vary across populations and traumas and cautioning against directly interpreting findings across populations. Furthermore, the effects of support satisfaction also vary across gender, with the role of support satisfaction on the prospective prediction of PTSD symptom severity found to be greater in females (Andrews, Brewin & Rose, 2003). These findings illustrate that the role of social support in respective resilience and risk to PTSD development varies across clinical populations and by demographic characteristics. Research furthering the understanding of the mechanisms by which social support influences PTSD development adaptively or detrimentally, could help to elucidate the causes of differing effect sizes across patient samples; however social support cannot be easily manipulated within a laboratory setting and as such prospective clinical investigations would be of preference.

2.6 ETIOLOGICAL MODELS OF PTSD: ACCOUNTING FOR INFLUENCE OF PRE- PERI- AND POST-TRAUMA PROCESSES

Models of PTSD development have traditionally embodied a cognitive (Brewin et al., 1996; Ehlers & Clark, 2000) or emotional processing (Foa & Riggs, 1993; Foa & Rothbaum, 1998; Lanius, 2010) framework, although more recently neurobiological mechanisms have being effectively incorporated into cognitive conceptualisation (Brewin et al., 2001, 2010). Although these models do account for aspects of previously documented risk factors across all levels of influence (pre- peri- and post-trauma), their predominant focus is on mechanisms involved in

peri-trauma and post-trauma risk. Due to the relatively little explicit specification within existing models of the range of pre-trauma biological and ecological risk factors which have been implicated in PTSD development across experimental literature (as outlined in section 2.3), the author proposes the utility of a diathesis stress conceptualization of PTSD as an addition to existing models; which would account for the importance of ecological and biological pre-trauma vulnerabilities and their dynamic relationship with peri-traumatic mechanisms which impart risk for PTSD development.

2.6.1 Models with a predominant peri- and post-trauma focus

2.6.1.1 Fear structure model

Foa and colleges have presented an information processing model of PTSD development (Foa, Steketee & Rothbaum, 1989), and later extended this into an emotion processing model (Foa & Riggs, 1993; Foa & Rothbaum, 1998), which builds upon the theoretical supposition of Lang (1977; 1979) that the memory network contains a separate information structures, with a sub-network representing fear structures. The subjective meaning associated with the trauma memory representation is stored within the fear structure, which differs from other information structures in that it contains situational and response information, which allows for readily execution of flight or avoidance behaviours. This fear structure is also posited to incorporate and be influenced by information relating to previous and current threat assumptions (Foa and Kozak, 1986). Foa et al (1989) suggest that when the threatening situation violates previously held safety assumptions this causes feelings of unpredictability and uncontrollability; which result in the formation of a larger, more generalisable fear structure and a constant state of fear and hyperarousal. As further a consequence of the safety violation, stimuli which would have previously been associated with safety become assessed as dangerous, resulting in a constant assessment of danger and a state of alertness. Furthermore, as a consequence of creating a large overgeneralised fear structure, the structure is less coherent and is easily activated by many stimuli. The activation of the memory structure produces re-experiencing symptoms such as flashbacks, intrusions and nightmares, whist the resulting activation of response information causes physiological hyperarousal and exaggerated startle response. Efforts to suppress activation of memory or response associations will result in avoidance towards an overgeneralised range of eliciting stimuli, with negative beliefs about the consequences of anxiety exacerbating the presence of avoidance behaviours. Within this model symptoms of emotional numbing and dissociation are

conceptualised as extreme avoidance behaviours and as such are posited to be associated with disorganised and incoherent fear structures in memory. As such, the extent to which the traumatic event violates safety assumptions determines the development of symptoms synonymous with PTSD; placing the primary emphasis on state dependent peri-traumatic processes.

It is of course possible that pre-determined beliefs would have an influence on peri-traumatic safety assumptions, and as such Foa and colleagues have subsequently extended the initial model to better account for and specify the impact of pre-trauma risk factors on PTSD development (Foa & Riggs, 1993; Foa & Rothbaum, 1998). Within this more emotion appraisal focused re-conceptualisation of the model individuals with more rigid pre-trauma views are posited to be at increased risk of developing fear structures in the face of trauma. These views could be of personal safety and predictability, which would be disconfirmed by the trauma, or of instability and unpredictability, which would be affirmed and reinforced by the trauma. Individual differences in the negative appraisals of peri- and post-trauma anxiety responses, such as physiological and behavioural responses, are also posited to exacerbate avoidance behaviours. It is held that rigid views and negative appraisals present at any stage of the trauma (i.e. pre, peri & post), can interact to reinforce avoidance, negative self-schemas and over exaggerated assessments of danger, which can lead to chronic PTSD. The emotion processing model of PTSD as well as accounting for the importance of peri-traumatic processes also incorporates the key role that pre-trauma rigid views and negative beliefs have in increasing vulnerability to PTSD development.

In order to remove an existing fear structure it is posited that, first, the fear structure must be activated to allow for it to be modified, and second, new corrective cognitive and affective information which is incompatible with the existing information stored in the fear structure must be integrated into the fear structure, weakening the structure and its associated physiological anxiety responses. Over time this process of physiological habituation will ultimately result in creation of a new coherent memory formation which carries a reduced emotional affect and can be better integrated with other information structures in the memory network. Exposure therapy works by allowing for repeated activation of the fear structure, evidenced by increased initial physiological and emotional responses toward exposure, and by gradually integrating new information to fill in gaps in the structure and incorporate safety information, thus weakening inconsistent representations and reducing fear related stimulus-response associations, evidenced as habituation within and across sessions.

Individuals with heightened levels of fear encoded within the initial fear structure are expected to show a slower trajectory of habituation in arousal and negative affect during exposure therapy treatment. Additionally, when the fear structure is large (for example when there is a large safety violation) it is more difficult to activate all areas of the structure necessary to instil change, resulting in overgenerailsed activation, promoting avoidance behaviours which reduce the integration of inconsistent information which could challenge the fear structure. As such, the emotion processing model would predict that individuals with heightened peri-traumatic fear responses and those with pre-trauma characteristics which are associated with the creation of a larger fear structure (e.g. rigid views and negative beliefs) would show a slower arousal habituation trajectory with exposure therapy.

2.6.1.1.2 Critical analysis of how the model accounts for the importance of pre- and peri- and post- trauma individual differences

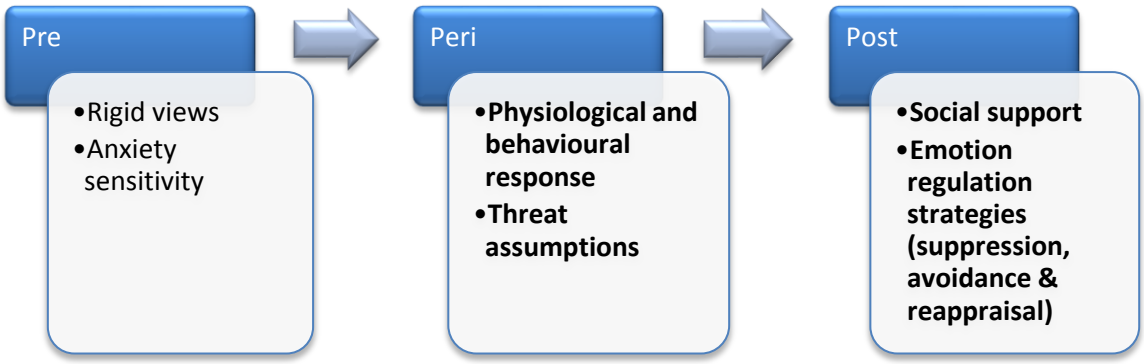


Figure 2.2: Individual difference risk and resilience factors outlined within the emotion processing model of PTSD development (Foa et al., 1989, Foa & Riggs, 1993; Foa & Rothbaum, 1998)

The primary focus of the model is on the creation of fear structures in response to threat violating and fear inducing traumatic events; fear structures can be augmented or reduced based on post-trauma processes (e.g. avoidance versus integration of inconsistent information). In highlighting the beneficial effect of re-activating the fear structure post-trauma and incorporating new corrective information the model also accounts for the possible adaptive role of post-trauma social support and emotional reappraisal strategies in assisting such processes. The model accounts for the importance of pre-trauma views by emphasising the role of safety violations in PTSD development. In addition, trait anxiety sensitivity (i.e. negative beliefs about the concomitance of anxiety) is highlighted as a potential risk factor for

PTSD development; as within the model generalised assessments of danger are posited to enhance symptomatic avoidance behaviours.

Although the emotion processing model can account for known peri- and post-trauma risk factors, its ability to account for pre-trauma risk factors is more limited (figure 2.2). Evidence discussed in the former sections of this thesis suggests that a number of pre-existing biological factors, personality traits and prior life events impart risk of PTSD development; although it could be supposed that the emotion processing model would hold that prior life events could influence the rigidity of pre-trauma views and trauma safety violations, the model does not explicitly account for mechanisms by which biological factors and personality traits influence PTSD symptomology and diagnosis. Furthermore, whilst accounting for peri-traumatic hyperarousal responses, the model does not adequately account for PTSD vulnerability associated with peri-traumatic dissociation and emotional numbing responses.

2.6.1.2 Dual representation theory

The dual-representation model of PTSD development (Brewin et al., 1996, 2001, 2010) posits that trauma memories are processed and laid down in two separate memory representations. The two memory systems, 'verbally accessible memory' (VAM) and 'situationally accessible memory' (SAM) operate in parallel, though one may dominate over the other. The VAM memory system encodes peri- and post-trauma memories for temporally contextualised information and evaluations which have received sufficient conscious processing. The formation of VAM memories are affected by increases in arousal and anxiety, which adversely affect attentional processes, and the salience of the current threat, which focuses attentional processes in on the source of threat. VAM memories are integrated with other autobiographical memories and can be voluntarily retrieved as written or oral narratives. Both primary (i.e. anger, anxiety) and secondary (i.e. shame, guilt) emotional responses are encoded in VAM. VAM representations are posited to be responsible for pathological negative beliefs and emotions associated with PTSD. In contrast, the SAM system codes for non-verbal information which has received little conscious attention. This information is stored as rich sensory memories which are not contextualized and are involuntarily activated by sensory external or internal cues or reminders. The lack of structure and temporal information encoded in these memory formations mean that they are difficult to incorporate with existing autobiographical representations and when triggered they result in re-experiencing of threat in the present tense, with senses and physiological reactions comparatively engaged as they

were at the initial time of trauma; accounting for the occurrence of flashbacks in PTSD. SAM memories only encode for primary emotions experienced peri-traumatically, this means that adaptive post-trauma evaluations, cannot be incorporated into or change SAM memories. It is posited that during trauma exposure memories are represented and stored within SAMs without sufficient processing and representation into VAMs, with peri-traumatic appraisals and emotions highly affected by past SAM representations.

Brewin has extended this cognitive-behavioural account of PTSD, to explain the influence of neurophysiological pathways in memory formation; with an initial extension focusing on neurological pathways implicated specifically within PTSD related literature on fear processing (Brewin, 2001), and a subsequent extension integrating the model within existing models of healthy memory and imagery (Brewin, 2010). The amygdala is known to be involved in fear processing and is posited to activate the fear structures for both memory systems, however the neurological pathway through which the memory is formed and fear information reaches the amygdala varies. VAM memories are posited to be relayed to the amygdala following initial formation within the hippocampus, forming contextualised memories. SAM memories are believed to be the product of memory formations within neurological connections to the amygdala, other than the hippocampus, producing sensory representations of perceptual situational features (Brewin, 2001). Integration within a neural systems model of healthy memory (Brewin, 2010) has allowed for further elaboration of the distinct neurobiological basis of SAM and VAM memory systems, whist highlighting the functional importance of communication between these systems. Whilst SAM representations are posited to be encoded and driven by the bottom-up sensory activation within early sensory cortical areas, amygdala and insula, VAM memories are encoded by and associated with top-down control by the prefrontal and medial prefrontal cortex, in addition to hippocampal areas. As well as accounting for neurological processes, the biological model of dual-processing also has the potential to explain fluctuations in peri-traumatic physiological responding. It has been posited that reductions in heart rate during trauma film viewing, which has been associated with increased intrusion development post-film, could be related to increases in SAM system inputs and reductions in VAM inputs (Holmes et al., 2004).

PTSD treatments supported by the dual-processing model include cognitive behavioural PTSD treatments such as exposure therapy, cognitive restructuring and imagery rescripting, as well alternative treatments addressing memory processing such as eye-movement desensitization and reprocessing (EMDR). Such therapies are posited to address faulty VAM representations

by challenging negative personal schemas via the integration of new adaptive information, allowing for development of a renewed sense of control and re-evaluation of one's sense of personal responsibility. It was originally posited that flashbacks could be treated via the habituation of stimulus-response activations across exposure and by creating new SAM representations of the trauma that have a reduced arousal and affect content, using cognitive restructuring, which override the original SAM memory (Brewin et al., 1996). However these ideas were revised in later publications (Brewin, 2001, 2010), suggesting that it the formation of new corresponding VAM representations which are more detailed, memorable and benign that the original SAM trauma memory, which are needed to block the automatic retrieval of the original SAM trauma memories on exposure to sensory cues or reminders and VAM memories. Furthermore, the creation of new positive VAM memories allows for consolidation via activation of prior positive SAM representations. In this sense exposure therapy works by focusing attention in on SAM memories, allowing for them to be adequately processed and contextualised into detailed hippocampally dependent VAM memories, which have a past-tense temporal representation and lack sensory cue activation, as well as facilitating increased integration of VAM representations within the autobiographical memory base. Therefore the revised model (Brewin 2001, 2010) holds that the original trauma memories are unchanged and additional comparable VAM memories are formed and compete for activation; this explains why after long period of recovery individuals can still experience flashbacks, if the sensory cues are specific enough to activate the original SAM memory, as opposed to the newly formed VAM memory. Cognitive restructuring allows for positive self-identities to be re-activated or strengthened by increasing the associative connections.

2.6.1.2.1 Critical analysis of how the model accounts for the importance of pre- and peri- and post- trauma individual differences

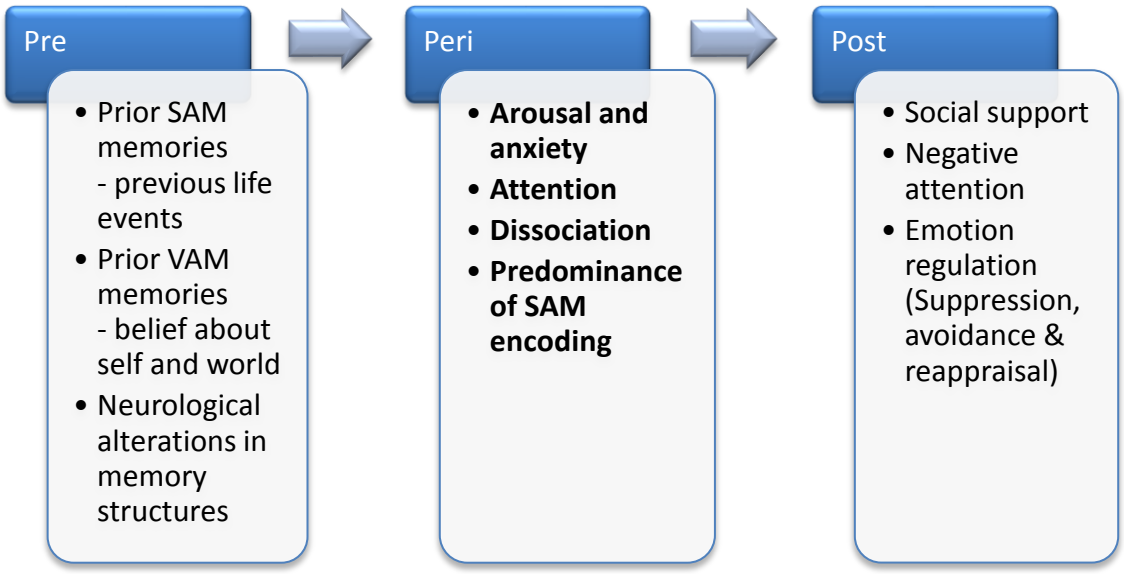


Figure 2.3: Individual difference risk and resilience factors outlined within the dual-processing model of PTSD development (Brewin et al., 1996, 2001, 2010)

The dual-processing model provides a thorough account of the influence of peri- and post-trauma risk factors in the development of PTSD and the neurological pathways involved (Brewin et al., 1996, 2001); with a recent update also highlighting the pre-traumatic importance of the functional health of memory structures (Brewin et al., 2010). Peri-traumatic arousal and dissociation responses are implicated in problems with adequate conscious processing and the predominance of SAM trauma memory formations, which result in PTSD development. The adaptive roles of post-trauma social support and reappraisal are also accounted for, in their ability to facilitate creation of contrasting VAM memories that may block SAM activations aiding in successful emotional processing and trauma memory integration; whilst thought suppression, avoidance and selective negative attention post-trauma would be expected to hinder the creation of VAMs and act to maintain SAM representations and PTSD symptomology.

In addition to explaining peri- and post-trauma risk factors, the dual representation model also accounts for a number of ecological and biological pre-trauma risk factors (figure 2.3). Negative cognitions about the self and the world, are believed to be a product of the reactivation of previous negative self-beliefs originating from prior negative life events and the inhibition of positive self-identities as a result of the traumatic event. In addition, the creation of SAM representations in response to a traumatic event is posited to be influenced by prior SAM memories that were laid down during previous traumatic or adversive life events. These areas of the model clearly illustrate the role of pre-trauma life events in PTSD vulnerability.

Furthermore, recent extensions of the dual-processing model provide a strong account of the influence of individual differences in the health and functioning of distinct memory structures implicated in the formation of SAM and VAM memory; highlighting the importance of biological pre-trauma characteristics in respective risk and resilience to the development of PTSD peri- and post-traumatically. However, although it can be assumed that a number of individual differences in personality, gender and genetics could affect the predisposition to adequately process and integrate trauma information via distinct neural pathways into the VAM system or biases towards the activation of brain systems responsible for the creation of SAM representations, the model itself does not explicitly specify their contribution to PTSD symptom development or elaborate about such mechanisms.

2.6.1.3 Ehlers and Clark cognitive model

Ehlers and Clark (2000) have proposed a cognitive account of PTSD development which holds that PTSD results from memory disturbances and negative appraisals, which produce a sense of current threat and result in the development of PTSD symptomology. PTSD is believed to be maintained by efforts to cognitively and behaviourally prevent symptoms and feelings, which succeed in the short term but paradoxically result in increases in symptom expression in the long term. The cognitive model posits that there are two routes to memory retrieval; the first involves conscious active retrieval of memories and the second results from automatic retrieval of memories following exposure to associated cues and triggers. Normal autobiographical memory integration results in suppression of the second retrieval type and biases towards more active retrieval processes. It is postulated that the form of peri-trauma processing, conceptual (i.e. contextualised, coherent and meaning based) vs. data driven (i.e. sensory impressions), during the encoding phase, affects these qualities of the trauma memory. Conceptual processing produces organised and meaning based memory formation available for active retrieval, while data driven processing creates disjointed sensory memories without a temporal trace which are susceptible to automatic cue based retrieval (for review see Roediger, 1990). Peri-traumatic processing therefore appears at the forefront of the mechanisms by which PTSD subsequently develops.

It is suggested that PTSD is associated with a lack of peri-traumatic conceptual processing, as a result of acute arousal or dissociation, resulting in data-driven traumatic processing. The fragmented and sensory based memory formation which is produced by data-driven

processing results in problems actively recalling trauma information in a coherent manner and facilitated cued based activations, resulting in intrusive memories and flashbacks. The lack of a temporal association within the trauma memory leads to ongoing feelings of threat and negative appraisals of the trauma and its sequelae, which act to further exacerbate assessments of current threat, resulting in hyperarousal, reactivity to trauma reminders and increased maladaptive coping strategies and avoidance behaviours (situational and social) which maintain feelings of fear, arousal and current threat in the long term. Maladaptive coping strategies, aimed at reducing PTSD symptoms and feelings of threat, include thought suppression, rumination, negative appraisals, dissociation, symptom control behaviours, safety behaviours, avoidance of trauma reminders or thoughts, ceasing past activities and self-medicating. These strategies are believed to maintain PTSD by producing pathological symptoms (e.g. intrusions and flashbacks) and preventing long term adaptive change in negative appraisal and trauma memory elaboration and integration. Whilst a number of these processing styles are known to vary pre-trauma (see section 2.3.2.1) within the cognitive model these factors are only discussed as maintenance factors and their presence pre-trauma, or potential to influence peri-traumatic responding is not explicitly discussed. As such, this model proposes that peri-trauma and post-trauma processes are predominantly implicated in the development of PSTD symptomology.

As PTSD maintenance is thought to involve the poor integration of the trauma memory into the autobiographical knowledge base and the expression of maladaptive appraisals and coping strategies, which maintain feelings of current threat and inhibit the occurrence of alterations in the trauma memory, respectively, change in these areas must therefore form the foundation of therapeutic interventions to treat PTSD. Ehlers and Clark (2000) outline a full CBT treatment protocol to address the issues which are held as fundamental within the cognitive model of PTSD. The diagnostic patient assessment allows the therapist an opportunity for an initial summary of the specific maintaining factors which should be the primary focus in following treatment sessions. Suggested therapeutic interventions, in line with the cognitive model of PTSD, include a thought suppression exercise to show how deliberate suppression of even neutral thoughts can be unsuccessful and counterproductive; encouraging a change in maladaptive suppression behaviours in response to intrusions and re-appraisal of negative appraisals of trauma intrusions as a normal and natural occurrence. Identifying potential triggers for intrusive memories allows for work addressing the possible overgeneralisation of negative or trauma appraisals towards objectively safe stimuli and contexts, whilst imagery techniques and education about objective details pertaining to the

trauma and the individuals' current state can alter negative subjective evaluations and appraisals that the patient has made, altering the meaning structure associated with the trauma memory. In vivo exposure to trauma related stimuli or contexts encourages changes in the memory representation via integration of new corrective information regarding the event and one's negative appraisals and can produce a concrete past tense memory. This can reduce automatic retrieval of the trauma memory and associated maladaptive cognitive evaluations and autonomic responses. Encouragement to reinstate activities that have been dropped subsequent to the traumatic event can aid in producing a contextualised past tense temporal trace for the trauma memory, reducing re-experiencing and hyperarousal symptoms. Immersive present tense imaginal reliving can produce adaptive changes in the nature of the trauma memory through automatic habituation of associated arousal responses across repeated exposures. Active cognitive restructuring techniques can allow for the integration of corrective information.

2.6.1.3.1 Critical analysis of how the model accounts for the importance of pre- and peri- and post- trauma individual differences

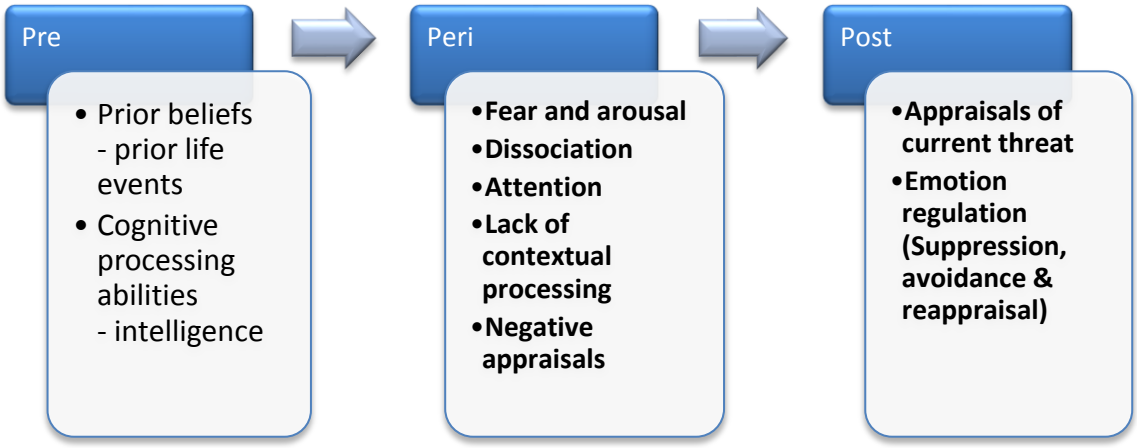


Figure 2.4: Individual difference risk and resilience factors outlined within the cognitive model of PTSD development (Ehlers & Clark, 2000)

The cognitive model of PTSD development places great emphasis on individual differences in peri-traumatic processes and post-trauma emotional regulation strategies. Whilst peri-traumatic arousal and dissociation detrimentally impact upon contextual processing and impart risk of PTSD symptom development, post-trauma maladaptive emotion regulation strategies (e.g. thought suppression) increase PTSD symptomology and inhibit engagement in adaptive reappraisal strategies. Peri-traumatic cognitive processing is posited to be adversely

affected by pre-trauma factors including previous life events, personal beliefs and lower intellectual ability, and peri-trauma factors including fear and anxiety levels, tiredness and intoxication with drugs or alcohol. As such, it is possible that cognitive processing may mediate the association between the pre-trauma ecological risk factors and PTSD symptom expression. Variables posited to affect the appraisals of the traumatic event and its sequelae include the inherent characteristics of the event itself and pre-trauma life events which can bias the meaning associated with the current trauma experience. Prior beliefs and life events are also posited to influence post-trauma tendencies to cognitively and behaviourally control post-trauma symptoms which act to maintain PTSD symptoms.

Despite the ability of the cognitive model to account for peri-, post- and pre-trauma life event risk factors, biological pre-trauma vulnerabilities and the important of personality traits are less well encapsulated within the model (figure 2.4). It could be posited that trait differences in emotion regulation could impact upon post-trauma emotional coping strategies and trait anxiety and anxiety sensitivity could impact upon peri-traumatic appraisals and avoidance, however the role of pre-trauma traits is not explicitly discussed within the model. Moreover, although biological pathways, such as stress induced increases in cortisol levels, are posited to affect encoding and the subsequent nature of trauma memory representations, the model does not explicitly account for the risk associated with gender or genetic individual differences.

2.6.1.4 Lanius emotion regulation model

Lanius (2010) has proposed a neural emotion dysregulation model of PTSD development, in which overmodulation and undermodulation of emotion differentially act upon the same neural regions to cause emotion dysregulation and result in the development of separate PTSD sub-types and symptom expressions. This model is a biological extension of the ideas of Horowitz (1986), who holds that disruption to the emotion modulation system is the main afferent of trauma exposure, with states of undermodulation of affect and reactivity resulting in intrusive symptoms, and states of overmodulation of affect and reactivity resulting in dissociative symptoms. The neural emotion dysregulation model (Lanius, 2010) stems from experimental studies showing differential neural activation patterns correlated with separate response patterns towards exposure to trauma reminders (Lanius, Bluhm, Lanius & Pain, 2006; Hopper, Frewen, van der Kolk & Lanius, 2007). The key premise of the model is that dissociative and reexperiencing states show opposite patterns of neural activation in medial prefrontal and limbic regions; brain areas responsible for emotion regulation and arousal

modulation. Dissociative PTSD is posited to be the result of emotional overmodulation (i.e. numbing) which is neurally mediated by medial prefrontal and dorsal anterior cingulate activation, resulting in midline prefrontal inhibition of limbic regions. Non-dissociative PTSD is posited to result from emotion undermodulation (i.e. increased arousal and affect) causing reexperiencing and hyperarousal symptoms, which is mediated by low ventromedial prefrontal and rostral anterior cingulate cortex activation resulting in a failure of prefrontal inhibition of the same limbic regions. It is posited that after a critical level of anxiety is encountered, this results in medial prefrontal cortex inhibition of limbic regions, which causes a reduction of sympathetic and emotional experiencing. Failure of inhibition results in reexpreiencing symptoms, while hyperinhibition results in dissociative symptoms. It is posited that chronic trauma exposure and long term abuse beginning at an early age increases tendencies to overmodulate emotional responses, increasing dissociative symptoms in these populations. Importantly, as well as constituting sub-type PTSD profiles of dissociation and hyperarousal, the model specifies that over- and under- modulation of affect and the accompanying neural response patterns can also occur simultaneously or on different occasions for a single individual; illustrating the dynamic effects of peri- and post-trauma emotion regulation processes.

According to the neural emotion dysregulation model of PTSD, symptom profiles of dissociation and reexperiencing will require different treatment interventions. When dissociative patterns are presented as the main feature of PTSD, treatment should address overmodulation of emotions, physiological reactions and trauma memories. Although exposure therapy is a held as a successful treatment for reexperiencing and hyperarousal, and as such would be effective in symptom alleviation within individuals who undermodulate their emotions, this approach may be less effective in treating a dissociative subtype. Dissociative patients are unable to adequately engage their emotions with trauma related information which is a necessary prerequisite for successful exposure therapy. Therefore, in treating dissociation it appears critical to work on reengaging emotional affect prior to exposure treatment; failure to do so could result in an increase in PTSD symptoms and impairments. As such the treatment in accordance with the emotion regulation model, accounts for different PTSD subtypes (dissociative and non dissociative) and for individual differences in emotion regulation styles which have the potential to influence emotional overmodulation (such as suppression). The authors point to the two stage treatment model of Cloitre, Koenen, Cohen & Han (2002), which proposes work addressing affect regulation, attachment schemas and grounding preceding exposure based therapy, as a potentially fruitful approach to adopt in the

treatment of dissociative PTSD. Further treatment research into dissociative subtypes of PTSD will allow for development of a phase oriented treatment model to address dissociation as a separate construct to the undermodulated emotional dysfunction more commonly expressed in PTSD patients which are successfully treated by exposure treatments and cognitive restructuring such as reappraisal.

2.6.1.4.1 Critical analysis of how the model accounts for the importance of pre- and peri- and post- trauma individual differences

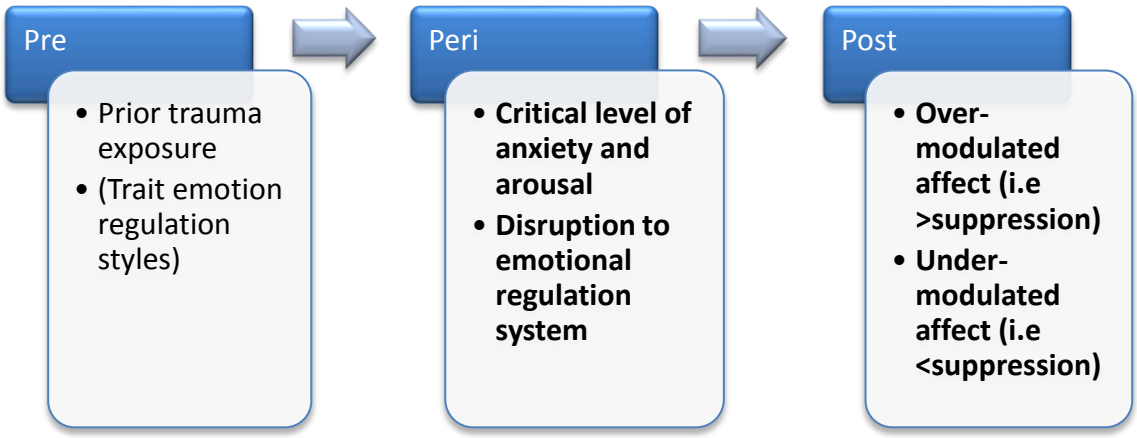


Figure 2.5: Individual difference risk and resilience factors outlined within the emotion regulation model of PTSD development (Lanius, 2010)

The emotion regulation model of PTSD development focuses primarily on the implications of peri- and post-trauma individual differences in emotional modulation and neural activation and inhibition, in producing dissociation and emotional numbing PTSD symptoms and reexperiencing PTSD symptoms. Dysfunctional over or under modulation of emotion is posited to occur following exposure to a critical level of anxiety, illustrating the importance of peri-traumatic subjective evaluations and physiological responses. In implicating over-modulation in emotional regulation, the model accounts for the pathological role of high levels of suppression and avoidance; interestingly however the stated role of under-modulation of emotion in hyperarousal profiles implicates that low levels of suppression may actually form a useful strategy in some circumstances. The cumulative role of previous traumatic life events is implicated in the development of a dissociative response profile, by the assertion that chronic trauma exposure and long term abuse beginning at an early age is a risk factor for a dissociative form of PTSD.

Despite the ability to account for risk associated with pre-trauma life events, peri-traumatic reactions and post-trauma emotional processing, the model fails to explicitly account for the importance of pre-trauma individual differences (figure 2.5). Although it is likely that individual differences in trait emotion regulation styles would affect peri- and post-trauma emotional modulation this link is not made within the literature. Furthermore, the role of gender, genetic factors and personality traits in risk of PTSD development are not accounted for within this model.

2.6.2 Models with an integrative pre-trauma focus

Cognitive and emotion focused models of PTSD development eloquently describe the influence of peri- and post-trauma factors in imparting vulnerability to PTSD symptomology, and whilst such models propose some influences of pre-trauma risk factors, however they fail to fully account for the range of biological and ecological factors which are highlighted by experimental research (as outlined within section 2.3). In order to address this shortfall within existing models of PTSD development, it has been proposed that the application of a diathesis stress model to PTSD would be of benefit.

2.6.2.1 Diathesis stress model

Diathesis stress models of pathology work on the premise that pre-existing biological, and emotional, cognitive and personality characteristics interact with situational stressors to influence individuals' vulnerability to abnormal states or disorders. Diathesis stress models have been proposed and empirically evaluated for the development of depression (Banks & Kerns, 1996; Coyne & Wiffer, 1995; Metalsky & Joiner, 1992; Monroe & Simmons, 1991; Spangler, Simons, Monroe & Thase, 1993, 1996, 1997) and schizophrenia (Walker & Diforio, 1997); more recently work has begun evaluating the efficacy of such a model in explanation of PTSD development (McKeever & Huff, 2003; Elwood et al., 2009). As outlined in section 2.3, research indicates that a range of biological, emotional, cognitive, psychosocial and psychological factors influence risk and resilience to the development of PTSD following trauma exposure; highlighting the applicability of such a model to the development of PTSD. Diathesis-stress models of PTSD highlight the importance of factors that predispose towards the development and etiology of the disorder following exposure to a traumatic event. The premise of a diathesis stress model of PTSD development is that predisposing risk factors predict trauma response severity in a cumulative manner, with a critical level of stress response acting as a necessary catalyst for the development of PTSD symptomology.

Based upon the considerable amount of research into PTSD risk factors, McKeever & Huff (2003) propose that there are three pathways involved in increasing the likelihood of PTSD development. Vulnerability pathways include 1) the residual stress response towards a trauma, 2) ecological factors linked to the self and the environment, encompassing diatheses such as social support, mood states, previous life events and personality, cognitive traits and coping styles (e.g. emotion regulation) with developmental or social origins, and 3) biological factors including genetic, physiological and neurological (anatomical or neurochemical alterations) diatheses. The ecological and biological individual difference pathways can be overtly expressed pre-trauma or can be dormant factors which become actively expressed in response to trauma exposure, whilst the 'residual stress' pathway, which occurs in response to the trauma exposure itself, acts as a necessary catalyst for the development of PTSD. The risk of PTSD development is asserted to be linearly related to the amount of residual stress and the number and combination of ecological and biological vulnerability diathesis an individual possesses. Furthermore, it is possible for a number of factors to interact, in a form in which each factor does not individually impart risk, but a specific pattern of interacting factors forms a single vulnerability diathesis (such as epigenetic risk factors).

Elwood et al (2009) specified that for a factor to be considered a vulnerability factor (diathesis), it should be causally related to the disorder, stable over time, endogenous and therefore latent. PTSD is assumed to develop when the severity of the trauma is sufficient to cause residual stress and activate the adversive effects of vulnerability diatheses on PTSD development. The higher the number of diatheses present, the lower the stress severity that is necessary to cause pathological activation via the residual stress pathway, conversely individuals with a low number of risk diatheses can be exposed to highly traumatic events and show no long term signs of pathology. Only an event which goes on to produce PTSD is incorporated into the residual stress pathway, any stressor which does not act as a catalyst for PTSD development is incorporated into the ecological or biological pathway. Prior stressful events, such as childhood abuse, are incorporated into the ecological pathway. The sequelae of such events can include alterations in cognitive and perceptual patterns which become biological diatheses, and alterations in neural networking (e.g. neural plasticity increasing connections between predominantly activated responses), anatomical atrophy (e.g. hippocampal damage in response to high levels of HPA axis activation) or epistasis (i.e. environmental stressors which interact with genes to alter functional gene expression) become biological diatheses. The original PTSD diathesis stress conceptualisation proposed by McKeever and Huff (2003), holds that although specific resilience factors may be apparent, the

model presumes that risk diatheses are of primary importance to understanding the development of PTSD. However, Elwood (2009) has proposed that a full diathesis stress model of PTSD must account for pre-, peri- and post- trauma psychosocial and biological factors which may influence vulnerability and resilience to the development of PSTD. Despite the differences across conceptualisations, the key assumptions of a diathesis stress model of PTSD is that a diverse range of pre-trauma factors impact upon peri-traumatic stress response severity to impart risk of PTSD development when a critical stress response level is reached.

The premise of the model, that there are risk diatheses present pre trauma which interact with residual stress to cause pathological responses, would lead to the assertion that preventative interventions, following trauma exposure or prior to trauma exposure in at highly exposed individuals (e.g. emergency services and soldiers), would be possible and preferred. A screening process based on known diatheses would be able to highlight individuals at increased risk of PTSD and allow for resources (i.e. assessments and interventions) to be focused predominantly on high risk individuals. This approach would allow for problems to be addressed before they become pathological ingrained responses. Interventions and treatments could be tailored to address the specific risk diatheses which are apparent in any given individual, with different protocols involving medication or psychological therapy proving more effective to address specific vulnerability pathways. Although preventative and screening programmes are effectively used and recommended (Department of Defense, 2004) within military and emergency service structures where individuals are at high risk of trauma exposure, this therapeutic approach is not implicated within models of PTSD, which predominantly focus on how PTSD develops in response to, and in the aftermath of, trauma exposure.

2.6.2.1.1 Critical analysis of how the model accounts for the importance of pre- and peri- and post- trauma individual differences

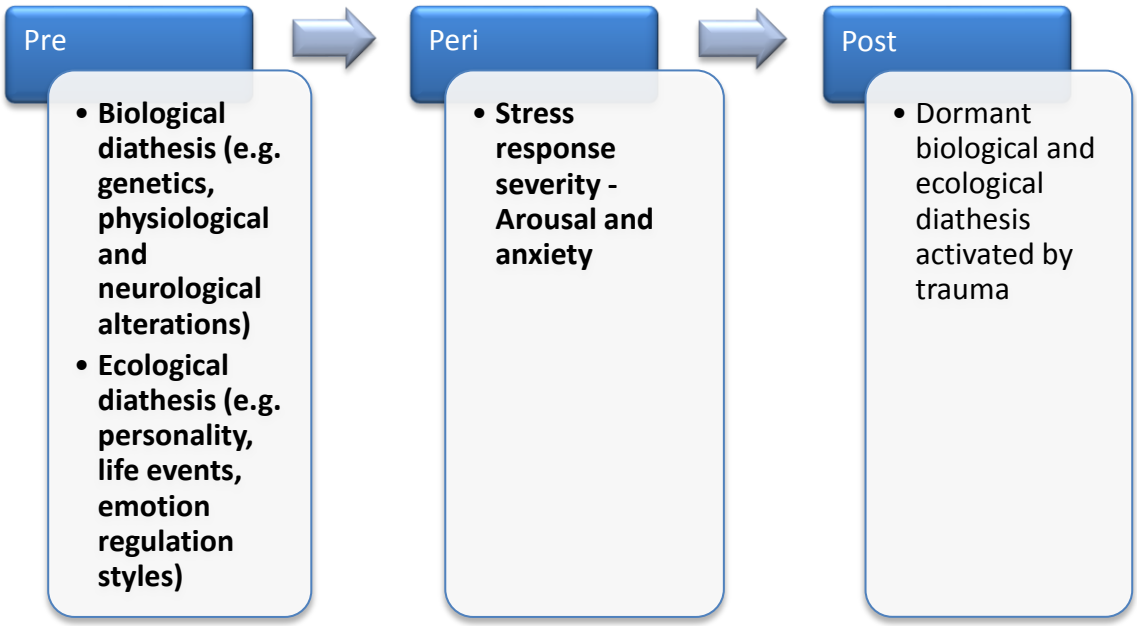


Figure 2.6: Individual difference risk and resilience factors outlined within a diathesis stress model of PTSD development (McKeever & Huff, 2003; Elwood et al., 2009)

The diathesis stress model of PTSD predominantly focuses on the cumulative influence of a diverse range of pre-trauma risk factors, accounting for known biological and ecological vulnerabilities, however the model also specifies that a critical peri-traumatic stress response is required for such diatheses to illustrate their pathological effects (figure 2.6). The role of peri-traumatic responses in acting as a catalyst for pre-trauma factors to predict risk of PTSD development implies that peri-traumatic responses likely mediate the association between pre-trauma risk factors and PTSD symptomology. However, as pre-trauma risk factors are posited to have a cumulative effect of reducing the critical level of stress response (i.e. peri-traumatic anxiety and arousal responses) which is required to activate the predictive links between pre-trauma risk factors and post-trauma pathology, it is possible that specific combinations of important pre-trauma risk factors could theoretically impart risk of PTSD development even under low levels of peri-traumatic responding; which would not then appear as peri-trauma response dependent mediations. Although diathesis stress models produce a promising account of pre-trauma risk factors and their dynamic association with peri-traumatic responding, they fail to elaborate on the explicit cognitive or emotional mechanisms by which risk factors exert their effects and predict PTSD development. A limitation of the diathesis stress conceptualisation is the lack of specificity in the mechanisms by which PTSD actually develops and is maintained post-trauma. Furthermore the importance of peri-traumatic processing responses as highlighted in all the PTSD models outlined above,

which is a well evidenced factor in the risk of PTSD development (for a review of the empirical evidence for the models see Brewin & Holmes, 2003), is neglected within the diathesis stress conceptualisations; with primary focus on the peri-traumatic stress response (i.e. anxiety and physiological responses). As such, it is proposed by the author that whilst a diathesis stress model may aid in the explanation of the diversity of known pre-trauma risk factors (see review section 2.3), and the mediative influences of peri-traumatic anxiety responses on the associations between pre-trauma factors and the development of PTSD symptom (Laposa & Alden, 2008), this is not an adequate alternative model; rather it has utility as a conceptual stance to be integrated into existing and well evidenced (Brewin & Holmes, 2003) PTSD models which primarily focus on peri- and post-trauma factors.

2.6.2.2 Charney (2004) Resilience and vulnerability model: PTSD specific diathesis stress model

The resilience and vulnerability model (Charney, 2004) forms an extension to theories and models of allostatic load (such as McEwan & Stellar, 1993 and Seeman, McEwen, Rowe & Singer, 2001), specifying the complex relationships between neurochemical, neuropeptide and hormonal mediators of psychopathology; as such this model forms a PTSD specific diathesis stress model. Allostasis refers to alterations in internal systems in response to external stressors and the resulting burden on the brain and body. Internal responsiveness to stress may prove adaptive in the short term; however an inability to regulate and terminate such processes following the removal of the stressor can result in maladaptive psychological and physiological dysfunction (i.e. allostasis). Eleven mediators of psychobiological responsiveness to stress, and contributors to allostatic load, are proposed; which can dynamically impart risk and resilience to psychopathological stress responses. Among the many risk factors implicated, the highest quartile for estrogen, and lowest quartile for dehydroepian-drosterone neuropeptide Y, serotonin receptor ($5HT_{1A}$) and testosterone highlight the important roles of female gender and NPS and 5HTTLPR gene polymorphisms, whilst resilience factors including the highest quartile for measures of testosterone, serotonin receptor ($5HT_{1A}$) illustrate the potentially protective role of male gender and the dynamic importance of 5HTTLPR. In addition to the biological factors, a number of psychological individual differences in pre-traumatic factors are also outlined and posited to be important in resilience and vulnerability; these include IQ, emotional regulation, attachment styles, self-view and coping style. Resilient individuals are posited to feel fear in response to traumatic stressors, however they have an ability to retain effective cognitive and behavioural functioning under such circumstances;

implicating individual differences in emotion regulation such as reappraisal, acceptance and personal coping as key to resilience toward PTSD symptom development. Although listed biological and psychological factors are held as important in predicting resilience and vulnerability towards maladaptive stress responsiveness, the authors clarify that this is by no means an exhaustive list and there are many other internal systems which will also contribute risk and resilience to pathological allostatic load.

The neural processes involved in pathological symptom development are also outlined within the risk and resilience model. Fear conditioning results when trauma related stimuli are overgeneralized and become conditioned to context, it is thought that cortical involvement in fear conditioning (relayed via different neurological pathways for cue-specific conditioned stimuli and contextual stimuli) provides a mechanism by which cognitive factors can moderate symptom expression in response to contextual cues (LeDoux, 2000). An excess of CRH together with gluocorticoid release is believed to interact with the noradrenergic system over engagement to produce indelible trauma memory traces and associated reexperiencing. When memories are reactivated by cue stimuli, this elicits a process of memory reconsolidation thought to involve activation of similar processes (NMDA receptors and β receptors) to those implicated in the original memory consolidation process. Resilient individuals have the inherent ability to attenuate their fear responses in the aftermath of traumatic exposure, this is known as extinction. Individuals who develop PTSD do not have such capabilities and require exposure based treatments to allow for fear response extinction via repeated presentation of the conditioned stimuli (trauma memory recall) in the absence of the unconditioned stimuli (traumatic event, life threat). Similar neural networks are posited to be involved in fear acquisition and fear extinction; involving glutamate activation of amygdala NMDA receptors, L-type calcium channels and medial prefrontal activation, with long term extinction facilitated by GABA, norepinephrine and dopamine systems. Social support is known to promote resilience, it is proposed that the neural mechanisms involved in such processes are key to elaborating our understanding of stress resilience and developing new treatment interventions. Animal research investigating social behaviour in rodents has implicated increased receptor expression of oxytocin and vasopressin within the nucleus accumbens and basal lateral amygdala, and increased vasopressin receptor density in the ventral pallidum and amygdala, in rodents expressing highly social behaviours compared to those showing high social withdrawal. The resilience and vulnerability model outlines three key neural mechanisms involved in risk and resilience towards pathological cognitive and behavioural PTSD symptom expression, 1) amygdala, which is implicated in fear conditioning and reward

mechanisms (reward systems may be important in reinforcing social behaviours), 2) nucleus accumbens, as involved in social behaviours and reward mechanisms and 3) medial prefrontal cortex, which is thought to affect fear conditioning, social behaviours and reward mechanisms.

The resilience and vulnerability model highlights the importance of a multifaceted approach to assessment and treatment of PTSD. The primary elaboration of existing treatment rationales is the specification of a number of neurochemical medical interventions which, in combination with traditional cognitive behavioural treatment techniques, could prove useful in facilitating increased adaptive change. Blocking neural mechanisms which maintain ST and LT fear, such as NMDA receptors in the amygdala, would aid in the development of a memory trace with a reduced fear component and hence lower automatic activation towards affect drive cues. Furthermore blocking of voltage gated calcium channels has the capacity to hinder LT memory storage, which would reduce the LT impact and intensity of fear memories. The interactive effects of CRH, glucocorticoids and noradrenergic overactivation and release, on fear conditioning and pathological trauma memory consolidation, may be addressed by administering the respective neurochemical antagonists to vulnerable individuals. Blocking the reconsolidation of trauma memories in response to exposure or cue reactivation may be achieved by the administration of NMDA receptor and β receptor agonists immediately following initial or re- exposure. Inadequate activation of the medial prefrontal cortex during extinction (i.e. reexposure treatment), is posited to result in persistent fear responses; this supposition supports the work of Lanius (2010), which proposes that the hyperarousal and reexperiencing sub-type of PTSD is the result of under activation of the medial prefrontal cortex and emotional undermodulation. Neurochemical treatment to facilitate extinction may be achieved by potentiation of NMDA receptors with the glycine agonist D-cycloserine, which could improve outcomes of exposure-based PTSD therapies. This model therefore highlights the role of pre-trauma individual differences in serotonin, noradrenergic and neuropeptide related genotypes; which have the ability to cumulatively influence peri-traumatic responding and PTSD symptom development, as well as influence the habituation of responses during exposure treatment.

2.6.2.2.1 Critical analysis of how the model accounts for the importance of pre- and peri- and post- trauma individual differences

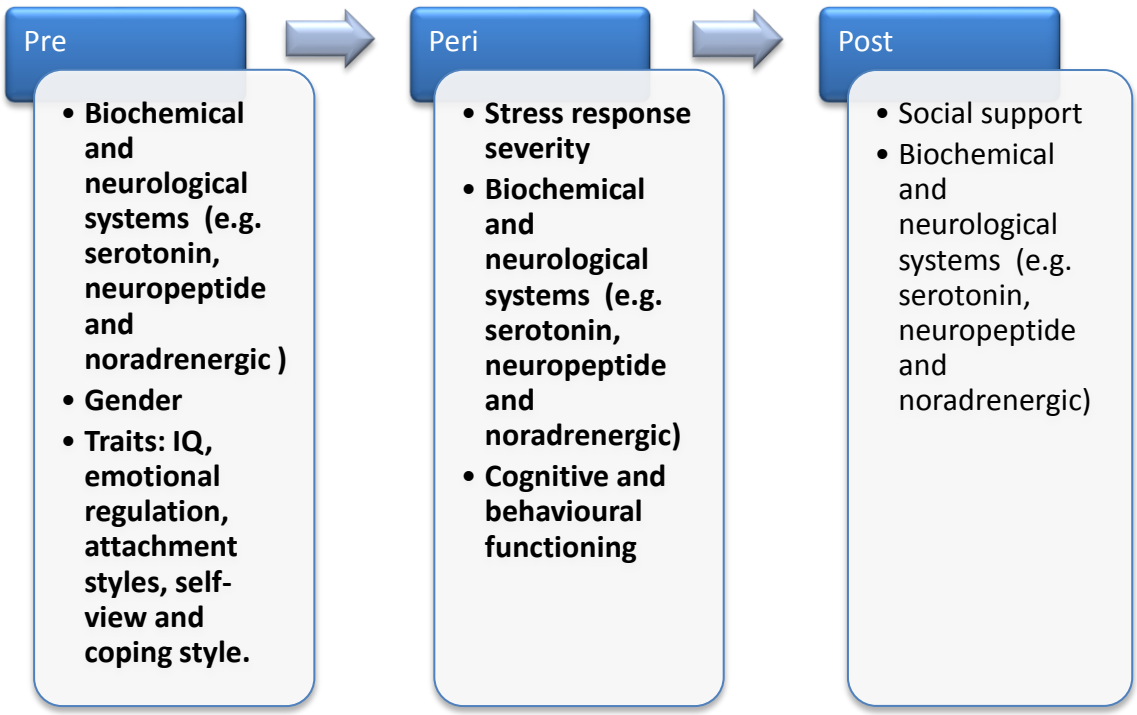


Figure 2.7: Individual difference risk and resilience factors outlined within the resilience and vulnerability model of PTSD development (Charney, 2004)

The primary focus of the resilience and vulnerability model is the explanation of neurochemical and neuroanatomical mechanisms which are implicated in risk and resilience towards the development of PTSD. Although such mechanisms will be partially determined pre-trauma, peri-traumatic stress responses also have the potential to dynamically affect the proposed mechanisms. As well as accounting for biological mechanisms the model highlights the role of individuals' abilities to retain effective cognitive and behavioural functioning in response to the trauma in imparting risk of PTSD development and the adaptive role of social support in facilitating recovery post-trauma. The model gives a strong account of the neural processes by which resilient responses and pathological symptoms can develop, offering a promising rationale for screening processes and alternative and supplementary treatment plans. In addition psychological pre-trauma individual differences in IQ, emotional regulation, attachment styles, self-view and coping style are also outlined and posited to be important in influencing peri-traumatic processes. Whilst this model provides a strong account of pre- and peri-trauma psychological and biological risk and resilience factors, the model does not adequately explain the associations with cognitive mechanisms which influence and maintain PTSD post-traumatically.

2.7 Critical level of vulnerability: Research evidence

Whilst cognitive and emotional models of PTSD development place emphasis on the role of peri- and post-trauma risk and resilience mechanisms in predicting the onset of PTSD[4], diathesis stress conceptualisations would specifically highlight the importance of a range of biological and ecological pre-trauma factors in PTSD risk and resilience and the role of peri-traumatic stress responses in acting as a catalyst to activate the pathological effects of pre-traumatic risk factors. As such the diathesis stress conceptualisation of PTSD development places an increased focus on the mediative role of peri-trauma arousal responses in the associations between pre-trauma factors and symptomology; although key pre-trauma diatheses may also reduce the level of peri-traumatic stress required to activate their pathological associations with symptomology and as such they may show more direct predictive relationships with post-trauma symptom development. Meta analysis and regression analysis have explored the relative contribution of PTSD risk and resilience factors at each level of influence, to clarify which level is most predictive of PTSD development and elucidate mediative peri-traumatic effects.

Meta-analysis has consistently shown that peri-traumatic and post-traumatic risk and resilience factors have larger effects sizes than pre-traumatic risk factors (Brewin et al., 2000; Ozer et al., 2003; Trickey, Siddaway, Meiser-Stedman, Serpell & Field, 2012). Illustrating that peri- and post-trauma factors have a larger role in the development of PTSD compared to pre-trauma characteristics. These results have been supported within a large scale (*N*=937) study measuring and accounting for pre- and peri-trauma factors within a hierachical regression design (Bernat, Ronfeldt, Calhoun & Arias, 1998). It was found that after controlling for pre-trauma risk factors (gender and life events) and the objective characteristics of the trauma itself, unique variance in predicting PTSD symptomology was explained by peri-trauma emotional reactions (8%), physiological reactions (4%) and dissociative responses (3%). However within the aforementioned meta-analysis, although different variations of pre-trauma factors were assessed, with pre-trauma variables consistently illustrating smaller effect sizes and two of the studies (Brewin et al., 2000; Trickey., 2012) including a biologically related variable (gender), due to the reduced amount of research investigating personality traits and genetic risk factors in PTSD these pre-trauma factors were not accounted for in the analysis. It therefore remains unclear what the additional predictive capacity afforded by psychological and genetic trait factors would be, and whether peri- and post-trauma risk factors would remain more important over and above the effects of such previously unaccounted for

[4] The role of pre-trauma risk factors in influencing peri- and post-trauma risk mechanisms is also accounted for, but to a lesser extent and less explicitly, within cognitive and emotional processing PTSD models.

premorbid factors. A large scale longitudinal study assessing the influence of personality traits and peri-traumatic dissociation has found that although both factors were associated with symptom development at 2-4 weeks post-trauma, personality dimensions, but not peri-traumatic dissociation, were predictive of PTSD development at 4-6 months post-trauma (Holeva & Tarrier, 2001). Although only dissociation responses were measured peri-traumatically within this study, the findings illustrate that the influences of personality variables are also important in the prediction of PTSD, providing preliminary evidence of their potential to have increased predictive capacities over certain peri-traumatic responses. As mentioned previously, the role of peri-trauma responses in mediating the associations between pre-trauma risk and resilience factors and PTSD symptomology has been shown within analogue research employing a trauma-film paradigm (Laposa & Alden, 2008). Findings illustrated that state anxiety following the trauma film mediated the relationship between pre-trauma factors (depression scores together with a number of personality traits (trait anxiety, trait dissociation)) and the subsequent frequency of intrusive memories of the trauma-film.

The results of current meta-analysis and experimental studies support the assertion of cognitive and emotion based models of PTSD that, although pre-trauma factors may play a part, peri- and post-trauma factors have a major role in imparting risk and resilience to the development of PTSD. However, with the lack of assessment of personality trait and genetics within such analyses, and findings indicating the potentially increased importance of trait variables, one cannot rule out the possibility that incorporation of a wider range of risk and resilience diatheses could produce a heightened and summative role of pre-trauma factors in the prediction of PTSD development and support the utility of a diathesis stress conceptualisation of PTSD. Furthermore, findings that peri-trauma responses mediate the association between pre-trauma risk factors and intrusion development illustrate the dynamic interplay between pre-trauma factors and peri-trauma responses, acting as a catalyst for pre-trauma vulnerability diatheses, as explicitly highlighted within a diathesis stress conceptualisation of PTSD.

2.8 Outstanding research areas

The principal cognitive and emotion based models of PTSD hold peri- and post-traumatic responses and processing as key to the development and maintenance of PTSD symptomology; whilst pre-trauma factors are discussed to an extent and are implicit in some of the processes summarised within the models, the influence of the wide range of pre-trauma factors (see

review section 2.3) in trauma-responding and PTSD development are not explicitly discussed. Although current literature supports the predominant importance of peri- and post trauma factors, research has neglected to adequately account for the wide range of vulnerability factors (biological and ecological) within a single study design; factors which would be proposed to influence PTSD development by a diathesis stress conceptualisation. A review of the literature assessing the known pre-trauma risk factors in PTSD development (see review section 2.3) has indeed illustrated that a wide range of biological (gender, genes) and ecological (personality traits, prior life events) risk and resilience diatheses are involved in the prediction of PTSD symptomology and diagnosis. As such, further research is needed to clarify the importance of peri- and post-traumatic factors in predicting PTSD symptom development and treatment response, whilst accounting for the range of biological and ecological pre-trauma factors that have been previously implicated in risk and resilience to PTSD. In addition, research has supported the potential for a dynamic interplay between peri-traumatic responses and the activation of the pathological effects of pre-trauma factors on intrusion development (Laposa & Alden, 2008); such findings are also in line with a diathesis stress model of PTSD development which posits that trauma responses act as a critical catalyst, with the level of peri-traumatic stress response which results in pathology believed to be influenced by the presence of pre-trauma risk factors. As the mediative influences of peri-traumatic responses are posited by a diathesis stress conceptualisation of PTSD, further research is needed to re-confirm these findings and investigate mediative relationships on other PTSD symptomatic profiles (i.e. recall accuracy and increased startle responses).

Although models of PTSD development hold peri-traumatic responses as a key contributing factor in the development of symptomology and pathology, clinical research into peri-traumatic responses has been greatly hindered by methodological design. Clinical studies employing both retrospective and prospective designs are jointly affected by an inability to measure physiological responding during the trauma exposure and often rely on unsatisfactory reporting of peri-traumatic responses after long post-trauma periods have elapsed. As trauma recall memory distortions are symptomatic of PTSD (Harvey & Bryant, 1999), it is likely that retrospective reporting of peri-traumatic responses will be highly influenced by the development of PTSD symptoms and as such the independent predictive contribution of peri-traumatic responses is impossible to disentangle. In order to allow for the peri-traumatic measurement of physiological responses and to account for self-report of peri-traumatic affect and dissociation responses with as little gap as possible from the trauma experience itself, the only feasible methodological design is an analogue trauma design. Whilst such a design has

previously been employed to measure physiological responses and associated impacts on memory intrusions (Holmes et al., 2004, Weidmann et al., 2009), further analogue studies are necessary to replicate these findings and investigate the role of pre-trauma risk and resilience factors in these associations.

As well as allowing for a clearer elucidation of peri-traumatic responses, analogue trauma designs allow for the controlled prospective investigation of the role of pre-, peri- and post-trauma mechanisms in the development and maintenance of PTSD phenotypic symptomology. As such, the analogue trauma design provides an invaluable tool for the investigation of a range of risk and resilience factors in the development of PTSD. Analogue trauma designs traditionally employed a trauma-film paradigm, with trauma films involving scenes of a stressful or traumatic event in accordance with the PTSD A1 diagnostic criterion (APA, 2000). However the individuals response to the film, although inducing negative mood and physiological arousal (see Holmes & Bourne (2008) for a review), does not involve 'intense' feelings of fear, helplessness or horror, as required for criterion A2 (APA, 2000). As such it has been discussed that the films would be better referred to as 'films with a traumatic content', however the abbreviated term of phrase 'trauma film' is widely used in the literature (Holmes & Bourne, 2008).

A disadvantage of the traditional trauma-film paradigm is that the trauma is not experienced from a first person perspective. When the event is experienced from a third person perspective there is likely to be increased detachment, which could alter peri-traumatic responses. Indeed, literature has shown that although a number of common neural mechanisms are associated with first and third person viewing within virtual reality (VR) worlds there are also differential neural activations associated with first and third person decision making (Vogeley et al., 2004); with first person perspectives involving mesial cortical areas implicated in spatial decision making and third person perspectives involving activations of cortical areas involved in spatial cognition. Furthermore, a heightened heart rate deceleration response (used as a measure of adversive stress responding), towards a stressful virtual reality (VR) scenario, has been found to occur when the scenario is experienced from a first person perspective compared to a third person perspective (Slater, Spanlang, Sanchez-Vives & Blake, 2010). Unlike the trauma-film paradigm traditionally used within analogue research into PTSD symptomology, VR worlds are easily manipulated for different experimental needs and allow the presentation of an immersive and stressful environment experienced from a first person perspective. VR involves the presentation of a computer generated 3D simulation, via an

immersive headset, large screens and/or table mounted goggles. This allows for environmental manipulations far beyond those possible in the everyday world. The increased immersive dimension associated with experiencing a trauma-film in a VR environment is advantageous when investigating analogue peri-trauma risk factors, especially emotional and physiological responses (Rumball & Karl, 2011; see appendix 1). Although there are clear advantages of using VR-trauma exposure as an experimental analogue trauma, research to date has predominantly employed the traditional trauma-film paradigm and investigations into the utility of the VR-trauma paradigm for use in analogue PTSD research are required.

As well as being a potentially useful paradigm for analogue trauma research, VR has already proved successful in the treatment of PTSD (for a review see Goncalves et al., 2012). Avoiding engaging with trauma reminders is symptomatic of PTSD and certain individuals who experience PTSD may have an inability to recall the traumatic event itself (e.g. if they experienced severe peri-trauma dissociation or were unconscious for large parts of the trauma). As such, some patients may be unable or unwilling to engage their imagination or emotions to an adequate extent during in vivo imaginal exposure therapy, inhibiting adequate change in maladaptive memory formations. Virtual reality exposure therapy (VRE) has been shown to be a useful tool to engage avoidant patients in exposure therapy (Difede & Hoffman, 2002); with the virtual environment easily customised to the individual patient's scenario and current level of distress during re-exposures. VRE has been used to treat PTSD with promising outcomes in road accident survivors (Beck et al., 2007), survivors of World Trade Centre attack (Difede & Hoffman, 2002; Difede et al., 2007) and soldiers post deployment (Rizzo et al., 2009; Wood et al., 2007) and in the front line (McLay et al., 2010). The successful application of VR in exposure treatment for PTSD, illustrates that VR can induce adequate emotional responses and feelings of immersion and presence to allow for modification of maladaptive trauma-related memory traces; supporting its utility as trauma analogue in laboratory investigations of PTSD symptom development.

2.9 Overview of current thesis research: Addressing outstanding research areas

As outlined above empirical research has yet to cumulatively account for the importance of the wide range of pre-trauma biological and ecological risk and resilience which have been individually implicated in PTSD symptom development (as summarised in section 2.3). Although cognitive and emotion based models of PTSD development specify and can implicitly account for a proportion of the pre-trauma risk factors which have been illustrated in the literature, integration of a diathesis stress conceptualization would allow for a fuller

elaboration of the mechanisms by which pre-trauma factors can influence peri- and post-trauma processing. The prospective evaluation of a range of pre-trauma biological (gender, genetics) and ecological (life events, personality and emotion regulation traits) risk factors and their influences on symptomology, via dynamic associations with peri-traumatic physiological (HR and SC) and emotional responses, will allow for investigation of the utility of application of a diathesis stress conceptualization of PTSD development as well as providing a platform to further test the heightened importance of peri-traumatic and post-traumatic factors over pre-trauma factors in symptomology as found in previous meta analysis (Brewin et al., 2000; Ozer et al., 2003; Trickey et al.,2012). As mentioned previously, the most practical research design for the elucidation of peri-traumatic physiological responses is an analogue trauma design in which peri-traumatic responses can be time locked to the presentation of a time-limited stressful trauma-like event. Evidence outlined above implicates VR technology as a particularly useful tool for the analogue investigation of peri-traumatic responses, as it allows for first person perspective and increased immersion when viewing the trauma-like event.

Within the current thesis in order to address these outstanding research areas, a VR-trauma paradigm will be employed across a series of studies addressing the predictive capacities of pre-peri- and post- trauma risk and resilience factors in PTSD-like symptomology. This research will test the effectiveness of VR-trauma paradigms to induce emotional stress responses and evaluate its usefulness within analogue PTSD research, addressing the question ***Is VR-trauma induction an effective tool for analogue trauma investigations?*** In accordance with literature illustrating the efficacy of VR in the treatment of PTSD (Goncalves et al., 2012) and the increased physiological responsivity associated with first person perspective taking within stressful contexts (Slater et al.,2010), it is hypothesised that *VR-trauma exposure will induce significant anxiety, negative mood induction and positive mood reduction*.

To investigate the utility of a diathesis stress conceptualisation of PTSD, pre-trauma factors assessed within these studies will include a range of biological and ecological diatheses; for which their respective influence on analogue PTSD symptomology and the potential for peri-traumatic mediation will be assessed. Peri-trauma responses will be assessed using self-report and physiological measurements, to account for arousal and dissociative responses and their respective associations with analogue PTSD symptomology. As such, across all studies within this thesis a core question will be: ***What is the relative importance of peri- versus pre-trauma factors in imparting risk and resilience to the development of PTSD related symptomology?***

Within the initial empirical study (chapters 5 and 6) the interplay between, and respective importance of, pre- and peri-trauma risk and resilience factors will be investigated. Within the second empirical study (chapters 7 and 8) post-trauma factors will additionally be manipulated, however the added importance of pre- and peri-trauma factors will also be investigated by controlling for the effects of the manipulation and exploring the added variance explained by individual differences in pre- and post-trauma variables. In line with the findings of recent meta-analysis (Brewin et al., 2000; Ozer et al., 2003; Trickey et al.,2012) and in line with cognitive, emotional processing and emotion regulation models of PTSD, it is hypothesised that *peri-trauma factors over pre-trauma factors will account for a greater proportion of variance in analogue PTSD symptom development, in line with cognitive, emotional processing and emotion regulation models of PTSD.* However, as the diathesis stress conceptualisation of PTSD highlights the importance of a range of biological and ecological risk factors and the mediating effect of peri-trauma responses, a proposition supported by experimental research findings of mediation (Laposa & Alden, 2008) and breadth of implicated pre-trauma risk factors across the literature (as reviewed in section 2.3), it is additionally hypothesised that *pre-trauma factors will be implicated in PTSD-like symptom development and will be activated to excerpt their influences on PTSD related symptoms via peri-traumatic mechanisms, in line with the diathesis stress model of PTSD.*

In addition the emphasis placed on emotion regulation within cognitive and emotion based models of PTSD development requires further investigation. A large amount of experimental work by Gross and colleagues has explored the adaptive role of reappraisal in emotion regulation and the maladaptive effects of behavioural suppression, as would be supported within cognitive and emotional processing models of PTSD development. However to date, only one experimental study has explored the effects of reappraisal manipulations following a stressful exposure as opposed to *during* the film viewing itself (Woud et al., 2012). Such a design allows for the investigation of the importance of post-trauma as opposed to peri-trauma emotion regulation. Post-trauma emotion regulation is in keeping with strategies individuals may use in the aftermath of the trauma which can either maintain or reduce PTSD symptomology and in accordance with reappraisal based post-trauma PTSD treatment interventions which supplement exposure based treatments within cognitive behavioural treatment models (NICE, 2005). As such, within chapters 7 and 8 post-trauma emotional regulation strategies will be explicitly manipulated to investigate the question: **What is the relative importance of post-trauma processing (suppression and reappraisal) in the development of PTSD-like symptoms and re-exposure response habituation?** The assessment

of a range of pre- peri- and post-trauma risk and resilience factors within a controlled analogue design will allow for investigation of the amount of variance in PTSD-like symptomology which is afforded by each level of vulnerability. In line with previous meta-analysis (which did however excluded the pre-trauma contribution of personality and genetics) and the emphasis on post-traumatic re-processing within cognitive and emotional models of PTSD it is hypothesised that *post-trauma processing manipulations will influence the development of PTSD-like symp*toms *and re-exposure response habituation*. Furthermore, research suggests trait styles of emotion regulation produce comparable profiles of responses to those associated with experimental manipulation of emotion regulation (Gross & John, 2003). As such within chapters 7 and 8 the influences of pre-trauma individual differences in trait emotion regulation in symptomatic associations will be accounted for and it is hypothesised that *pre-trauma emotion regulation styles will influence how post-trauma emotion regulation manipulations induce symptoms and influence re-exposure habituation, in line with the diathesis stress model of PTSD*.

The specific combination of factors which can best predict phenotypic symptom expression and treatment response is still unknown and an all inclusive study of this nature is warranted. This thesis aims to shed light on the best combination of risk factors (figure 2.8) to explain phenotypic variation. Such a profile of risk factors may be of use in prospectively highlighting individuals who are at greater risk of PTSD development following trauma exposure, allowing for preventative interventions.

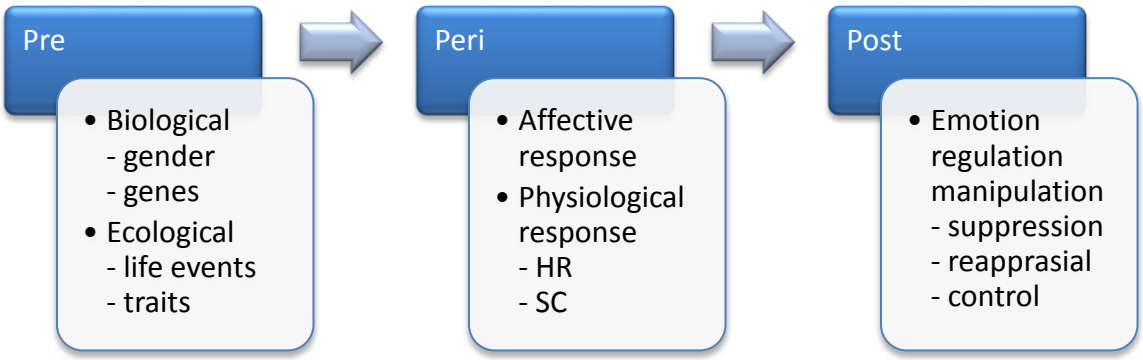


Figure 2.8: Individual difference risk and resilience factors explored within the current thesis

However, as is the case with many DSM diagnoses, there is a significant overlap of PTSD symptomology with other DSM-IV TR anxiety disorders (e.g. phobias and generalised anxiety disorders) and with mood disorders such as depression and dysphoria. As such, it does not seem intuitive to focus research investigation on shared psychiatric symptoms and careful

consideration must therefore be taken when selecting the analogue symptoms to investigate within the current thesis. The proceeding chapter will now outline the rationale for the choice of analogue PTSD-like symptomology, which are investigated within chapters 5-7, and analogue treatment response, which is studied within chapter 8. As well as elaborating on the specific profiles associated with pathological PTSD development and treatment resistance, the following chapter will outline findings relating to the importance of pre- peri- and post-trauma individual differences in such profiles; providing an important theoretical base on which to produce more detailed research questions and directional hypotheses for respective empirical chapters.

3 INDIVIDUAL DIFFERENCES IN PTSD SYMPTOM PROFILES AND TREATMENT OUTCOMES

A major criticism of the current DSM criteria for PTSD diagnosis is the high overlap with other disorders such as anxiety and depression (Brewin Lanius, Novac, Schnyder & Galea, 2009; McHugh & Treisman, 2007; Spitzer, First & Wakefield, 2007). Symptoms which are not unique to the diagnosis of PTSD include a diminished interest in activities, insomnia, concentration problems, irritability and anger, and restricted affect. Furthermore, although in PTSD diagnosis the trauma-related specificity of intrusive experiences and physiological distress act as a differentiator, intrusions and arousal are symptoms in general common to a number of other DSM disorders. The development of PTSD following trauma exposure, as opposed to depression, has been found to be distinguished by experiences of increased peri-traumatic heart rate around the time of the trauma, peri-trauma dissociation, as well as symptom profiles of vivid intrusive memories and exaggerated startle responses (Shalev et al., 1998). In addition to adding further support to the importance of peri-trauma responses in the development of PTSD, these results indicate that memory distortions and startle responses may be a strong pathological distinguisher between PTSD and depressive disorders. As such, although memory distortions are common to other anxiety disorders and exaggerated startle is apparent within other conditions; based on the findings of Shalev et al. (1998) they none the less appear strong candidates for an analogue experimental design aiming to elucidate factors associated with PTSD-like symptom profiles. As exaggerated physiological startle responses are an important characteristic of PTSD it follows that differential neural processing may be occurring; the measurement of event-related potentials (ERPs) is a useful tool for the elucidation of attentional involvement and processing speeds. Meta-analysis has illustrated the presence of ERP alterations in PTSD populations (Karl, Malta & Maercker, 2006) and studies have began to explore the associations with startle ERP responses in PTSD (for example Karl et al., 2007; Metzger, Pitman, Miller, Paige & Orr, 2008).

Furthermore, it has been illustrated that physiological stress sensitization and failure of extinction of trauma related response associations are important profiles in the maintenance of PTSD (Charney et al., 1993). Differential profiles of habituation in primary emotions and arousal responses appear to be an important post-trauma symptom associated with PTSD related pathology and treatment response, with studies illustrating individual differences in startle response habituation (Shalev et al, 2000; Orr, Lasko, Shalev & Pitman, 1995) and anxiety habituation in response to exposure treatment (Shalev, Orr & Pitman, 1992; van Minnen & Hagenaars, 2002), which are predictive of PTSD development and treatment success

respectively. In highlighting the role of anxiety and reflex response sensitization in PTSD, these findings are line with the dual-processing model of PTSD (see section 2.6.1.2) which states that the persistence of SAM trauma memories, which contain sensory and affective information and are involuntarily triggered, are important in the development and maintenance of PTSD (Brewin, 1999, 2001,2010).

This chapter will outline the literature from experimental and prospective studies pertaining to the importance of memory problems, startle responses and habituation profiles and exposure therapy habituation profiles, in PTSD pathology and treatment resistance respectively. Furthermore, as the current thesis will employ an analogue trauma design, it is preferable that the symptom profiles chosen as analogue symptom measures are in themselves predictive of full PTSD diagnosis, therefore representing a strong analogue of pathology; as such the predictive contribution of each of these symptoms to full PTSD diagnosis will be reviewed. In accordance with the focus of this thesis on individual differences in the prediction of PTSD development, current findings pertaining to the role of pre- peri- and post-trauma factors in predicting respective PTSD related symptomology (memory distortions, exaggerated startle responses and habituation, and alterations in ERP's towards pictures and startle stimuli) and treatment response profiles (emotional and physiological habituation to exposure therapy) will be also be outlined. This chapter will form an important theoretical base on which to produce more detailed research questions and directional hypotheses for respective empirical chapters.

3.1 Memory distortions in PTSD patients

Memory impairments are a characteristic feature of PTSD (Brewin, 2001), with patients experiencing intrusive sensory memories of the trauma, often in conjunction with impaired recall for specific details and temporal aspects of the trauma. The specific profiles of intrusive memories and free recall disorganisations which are experienced in PTSD and predictive of later pathology will be outlined in the following sections.

3.1.1 Intrusive trauma memories

Intrusive trauma memories are a common phenomenon in PTSD and are characterised by (often highly sensory and distressing) involuntary recollections, which can take either a verbal or visual form (for reviews see Falsetti, Monnier, Davis & Resnick, 2002; Reynolds & Brewin, 1999). As outlined within the previous chapter, the main models of PTSD maintenance posit

that as individuals try to suppress unwanted and distressing intrusive thoughts, this may have anxiolytic effects in the short term, but in the longer term this inhibits sufficient processing of these memories and ultimately facilitates increased intrusions (Ehlers & Clark, 2000; Brewin 1996, 2001,2010; Foa et al., 1989, 1993, 1998). Support for this proposition comes from literature illustrating that thought suppression shows a rebound effect (Wegner & Zankos, 1994), particularly for suppression of negatively valenced thoughts and memories (McNally & Ricciardi, 1996). Furthermore, patients with PTSD have been found to experience increased thought intrusions following the suppression of trauma-related thoughts (Shipherd & Beck, 2005). The presence of intrusive memories in PTSD has been related to deficits in inhibitory executive control processes, which are posited to globally impact upon the individuals' susceptibility to experiencing intrusions across modalities (Johnsen & Asbjornsen, 2009).

The presence of intrusive symptoms has been associated with an increase in the overall severity of PTSD diagnosis (Laposa & Alden, 2003), whilst the experience of trauma flashbacks within the initial weeks following rape, has been associated with an increased vulnerability towards PTSD diagnosis a year after the initial trauma (Rothbaum et al., 1992). Reports of emotional distress in response to intrusive trauma memories, within the initial post trauma phase, have been found to predict the subsequent frequency of intrusive thoughts in the following year (Schooler, Dougall & Baum, 1999) and to be an important predictor of PTSD symptomology 6 months post-trauma (Michael, Ehlers, Halligan & Clark, 2005). Furthermore, increases in physiological responses (HR and SC) during trauma imagery have been shown to be highly associated with PTSD diagnosis (Orr, Pitman, Lasko & Hertz, 1993). Although this study investigated voluntarily retrieved trauma imagery scripts as opposed to involuntary intrusive images (which are implicated with different neural mechanisms (Brewin, 2010)), the findings that imagery based arousal responses are associated with pathology calls for the investigation of physiological responses during traumatic intrusions, to elucidate their associations as a potential pathological associate. In summary the findings suggest that intrusive memories and associated affective responses form not only a PTSD symptom in themselves but can also predict subsequent PTSD diagnosis, therefore highlighting memory intrusions as a useful PTSD symptom measure for investigation within analogue designs which aim to assess factors associated with potential susceptibility to PTSD development; whilst the preliminary investigation of physiological arousal responses during intrusive memories within analogue designs is also warranted to explore mechanisms which influence such responses and develop research avenues for future clinical study.

Within patient studies, trait tendencies to suppress thoughts have been associated with increased traumatic intrusions (Vasquez, Hervas & Perez-Sales, 2008); supporting models of PTSD development in the role of thought suppression in intrusion development and implicating pre-trauma trait coping strategies in the susceptibility towards traumatic intrusions. Analogue trauma-film studies have highlighted the importance of peri-trauma factors in the development of intrusive trauma-film memories, in particular peri-traumatic data driven processing (Laposa & Rector, 2012), dissociation and HR decelerations have been associated with increased intrusive memories (for a review see Holmes & Bourne, 2008); supporting cognitive and emotion processing models of PTSD development. Analogue investigations have also explored the contribution of pre-trauma trait factors in the development of intrusions, illustrating that the effects of pre-trauma trait anxiety, depression and trait dissociation on intrusion development are mediated by state anxiety induced by the trauma-film exposure; supporting the dynamic interplay between pre- and peri-trauma factors highlighted by diathesis stress conceptualisations of PTSD development. Genetic studies have implicated the ADRA2B s allele in general increases in trauma memory intrusions, although this association was found to be independent of PTSD diagnosis (de Quervain et al., 2007); implicating the noradrengeric gene as a potential pre-trauma predictor of intrusion development, that may not be a PTSD specific mechanism in itself.

In summary intrusive trauma memories and associated affective responses and physiological reactions appear to be a useful PTSD symptom analogue for measurement within laboratory trauma paradigms, with research supporting their predictive associations with long-term PTSD diagnosis and symptomology and illustrating the role of pre- and peri-traumatic individual differences in the frequency of intrusive memories. However, research has yet to explore the contribution of genotypes or life events to the prediction of the frequency of intrusive memories or investigate pre- and peri-traumatic individual difference profiles that may be associated with intrusion characteristics or physiological responses; such research would elaborate our understanding of the respective role of peri-traumatic physiology and intrusion related physiology.

3.1.2 Recall of trauma

As well as vividly re-experiencing sensory aspects of the trauma related memory in the form of intrusions, an additional memory disturbance is also apparent in PTSD patients, in the disorganized and incomplete nature of the autobiographical trauma memory trace. The

sequence and structure of the trauma memory is often disturbed, with impaired recall for contextualised aspects (Harvey & Bryant, 1999). Therapeutic success has been associated with the creation of a coherent trauma memory formation (Foa, Molnar & Cashman, 1995; van Minnen, Dijkstra & Roelofs, 2002). The role of incomplete and disorganised trauma memories in the development of PTSD is highlighted within existing models which emphasise peri- and post traumatic memory encoding and consolidation processes (Ehlers & Clark, 2000; Brewin 1996, 2001,2010; Foa et al., 1989, 1993, 1998). Meta-analysis of general neutral memory problems in PTSD has shown deficits in immediate and delayed recall (Brewin, Kleiner, Vasterling & Field, 2007); however cued and free recall were not separated for analysis. Interestingly, examination of general memory recall for a list of learnt items has shown that whilst free recall was impaired in PTSD patients compared to trauma exposure controls, cued recall was intact in PTSD; implicating potential differences across assessment measures (LaGarde et al., 2010).

Memory disorganisation post-trauma has been shown to be predictive of current PTSD diagnosis (Murray et al., 2002; Halligan, Michael, Clark & Ehlers, 2003); with memory difficulties in the first weeks following trauma associated with an increased likelihood to be diagnosed with PTSD at 4 months (Engelhard, van den Hout, Kindt, Arntz & Schouten, 2003), 6 months (Halligan, Michael, Clark & Ehlers, 2003) and one year (Rothbaum et al., 1992). The association between incoherent, disorganized and less detailed memories and overall PTSD symptomology, including arousal, avoidance and intrusions, has been replicated in an analogue sample exposed to a trauma film (Halligan, Clark & Ehlers, 2002). These findings illustrate that not only are trauma memory omissions and distortions a PTSD symptom in their own right but they also predict current and prospective PTSD full diagnosis.

The development of disordered and fragmented trauma-recall, like intrusive memories, has also been associated with individual differences in peri-traumatic responding. Prospective patient studies have illustrated that peri-trauma dissociation (Zoellner, Alvarez-Conrad & Foa, 2002), data-driven (i.e. sensory) processing and lack of self-referent processing are associated with more *disorganized* (i.e. sequencing errors) trauma memories (Halligan, et al., 2003); whilst the influence of peri-traumatic dissociation on memory *fragmentation* (i.e. content omissions) in PTSD patients has been shown Engelhard et al. (2003). Memory fragmentation and thought suppression were also found to mediate the relationship between dissociative responses and acute PTSD symptomology (Engelhard et al., 2003); again highlighting the measurement of recall memory and intrusions as a useful symptom analogue within laboratory

designs. Furthermore general population studies have found that the BDNF Met allele is associated with poorer episodic memory (Egan et al., 2003) and the NPSR A allele is associated with memory recall impairments (Lennertz et al, 2012); implicating these two genetic alleles as potential pre-trauma risk factors which could influence trauma related recall-accuracy, creating a more fragmented trauma memory.

In summary, these findings suggest that measurement of trauma memory recall fragmentation (i.e omission errors) and disorganisation (i.e. sequencing errors) is useful as an analogue PTSD symptom measure, within laboratory studies aiming to explore the predictive influences of pre- and peri-traumatic individual difference factors in PTSD development. Literature to date has illustrated the importance of peri-traumatic responses in the development of memory fragmentation and disorganisation, but the influences of pre-trauma factors have yet to be explored. In addition, a number of the existing studies exploring peri-traumatic associations rely simply on self-report of memory fragmentation and disorganisation (Halligan et al., 2003; Engelhard et al., 2003); a prospective study examining the predictive effects of a range of pre- and peri-traumatic responses and measuring memory distortions via the analysis of both explicit free recall narratives and cued recall narratives is warranted, to explore differences in predictive associations across assessment measures.

3.2 Startle responses in PTSD patients

Startle responses are a natural and unconscious defence response, associated with reflex eye blink and increased heart rate and sweating. Whilst startle responses can be induced by a number of stimuli, including eye puffs (Hawk & Cook, 1997) and visual probes (VanOyen Witvliet & Vrana, 2000), PTSD literature has focused on the more common paradigm of acoustically elicited startle responses. Acoustic startle responses are typically tested by presentation of white noise startle probes, which are manipulated to have an instantaneous rise and fall time, however a number of researchers have also investigated more ecologically valid startle responses towards naturalistic sounds such as gun shots.

In accordance with symptoms of hyperarousal and intense fear responses, PTSD is generally found to be associated with elevated psychophysiological responses (Pole, 2007). Psychophysiological symptomology in PTSD includes emotion-related reflex and autonomic responses. These physiological mechanisms can be objectively studied using well-controlled laboratory methods to measure facial and bodily muscle activity using electromyography (EMG), and to measure sympathetic activation using electrocardiogram (ECG, which can be

used to investigate heart rate (HR)), and measure skin conductance (SC, which can be used to assess skin conductance response (SCR) and skin conductance level (SCL)) (see section 4.1.3 for a full outline of EMG, HR and SC methodologies). Whilst psychophysiological measurements allow for the objective evaluation of reflex (eye-blink EMG) and arousal responses (HR and SC) towards startling stimuli, measurements of self-reported anxiety and affect allow for the subjective evaluations of arousal, and measurements of startle related event-related potentials (ERPs, a stimulus-locked average of electroencephalographic (EEG) recordings) allow for the elucidation of neurological attention and processing responses (see section 4.1.3 for a full outline of EEG and ERP methodologies).

3.2.1 Exaggerated reflex (EMG) and physiological (HR & SC) startle responses

In patients with PTSD a commonly reported symptom of hyperarousal is exaggerated startle reflex responding (as measured by orbicularis occuli (eyeblink) EMG) and autonomic startle responding (as measured by HR and SC). A number of studies investigating the effects of white noise startle probes have illustrated that the habituation (as measured by trials to reach a criterion of non-response or the response regression slope) and magnitude of reflex eye-blink startle responses in patients with PTSD is distinguishable from that of trauma-controls and non-trauma controls (Shalev, Orr, Peri, Schreiber & Pitman, 1992; Morgan, Grillon, Southwick, Davis & Charney, 1995; Orr, Lasko, Shalev & Pitman, 1995; Shalev et al, 2000; Rothbaum, Kozak, Foa & Whitaker, 2001). However, other studies have failed to find PTSD specific augmentation of reflex eye-blink startle but have shown augmentation of HR (Orr et al, 2003) and SC responses (Orr, Solomon, Peri, Pitman & Shalev). A meta-analysis of the startle literature has found PTSD to be associated with increases in facial EMG startle reflex, HR amplitudes and SC habituation in response to white noise startle stimuli (Pole, 2007). Interestingly however, Casada, Amdur, Larsen and Liberzon (1998) failed to find HR and EMG startle related differences in the PTSD group towards white noise startle sounds, whereas trauma related (combat) sounds did induced significant increases in both physiological measures in the PTSD group compared to the control group; suggesting that trauma relevant sounds may be a stronger distinguisher of pathological physiological startle responses. In support of this proposition other studies have illustrated startle reflex response facilitation in PTSD patients towards trauma related foreground pictures (Carlson, Singelis & Chemtob, 1997). The finding of increased startle responses in PTSD, and in particular the augmentation towards trauma contexts and sounds, can be interpreted in accordance with the motivational priming hypothesis of Lang, Bradley and Cuthbert (1998). Lang et al (1998) describe emotional

states as motivational systems which modulate associated action programs; augmenting consistent reflexes and inhibiting inconsistent ones. Negative emotions are therefore posited to augment the defence reflex startle response. This hypothesis offers a rationale for general startle augmentation in PTSD, where generalised arousal and threat attribution are symptomatic, as reviewed above, and increased augmentation is facilitated towards trauma related startle in particular.

Although startle responses are clearly an important symptom of PTSD as outlined above and as specified with DSM criterion D (APA, 2000), mixed evidence exists as to whether the development of startle responses in the aftermath of trauma exposure is predictive of current and subsequent PTSD diagnosis, or whether they only develop in line with full pathology. Whilst a number of prospective studies have shown that physiological startle responses develop in line with the acquisition of PTSD (Griffin, 2008; Shalev et al., 2000); other prospective research has illustrated that increased pre-trauma SC startle responses predict post-trauma PTSD severity (Guthrie & Bryant, 2005), supporting a view of exaggerated startle responding as a vulnerability factor for subsequent PTSD development. Recent rat models of PTSD-like phenotypes have found that exposure to a mild stressor, which in itself does not induce pathology, can produce measureable increases in startle responding within a subset of rats which are found to go on to develop PTSD phenotypic symptoms following later fear conditioning (Nallor, Buntig & Vazdarjanova, 2011); implying that startle responses following stressors may form a strong indicator of risk for pathological PTSD development.

In line with findings of stress related activation of pathologically predictive startle responses in phenotypic rat models, it has been proposed that elevated startle develops as a result of excessive negative emotions (Lang, Bradley & Cuthbert, 1998), which result from a general hypersensitivity in responding to contextual threat cues. Although the experience of exaggerated startle responses within explicitly threatening contexts, such as those directly preceding an electric shock, may be a normal response showing no clear pathological differentiation, PTSD diagnosis has been associated with exaggerated startle responses towards exposure to contextual threat cues (Grillon, Morgan, Davis & Southwick, 1998; Pole, Neylan, Best, Orr & Marmar, 2003). As such, increased startle magnitudes in PTSD veterans compared to non-PTSD veteran controls have been found for shock anticipation and during perceived contextually threatening baselines, but not for startle measures in explicitly threatening contexts directly preceding an electric shock (Grillon et al., 1998; Morgan et al., 1995). Exaggerated baseline startle in PTSD veterans compared to non-PTSD veteran controls

is not apparent in the absence of stress when individuals are tested in familiar contexts. Therefore exaggerated startle towards contextual anticipatory threat in PTSD patients can be taken as evidence of a conditioned emotional stress response, which has become generalised to stressful contexts (Morgan et al., 1995) and hence exaggerated baseline responding is not always observed in PTSD (Grillon, Morgan, Southwick, Davis & Charney, 1996). Furthermore, exaggerated startle during baseline (no threat), is indicative of a conditioned emotional stress response which has become generalised to unfamiliar contexts; this is supported by evidence that exaggerated startle responses in PTSD are associated with stress sensitization, with PTSD patients showing a lack of differential conditioning (Glover et al, 2011) and increases in baseline responding prior to a re conditioning phase, but a lack of group differences at initial assessment pre-conditioning (Grillon & Morgan, 1999). Overall the findings suggest that the increased physiological startle responses following stress exposure and within contextually threatening contexts are associated with pathological PTSD diagnosis, however research to date is limited in its generalisability focusing predominantly on male veterans.

Whilst a large body of work has explored individual difference factors in the prediction of post-trauma memory impairments there is a lack of literature exploring associations with exaggerated startle symptomology in PTSD. Within general population studies personality traits, such as harm avoidance (Corr, Kumari, Wilson, Checkley & Gray, 1997), as well as female gender (Quevedo et al., 2009), have been associated with alterations in startle responses; however other studies have found that trait anxiety has no effects on startle responses (Grillon, Ameli, Foot & Davis, 1993). Genetic factors have been associated with differential startle responding, with findings illustrating increased amygdala activation during startle probe presentation in BDNF Met allele carriers (Londsdorf et al., 2010) and augmentation of reflex EMG startle in NPS A allele carriers (Fendt et al, 2011; Okamura, et al., 2011; Lennertz et al, 2012). Furthermore, research on emotion regulation has shown that concurrent reappraisal strategies during startle probe presentations can effectively reduce reflex eye-blink responses (Jackson, Malmstadt, Larson, & Davidson, 2000). These findings suggest that pre-trauma genetic and trait factors and post-trauma emotion regulation manipulations have the potential to predict differences in startle responding following trauma exposure and as such further research to explore associations within a longitudinal design measuring the influences of peri-trauma factors is called for.

3.2.2 ERP startle responses

It is believed that exaggerated startle responses in PTSD occur as a result of generalised threat attribution and processing, indicating that ERP measurements of startle processing would aid in the elucidation of the potential electrophysiological mechanisms responsible for PTSD associated exaggerated startle responding (Amrhein, Muhlberger, Pauli & Wiedermann, 2004). ERP components are composed of a number of positive (P) and negative (N) waveforms which are denoted by abbreviations which represent their sign and the time frame (in milliseconds (ms)) in which they occur (for example 'P2' represents a positive ERP component which occurs at around 200ms following the stimulus to which the EEG measurement has been time-locked). Experimental testing of the situations in which different ERP components occur and fluctuate has allowed for increased consensus on what individual components represent in relation to specific cognitive processes (Luck, 2005). Indeed, meta-analysis of ERP studies into PTSD specific changes has shown consistent alterations in the amplitude and latency of ERP components (Karl, Malta & Maercker, 2006). Findings of the meta-analysis illustrated that P2 amplitudes, a component elicited by auditory stimuli, significantly correlate with the severity of PTSD symptomology and show differentiation by gender. Adult males were found to show a significantly lower P2 slope to auditory stimuli of increasing intensities, suggesting that males with PTSD develop a sensory system tuned to shut out increased stimulation. The P3 ERP response is a component associated with attentional processes, and as such is elicited in response to a number of stimuli (pictures and sounds) and all paradigms in which individuals are attending to stimuli, such as simple picture viewing or sound tasks and stimuli requiring responses. The P3 has an earlier component, P3a, and later component, P3b. Reduced P3b amplitudes and faster latencies towards neutral targets, in the context of neutral or no distracters, were found to be associated with trauma exposure rather than PTSD specifically. Interestingly this finding demonstrates that altered neurophysiology can develop post-trauma, independently of PTSD. PTSD specific electrophysiological increases were however apparent in early and late P3 amplitudes towards neutral stimuli in the context of trauma-related distracters; illustrating that information processing in PTSD may be specifically enhanced towards contextually threatening stimuli.

The existence of electrophysiological abnormalities in PTSD is illustrative of the biological basis of information processing deficits in PTSD; with these electrophysiological responses associated with the development and/or pathology of PTSD. As such, the investigation of startle related ERPs would be beneficial in furthering our understanding of how startle responses are associated with threat attribution and processing, elucidating the biological

basis for startle processing abnormalities in PSTD. Furthermore, the findings that P2 response alterations in PTSD patients were dependent on gender, illustrates that pre-trauma characteristics may influence ERP related pathological processing alterations following trauma exposure.

Although a number of studies have investigated the differential physiological afferents of startle responding in PTSD, less research has been carried out into accompanying pathological alterations in ERP processing of startle stimuli. Investigation of startle related ERP components in healthy population studies has shown that the profile of ERPs in response to startle include an early negativity (N1), a peak in positivity around 200ms (P2) and a second positivity around 300ms (P3) (for example see Cuthbert, Schupp, Bradley, McManis & Lang, 1998). As early components, especially when measured in response to a startle stimulus, are more contaminated by eyeblink artefact, work has predominantly focussed on factors affecting P2 and P3 amplitudes and latencies. Evidence suggests that the P3 towards startling stimuli is not simply a direct component of the reflex EMG startle response, showing a differential course of habituation over trials as the surprise value of the startle stimulus reduces, though it may share a common neurophysiologic mechanism as it has shown a comparable total number of trials to reach asymptotic levels (Hirano, Russell, Ornitz & Liu, 1996). As such the measurement of P3 responses produces additional information in regards to startle response alterations. The P3 response is thought to reflect the cognitive evaluation and processing of the sensory and affective properties of the startle stimulus (Sugawara, Sadeghpour, de Traversay & Ornitz, 1994), whilst the P2 startle response reflects earlier encoding and attentional allocation processes which are also influenced by arousal and valence (Cuthbert et al., 1998; Schupp et al., 1997). Research exploring startle ERP alterations in PTSD patients is in its infancy but findings to date implicate differences in P2 amplitudes and central serotonergic activity. While studies exploring P2 intensity slopes in male veterans have found a reduced intensity P2 amplitude slope towards increasing sound intensities to be a PTSD specific mechanism, differentiating from trauma control groups and posited to represent an increased state of protective inhibition and heightened serotonin activity in PTSD patients when exposed to startling sounds (Paige, Reid, Allen & Newton, 1990; Lewine, Thoma, Provencal, Edgar, Miller & Canive, 2002). Others have shown that the opposite pattern , of steeper P2 amplitudes to differentiate between monozygotic twins with PTSD, compared to their non-PTSD twin at startle sound intensities (Metzger et al., 2000); suggesting that low serotonergic activity may be a longer term consequence of PTSD, with heightened P2 intensity slopes showing a relationship with PTSD severity and reexperiencing symptoms. Increased P2 sound intensity

slopes have also been reported within children with PTSD resulting from long term abuse (McPherson, Newton, Ackerman, Oglesby & Dykman, 1997) and female PTSD patients (Metzger et al., 2002); suggesting that some patients with PTSD have deficiencies in cortical inhibitory responses which protect against overstimulation from startling sounds. The differential findings in regard to P2 intensity response slope amplitudes are of particular interest in light of the findings of Karl et al (2007) that P2 startle amplitudes within PTSD patients were moderated by serotonin gene 5HTTLPR allelic variations, with increased P2 startle amplitudes apparent in s allele carriers and reduced P2 startle amplitudes in l allele carriers. These findings suggest that differential P2 amplitudes towards startling sounds may represent biological subtypes of PTSD distinguishing the presence of differential symptom profiles. Cognitive literature investigating ERP responses in the general population has illustrated that concurrent reappraisal of images reduces the P3 amplitudes towards negative pictures (Gootjes, Fanken, & Van Strien, 2011), illustrating the potential for startle ERP modulation by post-trauma emotion regulation manipulations, as well as findings of an association between extroversion and increased P2 amplitudes (Bartussek, Becker, Diedrich, Naumann & Maier, 1996). These findings highlight the importance of individual differences in modulating the effects of startle ERP responses, however further research is needed to explore role of pre-,peri- and post-trauma factors in the development of differential ERP startle responses following trauma exposure and their associations with different symptomology.

3.3 Exposure therapy: Habituation

As outlined at the beginning of the chapter, in addition to individual differences in startle response habituation (Shalev et al, 2000; Orr, Lasko, Shalev & Pitman, 1995), anxiety habituation in response to exposure treatment have been shown to be predictive of subsequent treatment success (Shalev, Orr & Pitman, 1992; van Minnen & Hagenaars, 2002). These findings implicate the utility of anxiety and arousal response habituation measures as analogue markers of treatment response or treatment resistance. The literature in regards to this topic will now be summarised and reviewed.

Traditionally there are three forms of exposure therapy 1) in-vivo exposure, in which patients are exposed to a feared stimulus itself, 2) interoceptive exposure, requiring engagement of physiological and bodily sensations relating to the fear, and 3) imaginal exposure, involving therapist guided patient led recall of the trauma in a first person narrative form. Exposure therapy has proved an efficient and effective treatment for PTSD (Foa, 2011) and is supported within models of PTSD development as outlined in chapter 2. Imaginal exposure therapy is

believed to result in PTSD symptom improvement in part through desensitisation to trauma stimuli (Keane & Kaloupek, 1996). It has been shown that exaggerated physiological responses towards ideographic trauma images which are present prior to therapy are normalised following exposure therapy addressing these trauma images, interestingly however trauma related images which were not the focus of therapy continued to facilitate physiological responsivity (Shalev, Orr & Pitman, 1992). These findings suggest that physiological habituation towards re-exposure is a promising indicator of effective desensitization treatment. Furthermore, habituation in self-reported anxiety between the first and second session of imaginal reliving exposure therapy has been related to improvement in long term treatment outcome (van Minnen & Hagenaars, 2002), suggesting that measurements of habituation across the first 2 exposure sessions predict individual differences in final treatment outcomes. These findings suggest that measurement of habituation in physiological and self report anxiety responses towards 2 trauma re-exposures in a sample exposed to a laboratory trauma may provide a useful analogue of individual differences in treatment response.

A small number of studies have investigated the influence of pre-trauma individual differences in exposure treatment response. It has been shown that both gender and phenotypic expression of the 5HTTLPR polymorphisms can influence the efficiency of exposure therapy in retaining treatment gains. Comparable symptom reduction has been shown across genders immediately post-treatment but at 6 months post-treatment males have been found to show increased PTSD symptom severity (Felmingham & Bryant, 2012); whilst the 5HTTLPR s (and LG) allele has been associated with more severe PTSD symptoms at 6 months-post treatment (Bryant et al., 2010).

A large amount of research has explored the influence of the concurrent use of emotion regulation strategies to supplement exposure therapy and improve outcomes, by association implicating individual differences in emotional coping styles as a potential pre-trauma factor influencing treatment response. Although some research has claimed that combined cognitive (i.e. reappraisal strategies) and behavioural (i.e. exposure) interventions are no more effective than behavioural techniques alone (Longmore & Worrell, 2007), other reviews have found cognitive techniques to be a useful and effective treatment (Hassija & Gray, 2010) with comparable clinical efficacy when compared to behavioural interventions (Marks , Lovell, Noshirvani, Thrasher & Livanou, 1998; Tarrier et al., 1999). Interestingly, as laboratory research has illustrated that reappraisal can effectively reduce self-reported affect but has no influence on physiological responses to negative stimuli (for review see Gross, 2002), it is possible that

reappraisal techniques may aid in the habituation of self-reported emotion but not physiological arousal during exposure therapy. Research has also implicated behavioural suppression in alterations in treatment response, with a reduction in facial fear responses associated with poorer treatment outcomes (Foa, Riggs, Massie & Yarczower, 1995). The findings to date implicate pre-trauma biological factors (gender and genetics) and emotion regulation trait styles as well as post-trauma coping strategies and interventions in influencing treatment outcomes and maintenance of treatment gains. Further research is called for to investigate the role of pre-trauma emotion regulation styles and post-trauma emotion regulation instructions in influencing habituation of responses over re-exposures, and to elucidate pre- and peri-trauma individual differences, which may modify exposure treatment habituation profiles.

Whilst traditional imaginal exposure therapy has proved effective for a large number of PTSD patients there are a sub-group of patients, with dissociative symptom profiles (Ginzburg et al., 2006) and others with severe peri-trauma memory loss (e.g. head injury, concussion, drugging), for whom engagement in traditional exposure techniques may be prohibited. A promising new exposure-based technique, which can be employed when memory fragmentation or dissociation inhibit engagement with traditional exposure, is virtual reality exposure therapy (VRET). VRET involves the construction of patient tailored VR worlds, which can be manipulated and modified to gradually increase the severity of the VR events so as to reduce dissociative responses that may occur when events seem too anxiety provoking to engage in. VRET has proved to be as effective as traditional exposure techniques in treatment of PTSD in general (Goncalves et al., 2012) and has been shown to alleviate PTSD symptoms in individuals who are unable to engage in traditional exposure methods (Difede & Hoffman, 2002). Whilst VRET has shown to be effective and efficient further research is needed to investigate the added efficacy afforded by cognitive reappraisal techniques and individual difference risk and resilience factors, which may predict VRET related habituation in anxiety responses.

3.4 Summary and outstanding research areas

Current research findings illustrate that, as well as differentiating PTSD diagnosis from depression diagnosis (Shalev et al., 1998), memory distortions and startle response profiles following trauma exposure are not only symptomatic of PTSD but can predict full pathological development. Whilst trauma-related memory intrusions and recall distortions have been successfully investigated within analogue trauma-film designs (for review see Holmes &

Bourne, 2008), laboratory research has yet to investigate hyperarousal related PTSD symptomology via measurement of exaggerated startle responding post-trauma-film. However phenotypic rat models support the ability to measure alterations in startle responding following stress exposure which were found to be predictive of subsequent pathological responding following full trauma exposure; herein evidencing the ability to measure meaningful individual differences in startle responding within a trauma-film paradigm. As such, the measurement of trauma related cued recall accuracy, free recall accuracy and disorganisation, and psychophysiological startle responding towards neutral and trauma stimuli, within laboratory trauma designs appears to be a useful analogue of PTSD symptomology with wider implications for risk of pathological PTSD diagnosis. Furthermore, as research has illustrated that exposure related treatment outcomes can be predicted by physiological habituation profiles and the habituation in self-reported anxiety across the initial 2 exposure sessions, measurement of arousal response profiles towards a small number of trauma-film re-exposures appears to be a useful analogue of potential treatment response outcomes with exposure therapy.

Individual difference research to date has focused primarily on the influences of peri-traumatic responses and processing manipulations in altering trauma related memory distortions; this focus has been driven by research evidencing current cognitive models of PTSD development. Findings have supported the role of peri-traumatic processing biases and peri-traumatic responses such as dissociation and HR in predicting PTSD related memory distortions. However research employing objective experimenter determined analysis of trauma recall distortion rather than relying on participant self-report of memory disorganisation and fragmentation is needed to confirm the influences of peri-traumatic responses. In addition, investigation of the influence of biological and ecological pre-trauma factors in predicting trauma related memory distortions is necessary, with evidence that peri-trauma factors can mediate the influences of pre-trauma trait factors on the frequency of intrusive memories following trauma (Laposa & Alden, 2008) supporting the role of peri-trauma responses as a catalyst to activate pre-trauma vulnerabilities as proposed within diathesis stress conceptualisations of PTSD (McKeever & Huff, 2003; Elwood et al., 2009).

Although empirical research has investigated the influence of individual differences on general alterations in startle responding, showing that gender (Quevedo et al., 2009), genes (for example Londsdorf et al., 2010), traits (Corr et al., 1997) and reappraisal manipulations (Jackson et al., 2000) influence startle responding, research exploring predictors of post-traumatic psychophysiological startle responses in patients or in trauma-analogue designs is

lacking. It is posited that the role of threat attribution and processing biases in contributing to exaggerated EMG startle responding in PTSD suggests that ERP startle responses may also be altered in PTSD. ERP processing alterations have been implicated in PTSD pathology (Karl et al., 2006). However studies exploring P2 startle responses implicate differences in central serotonergic activity as altering P2 amplitudes within PTSD patients and potentially representing a biological marker which differentiates between different PTSD sub-types and symptomology (for example, Karl et al., 2007, Lewine et al., 2002; Metzger et al., 2008). Within the cognitive literature ERP responses have been found to be altered in amplitude by reappraisal emotion regulation techniques (Gootjes et al., 2011). As such, the investigation of pre-trauma factors, peri-trauma responses and post-trauma emotion regulation strategies in the prediction of differential startle responses following trauma exposure, or trauma-film exposure, is an important avenue for further research. Furthermore, whilst research has implicated pre-trauma individual differences in alterations in long term treatment gains following exposure therapy, research is needed to explore the role of pre- peri- and post-trauma individual differences in influencing re-exposure response habituation.

3.5 Overview of current thesis research: Overall and chapter specific research questions

As outlined in Chapter 2 a number of individual differences in biological and ecological pre-trauma factors, peri-trauma responses and post-trauma coping strategies have been implicated in PTSD severity and diagnosis. With a lack of research incorporating a number of pre-trauma factors within a single design and investigating the peri-traumatic physiological responses[5], a prospective analogue investigation allowing for accurate measurement of physiological trauma responses is called for; with a VR-trauma paradigm allowing for exposure from a first person perspective and hence a more immersive experience in which to measure physiological responses. As such, within the current thesis 2 large scale VR-trauma analogue studies will be carried out, measuring a range of pre- peri- and post-trauma emotional coping strategies. The core thesis questions outlined at the end of chapter 2 highlighted that the use of a VR-trauma paradigm will evidence the utility of a VR trauma film as an analogue trauma stimulus. The use of a prospective design will enable precise measurement of peri-traumatic responses and allow for evaluation of the influence of peri- and post-trauma factors in accordance with cognitive and emotional processing models. Furthermore, the utility of a diathesis stress conceptualisation of PTSD, as an addition to existing PTSD models, will be

[5] Peri-traumatic physiological responses have only been investigated in relation to the development of trauma-film-related intrusive trauma memories (Holmes et al., 2004)

tested by exploring the influence of a range of pre-trauma factors and the mediative influences of peri-trauma factors.

The PTSD-like symptom analogues to be investigated within this thesis were derived in accordance with the literature outlined within this chapter, and will include the assessment of VR-trauma-memory (intrusions and recall) and startle responding (EMG, HR, SC, EMG). In addition, analogue VRET treatment response will be investigated via measurement of anxiety and arousal habituation responses towards 2 VR-trauma re-exposures. These outcome measures will allow for investigation of the outstanding research areas outlined in section 3.4.

The initial study within this thesis will explore the influences of pre- and peri-trauma factors in predicting reflex and electrophysiological startle responses towards neutral and trauma related startle sounds and contexts (Chapter 5) and VR-trauma related memory distortions in free recall, cued recall and intrusions (Chapter 6). Whilst the final study, as well as investigating pre- and peri-trauma factors, will explore the effects of post-trauma emotion regulation manipulations (acceptance and coping based reappraisal, behavioural suppression and a control group instructed to view normally) on concurrent reflex and electrophysiological startle responses (Chapter 7) and 2 VR-trauma re-exposures (VRET treatment analogue) (Chapter 8). In addition to addressing the overarching thesis questions and hypothesises as derived within Chapter 2, a number of chapter specific research questions will address outstanding research questions in relation to the analogue symptom or analogue treatment response addressed within each empirical chapter. An overview of the Chapter specific research questions is outlined below and directional hypothesis are outlined within the respective empirical chapters.

3.5.1 Chapter specific research questions

3.5.1.1 Study 1a (Chapter 5): Predicting acoustic startle responses

Q1: Are affective and electrophysiological startle mechanisms sensitive to trauma versus neutral valence effects following exposure to a virtual reality trauma?

Q2: What are the predictive effects of pre-trauma individual differences on startle responses?

Q 3: What are the predictive effects of peri-trauma individual differences on startle responses?

3.5.1.2 Study 1b (Chapter 6): Predicting memory distortions and suppression related intrusions

Q1. What are the predictive effects of pre-trauma individual differences on post-VR memory distortions, intrusive trauma memories and physiological responding at the time of the intrusive memories?

Q2. What are the predictive effects of peri-traumatic responses on post-VR memory distortions, intrusive trauma memories and physiological responding at the time of the intrusive memories?

3.5.1.3 Study 2a (Chapter 7): Post-trauma emotion regulation and startle responses

Q1: Are affective and electrophysiological startle mechanisms sensitive to trauma versus neutral valence effects following exposure to a virtual reality trauma? And is there ER manipulation dependent differences in responses, when individuals are required to regulate their emotions to trauma stimuli (TR), receive uninstructed exposure to trauma stimuli (TV) and receive uninstructed exposure to neutral stimuli (N)?

Q2: Do explicitly instructed emotion regulation strategies influence affective, physiological (eye-blink, HR and SC) and brain processing (ERP) startle responses?

Q 3: Are experimental manipulations of reappraisal and suppression associated with differential startle responding when the effects of trait emotion regulation styles (reappraisal and suppression) are controlled for?

Q4: Are pre- and peri-trauma individual difference profiles predictive of altered startle responding, over and above the effects of manipulated emotion regulation strategies?

3.5.1.4 Study 2b (Chapter 8): Post-trauma emotion regulation and VR re-exposure

Q1: What influence do reappraisal and behavioural suppression strategies have on the habituation of physiological and emotional responses to analogue VRET?

Q2: Are experimental manipulations of reappraisal and suppression associated with differential changes in psychological and emotional responding to analogue VRET when the effects of trait emotion regulation styles (reappraisal and suppression) are controlled for?

Q3. Does analogue VRET show significant reductions in emotional and physiological response profiles compared to initial trauma responses?

Q4. Do individual differences predict the course of psychological and emotional responding, from initial VR trauma exposure to VRET habituation?

4 MEASURES AND METHODS

As the proceeding 4 empirical chapters (Chapters 5-8) are the product of two large scale analogue laboratory VR-trauma studies, this chapter will form an outline of the measures used across both studies and a description of the methodology (participants, procedure and data pre-processing). This will allow for contextualisation of the 4 empirical chapters within the larger structure of the 2 experimental designs in which they were carried out, as well as preventing duplication of content across empirical chapters. Within the methods sections of the empirical chapters a brief summary of the chapter specific procedure will be given, however the reader will predominantly be referred back to relevant sections within this overarching methods chapter.

4.1 MEASURES

A number of the measures and apparatus used within this thesis were common to both studies. As such, before describing the specific methodology of each of the two VR-trauma analogue studies, the preceding section will outline all the measures and apparatus which were used across both studies. Chapter numbers in parenthesis at the end of each measure will be used to indicate which empirical chapter/s the measure is applicable to.

4.1.1 Psychometrics

4.1.1.1 Screening questionnaires

4.1.1.1.1 EEG and VR screening questionnaire (Chapters 5, 6, 7 & 8) Appendix 2

Variables which excluded participation based on alterations in EEG signals or any risks to a participant's physical or mental health that could occur as a result of exposure to a laboratory stressor (VR-trauma) were assessed via a specifically designed EEG and VR screening questionnaire. This included handedness, age, physical and mental health problems and fluency in English.

4.1.1.1.2 Mini international neuropsychiatric interview (MINI) (Chapters 5 & 6)

The mini international neuropsychiatric interview (MINI) is a clinician administered diagnostic assessment for the major DSM-IV Axis 1 disorders. An advantage of the MINI is that it can be completed in a shorter amount of time (median 15 minutes) than the SCID-P DSM-III-R assessment instrument (Sheehan et al, 1997).The MINI is divided into modules by disorder allowing for selection of relevant sections; all modules were covered in this study however

individuals who scored positive from current PTSD or depression in the telephone screening were excluded. The MINI has been found to have high reliability across testing sessions and raters for both PTSD (κ=.73 and κ=.95 respectively) and depression (κ=.87 and κ =1.00 respectively), as well as illustrating consistency with SCID diagnosis for PTSD (κ=.78) and depression (κ=.84) (Sheehan et al, 1998). Within this experiment the remaining sections of the MINI version 5.0.0 were used as a measure of possible Axis 1 disorders, rather than as a clear diagnostic tool; as the researcher was not clinically qualified to make a categorical diagnostic judgement, and this level of diagnostic specificity was not required.

4.1.1.1.3 Beck depression inventory (BDI-II) (Chapters 5 & 6)

A commonly used measure of depressive symptoms is the Beck depression inventory (BDI-II). The BDI is a 21 item questionnaire, initially developed by Beck in 1961 and revised by Beck, Steer, Ball & Ranieri in 1996. Cut off scores for different levels of depression are as follows: 14-19 indicating mild depression, 20-28 moderate depression and 29-63 severe depression. The BDI-II requires evaluation of feeling and behaviours experienced within the last two weeks and has been shown to be a reliable measure of current depression in both a psychiatric outpatient sample (α=.91; Beck et al., 1996) and within student populations (α=.90; Storch, Roberti & Roth, 2004). The validity of the BDI-II has also been confirmed within student populations, with high correlations between the BDI-II and the depression section from the Structured Clinical Interview for DSM-IV disorders (r=.83; Sprinkle et al., 2002). Within the current experiment participants with current depression were excluded using the MINI, and as such this questionnaire only tested individual differences in non-clinical levels of depression.

4.1.1.1.4 Patient health questionnaire (PHQ9) (Chapters 7 & 8)

The patient health questionnaire (PHQ-9) is a standardised questionnaire often used to assess depressive symptoms in primary mental health settings. The PHQ-9 has excellent reliability (internal α=.89; test re-test α=.84) and is a valid measure for discriminating depression, with ROC analysis showing the area under the curve for diagnosing depression in PHQ-9 being 0.95 (Kroenke, Spitzer & Williams, 2001). Questions are scored from “0” (not at all) to “3” (nearly every day), with higher total scores indicating increased current depressive state. Although it is not a diagnostic tool, standardised cut-off scores can be used to conclude a tentative diagnosis. Individuals with score $\geq$ 10 have been shown to have a depression diagnosis with 88% sensitivity and 88% specificity (Kroenke et al, 2001). For use as an assessment tool a score $\geq$ 2 on either question one (little interest of pleasure in doing things) or question two (feeling

down, depressed, or hopeless) must also be present to make a tentative depression diagnosis. Within the current experiment the assessment tool diagnostic cut off from the PHQ-9 was used as a screening tool for study exclusion.

4.1.1.1.5 Primary care screening for PTSD (PC-PTSD) (Chapters 7 & 8)

The primary care screening for PTSD (PC-PTSD) is 4 item standardised questionnaire, assessing possible PTSD diagnosis (Prins et al, 2003). The advantage of this questionnaire is that is it extremely fast to complete and can be filled out by self-report, with simple "yes" "no" answers. Each of the 4 questions taps into a different criterion (re-experiencing, avoidance, hyper-vigilance and numbing) of the DSM-IV diagnosis and as such questions relate to experiences in the "past month". The PC-PTSD has been validated in patient samples showing good reliability (Prins et al, 2003; Bliese, Wright, Alder, Cabrera, Castro & Hodge, 2008); a cut-off score of $\geq$ 3 has been found to be adequately categorise PTSD diagnosis with a 78% sensitivity and 87% specificity and compares well to longer diagnostic tools such as the PCL (Prins et al, 2004) and general health questionnaire-12 (GHQ-12) (Ouimette, Wade, Prins & Schohn, 2008). Within the current experiment the PC-PTSD was used as an online self-report measure to screen individuals for exclusion from the study if they endorsed a current PTSD diagnosis on this questionnaire. Participants only filled out this questionnaire if they reported having experienced one or more traumatic events in their lifetime on the CAPS trauma checklist (section 4.1.1.3.2); if more than one traumatic event had been experienced participants were required to fill out these questions in relation to the event that troubled them most currently.

4.1.1.2 Trait questionnaires

4.1.1.2.1 Anxiety sensitivity index (ASI) (Chapters 5, 6, 7 & 8)

The anxiety sensitivity index (ASI) (Reiss, Paterson, Gurksy, McNally, 1986), is a reliable and validated measure of an individual's emotional and cognitive evaluations in relation to the physiological symptoms which accompany stress and anxiety. Increased scores indicate an increased propensity to assign a negative evaluation and catastrophise in reaction to autonomic arousal, for example coming to the conclusion that experiencing an increased heart rate in relation to a stressor means that you are having a heart attack. High scores have been found in individuals suffering from a number of anxiety disorders (Reiss et al, 1986; Schmidt, Lerew & Jackson, 1999; Fedroff et al., 2000). Within this thesis the ASI was used as a pre-trauma trait variable to assess its predictive association with PTSD-like profiles following

trauma exposure. As ASI scores have shown high test re-test reliability (r=.75) in previous studies (Reiss, Paterson, Gurksy, McNally, 1986), in the initial study within this thesis ASI scores were assessed at the end of the experimental session to reduce possible fatigue effects during computer tasks if participants were required to fill out trait questionnaires at the start of the session. However within study 2, to assure that study one ASI scores could not have been influenced by the fact that they were collected following VR-trauma exposure, ASI scores were measured before (online) and after the experimental session (end of laboratory session), to test for retest reliability following VR-trauma exposure, and as such check the validity of ASI as true trait measure. In line with previously published findings the ASI scores did not significantly differ from pre (M=32.83) to post (M=32.13) experimental session ($t(53)=.79$, $p=.43$), with high internal consistency present across both measurements ($\alpha=.83$) and high test re-test reliability ($r(52)=.71$, $p<.001$).

4.1.1.2.2 State trait anxiety Inventory (STAI) (Chapters 5, 6, 7 & 8)

The state trait anxiety inventory (STAI) was designed by Laux, Glanzmann, Schaffner and Spielberger in 1981. This standardised inventory consists of two sub-versions measuring anxiety, both made up of 16 items; the first assessing state anxiety (see section 4.1.1.5.1) and the second trait anxiety. The trait version (STAI-T) is a measure of an individual's dispositional propensity to feel or express anxiety (i.e how they generally feel or respond) and as such remains relatively stable over time (r=.88), with good internal consistency ($\alpha>.89$) (Gros, Antony, Simms, & McCabe, 2007). Within the current thesis STAI-T scores were measured as a trait anxiety factor to assess predictive relationships with PTSD-like profiles following VR-trauma exposure.

4.1.1.2.3 Harm avoidance (HA) (Chapters 5, 6, 7 & 8)

The Harm avoidance (HA) scale is a sub-scale from the Tridimensional personality questionnaire (TPQ) (Cloninger, 1987), it is made up of 26 self-report items which tap a personality trait associated with worrying, pessimism, shyness/ fearfulness and fatigue. Questions include "It might be fun learning to walk the tightrope" and "I would enjoy learning to handle poisonous snakes" and responses are marked as either "true" or "false" or two alternate options are given and the individual must choose the one that best describes them. Some items are reversed and as such are reverse scored before collating the total score. The HA sub-scale of the TPQ has been shown to be reliable within normative and student samples (internal consistency ($\alpha=.87$) Otter, Huber & Bonner, 1995; test re-test ($\alpha=.85$) Sher, 1995).

Within the current experiment HA was measured as a pre-trauma trait factor to assess predictive relationships with PTSD-like profiles following VR-trauma exposure.

4.1.1.2.4 Emotion regulation questionnaire (ERQ) (Chapters 7 & 8)

The emotion regulation questionnaire (ERQ) was designed by Gross & John (2003) to assess suppression and reappraisal emotion regulation strategies in a 10 item questionnaire, with the first 6 items tapping reappraisal (e.g. "When I want to feel more positive emotion, I change the way I'm thinking about the situation") and 4 items tapping suppression (e.g. "When I am feeling emotions, I make sure not to express them"). Both the sub-scales of the ERQ have shown reliability across a 3 month testing period (both α=.69) and good internal consistency (reappraisal α=.79, suppression α=.73); reappraisal items have been positively associated with well-being, whilst the suppression items have shown negative associations with well-being (Gross & John, 2003). Within the current experiment both sub-scales of the ERQ were measured as a pre-trauma trait factor to assess predictive relationships with PTSD-like profiles following VR-trauma exposure and their influence on the effectiveness of emotion regulation manipulations.

4.1.1.3 Life events questionnaires

4.1.1.3.1 Traumatic life events checklist (Chapters 5 & 6): Appendix 3

A 9 item traumatic life event checklist was designed to cover a range of traumatic events, such as *'Have you ever been in any situation in which you feared you might be killed or seriously injured?'*. Within the current experiment prior traumatic life events were measured as a pre-trauma factor to assess their predictive relationships with PTSD-like profiles following VR-trauma exposure.

4.1.1.3.2 Traumatic events checklist- from the clinician administered PTSD scale (CAPS) (Chapters 7 & 8)

The Clinician administered PTSD scale (CAPS) is a structured interview used by clinicians' as a diagnostic tool to assess PTSD. As a pre-screening for the CAPS a traumatic event checklist is carried out to determine the extent of traumatic events experienced by a patient and to allow the clinician to make a judgement about which traumatic event will become the focus of the rest of the PTSD diagnostic interview. The events checklist consists of a list of 17 events (e.g. Fire or explosion,) and requires individuals to indicate whether each event has "happened to them" "witnessed", "learnt about", "does not apply", or "not sure". Within the current study

this measure assessed the number and nature of traumatic events experienced by participants, this score was used as a predictor variable to assess relationships between traumatic events and PTSD-like profiles following VR-trauma exposure. However, in addition, if participants endorsed one or more items then the online questionnaire asked them to fill out the PCL-PTSD questionnaire to assess current PTSD diagnosis (see section 4.1.1.1.5).

4.1.1.3.3 Social Readjustment Rating Scale (SRRS) (Chapters 5, 6, 7 & 8)

The social readjustment rating scale (SRRS) was developed by Holmes and Rahe in 1967. The SRRS is a measure of normal (i.e. non-traumatic) stressful life events which have occurred in the last year or in the individuals' lifetime. Events are both positive and negative in nature and have been assigned different corresponding 'stress units', these units were allocated based upon a large scale initial study carried out in America in which 394 individuals independently rated the stress they would associate with 43 different events (Holmes & Rahe, 1967). A child and adolescent version has subsequently been produced, although this version is yet to be tested for reliability and validity. The adult version of this measure has been validated, as a useful measure of stress instilled by everyday events (Holmes & Rahe, 1976; Scully, Tosi & Banning, 2000) and stress weightings have shown temporal reliability (with *r* ranging from .59 to .83), especially in healthy controls (Gerst, Grant, Yager & Sweetwood, 1978), however the test-retest reliability for item endorsement is suspected to be low, in accordance with recollection accuracy being an issue in retrospective reporting, especially when reporting lifetime occurrence of events (Turner & Wheaton, 1995).

In study one the child and adolescent version of the SRRSSRRS was used as the majority of participants had only just reached adult hood, unfortunately a disadvantage of the child version was that there are no published reliability or validity statistics. It was therefore decided that in this second study the adult version of the SRRS would be used for key analysis, whilst the child version would also be completed to explore the consistency across the two SRSS measures; forming a tentative check of the reliability of study one child SRRS data. The two SRRS measure showed moderate internal consistency across their total scores (α=.67) and moderate test re-test reliability ($r(120)=.51$, $p<.001$). Although both SRRS values were positively skewed, transformations only successfully normalised adult SRRS scores.

4.1.1.4 State questionnaires

4.1.1.4.1 State trait anxiety Inventory (STAI) (Chapters 5, 6, 7 & 8)

The second sub-version of the STAI questionnaire outlined in section 4.1.1.2.2 can be used as a measure of state changes in anxiety. The state version (STAI-S) is concerned with transient feelings of anxiety which are apparent at the time of assessment and may change over time; this version can therefore be used to assess changes in anxiety which occur in response to external situations. Within the current experiment the STAI-S was assessed pre- and post-VR viewing and change scores were computed to represent VR-induced anxiety.

4.1.1.4.2 VR Self-assessment (mood) manikin (SAM) (Chapters 5 & 6): Appendix 4

Lang (1980) developed a series of visual manikins as a self-assessment tool to aid in the visual distinction between different internal states (pleasure, arousal and dominance). SAM manikins have been found to be a highly effective and efficient tool for the assessment in emotional responding (Bradley & Lang, 1994), showing reliability and validity (e.g Hodes, Cook & Lang, 1985; Lang, 1980). The SAM-mood manikins used in this study included the arousal SAM, which depict 5 figures progressing from wide eyed and explosive to closed eyed and relaxed, and a dominance SAM, illustrating 5 figures progressing in size from very small inside the box it is within to very large and overfilling the box it is within, all SAM assessments are scored along a continuous 9 point scale.

4.1.1.4.3 Visual analogue (VAS) mood scale (Chapters 5, 6, 7 & 8): Appendix 5

A series of visual analogue scales (VAS) were designed to assess state mood. Participants were asked to put a cross at any position along the line to indicate to what extent they felt a list of emotions , with 0 at one extreme indicating ‘not at all’ and 10 at the other extreme indicating ‘extremely’. Although VAS scales have been shown to be comparable in terms of distributions of responses (Couper, Tourangeau & Conrad, 2006), it was felt that the use of VAS scales would reduce the chance of individuals remembering what value they endorsed pre-task (if a numbered scale had been used), and this influencing their post-task scores. Mood induction as a consequence of VR viewing was sub-divided into low mood and anxiety scores. Mood was measured pre and post VR on a visual analogue scale of current agreement with individual mood states, with 0 indicating “not at all” and 10 “extremely”; scores were taken to the nearest one decimal place. Anxiety was assessed on a single item, whilst low mood was calculated as the sum of sadness, depression, hopelessness and happiness (reverse scored). Change scores were calculated by computing the post minus pre value.

4.1.1.4.4 Peri-trauma dissociation measure (Chapters 5, 6, 7 & 8): Appendix 6

A number of items were measured to explore the experience of dissociation during the VR viewing, however it was felt that some of these items better tapped the believability of the VR software itself and the subsequent lack of emotionality induced by the VR medium itself (e.g. "how distracted were you by non-related activities (e.g. other people, equipment)?", "did you feel emotionally numb during the scenario?"); rather than dissociation in its form as described within patient trauma literature. Principal axis factoring, with oblimin rotation, was carried out to allow for a better separation of items which related to the experience of dissociation during the VR trauma film. The scree plots of both studies data indicated a cut off of three factors. The main factor which emerged in study one, related to emotionality induced by the VR, however as mood change was more effectively measured by the former change scores, this factor was not considered for inclusion in the dissociation scale. Comparable factors emerged across the two studies, tapping items relating to dissociation and immersion in the VR scenario (factors 2 and 3 in study one, and factors 1 and 2 in study two, see appendix 7 table A7.1). As both relevant factors included items relating to dissociation, items with loadings >.5 on either factor, across both studies, were summed to create a single dissociation factor (made up of: reduced attention paid to the VR, watching VR from third person perspective, not at all engaged in VR scenario, VR did not at all simulate how you might feel in the real world, senses not at all involved by the VR, having moments where you blanked out, spaced out, or in some other way felt that you were not part of the experience).

4.1.1.5 Memory questionnaires

4.1.1.5.1 VR-trauma free recall (Chapter 6): Appendix 8

A free recall test was used in order to measure the accuracy of the participants' memory for the VR-trauma scenario. Participants were asked to write down as much detail as they could remember about the entire scenario from beginning to end in the correct order, there was no time limit imposed upon this recall task so that individuals could write down all that they remembered.

4.1.1.5.2 Multiple choice cued VR-trauma recall questionnaire (Chapter 6): Appendix 9

A study specific multiple choice memory test was designed to assess participants cued recall accuracy for a mixture of items that were seen or heard throughout the course of the VR-scenario. These questions related to both specific details which were observed at a particular time point in the scenario, such as *'At the end of the second street there was: a) a mosque, b)*

an oil tanker, c) a trailer with bombs in it, d) a burnt out bus', and to the number of times a specific event occurred, such as '*During the entire scenario how many individuals ran in front of your truck: a) one, b) two, c) three, d) four*'. The number of incorrect items was totalled and used as a measure of cued recall inaccuracy.

4.1.1.5.3 Thought suppression questionnaire (Chapter 6): Appendix 10

This questionnaire was custom designed to gather information about the nature (verbal or visual) and distress level (as a percentage) caused by intrusive memories during the thought suppression task.

4.1.2 Genotyping (Chapter 5 & 6)

DNA sampling was collected and isolated using Oragene® DNA self collection kit and protocol (DNA, Genotek, Ottawa, Canada). DNA samples were sent to the University of Wurzberg for extraction of geneotypic information by the laboratory of Professor Andreas Reif. Genotypes were determined for 5-HTTLPR, BDNF, NPS, D2 Taq1, ADRA2B and A2A 1976, using the standard polymerase chain reaction (PCR) procedures.

For the regulatory promoter region of the serotonin transporter gene (5-HTTLPR), all base pair polymorphisms including the A/G SNP, were genotyped. Due to the small sample size, functional genotype groups were created by grouping together functionally equivalent alleles. 5-HTTLPR S and/or L_G allele carriers were grouped together ('S group') for statistical analysis, due to their equivalent expression profiles (Hu et al., 2005,2006; Wendland et al., 2006) and compared with an L_A homozygotes ('L group'). Genotypic information was unable to be extracted for two participants on the 5-HTTLPR polymorphism.

For the analysis of BDNF polymorphisms, carriers of the A allele were grouped together and compared to G homozygotes. Genotypic information from one participant was unable to be extracted for the BDNF polymorphism. NPS T allele carriers were grouped and compared to A homozygote carriers.D2 TAQ 1A T allele carriers were grouped together and compared to homozygote C carriers.ADRA2B S allele carriers were grouped and compared to l allele homozygote carriers.

4.1.3 Psychophysiological Responses

4.1.3.1 Electroencephalogram (EEG)

Electroencephelography (EEG) allows for the recording of the electrical potentials (action potentials) of brain neurons close to the brain surface via placement of electrical sensors across the scalp and forehead, with a high temporal resolution (Tortora & Derrickson, 2006). When EEG is recorded in response to a number of comparable stimulus types (ideally $\geq$30 stimuli of any given type), time-locked epochs of encephalographic responses, can be extracted around each stimulus (e.g. 200ms prior to stimulus until 800ms post stimulus) and averaged across stimulus type. This time and stimulus locked averaging of EEG data creates an event related potential (ERP). The measurement and analysis of ERPs is a valuable tool for exploring transient mental states. EPRs are labelled according to their polarity (positive or negative) and the post-stimulus time in ms at which they occur (e.g. a positive peak at 400ms will be known as P400). Based on a plethora of research studies, specific ERP components have different known functional properties in terms of their cognitive and emotional information processing functions, which vary according to the stimulus characteristics (such as valence, salience, volume and length). Furthermore specific sets of ERPs are known to occur together in relation to different stimulus types (such as pictures, sounds or faces). Alterations in the amplitude and latency of different ERP components across groups and/or stimulus characteristics can be used to deduce respective changes in information processing.

Within this thesis EEG data was acquired using 64 active Ag/AgCl electrode embedded in a cap (ActiCap, Brain Products, Munich, Germany), connected to EEG amplifiers (Brain Amp, Brain Products, Munich, Germany), and recorded via a computer running Brain Vision Recorder software (Brain Products, Munich, Germany). The EEG was continuously sampled at 500 Hz with a bandpass of 0.016-100 Hz. Electrode recording impedances were held beneath 10kΩ. All EEG channels were recorded against a Vertex reference (Cz) and converted off-line to an average ear lobe reference, with the ground at AFz. There were 62 recording electrodes on the scalp in a 10-10 configuration and two on the earlobes. See section 4.2.1.3.2 for EEG data cleaning and pre-processing steps.

4.1.3.2 Autonomic nervous system and the defence reaction

The autonomic nervous system consists of two sub divisions, the sympathetic and parasympathetic nervous systems, which are regulated by higher order brain regions and the input of emotional and sensory information. The majority of visceral organs receive projections from both the sympathetic and parasympathetic nervous systems including a number of different organs such as the eye, gut, salivary glands, lungs and heart; however in most cases the operation of the two systems upon these organs is opposing, allowing for a shift in

activation or deactivation depending upon current external factors and the optimum internal requirements. Examples of the antagonistic relationship between innervations by the two systems include a sympathetic increase vs. parasympathetic decrease in heart rate, sympathetic vasoconstriction vs. parasympathetic vasodilatation of salivary glands and sympathetic decreases vs. parasympathetic increases in gut motility. However, sympathetic projections specifically innervate the sweat glands, pupil dilation and skin hair muscles, while independent parasympathetic projections innervate the pupil constriction and focusing of the eyes. When danger is perceived the hypothalamus activates the reflex defence reaction (also known as the 'fight or flight response') of the autonomic nervous system, in which the sympathetic vasoconstrictor tone is inhibited, overriding normal control and resulting in pupil dilation, skin hairs standing on end, and increases in blood pressure, heart rate, cardiac output, blood flow towards the muscles.

Within this thesis autonomic nervous system measures described below (SC,HR,EMG) were recorded using a BIOPAC™ MP150 system connected to a computer running a commercially available software AcqKnowledge 4.1 (BIOPAC Systems; Goleta, CA), with acquisition sampling rate of 2000Hz. These data were filtered and corrected offline using specialised analysis programmes within the AcqKnowledge 4.1 software; as described in the respective sections below.

4.1.3.2.1 Electrodermal activity (Skin conductance (SC))

There are two main types of sweat gland, eccrine and apocrine, the former predominantly regulating body temperature and having a small role in removing waste products from the body, and the latter stimulated by emotional stress and sexual excitement. Eccrine sweat glands are located throughout the entire body, but a large number reside on the palms, forehead and soles of the feet. Apocrine sweat glands are predominantly found within the groin, armpit and breasts (Tortora & Derrickson, 2006, pp.155). Activation of the sympathetic nervous system results in increases in localised sweat secretion in areas such as the palms of the hands; this is known as "adrenergic sweating" (Ganong, 2005, pp.228-229).

Within this thesis SC was recorded from bipolar Ag/AgCl reusable strap electrodes on the medial phalanx of the *middle and ring finger of the left hand (all participants were right handed), at a sampling rate of 125Hz*.The measurement of SC acted as the ground for the ECG and EMG electrode measurements. No filters were run on SC data; however the data was manually screened for recording or movement artefacts, of which none were found within data portions of interest.

4.1.3.2.2 Electrocardiogram (ECG)

The electrocardiogram allows for the measurement of the electrical activity of the heart. Action potentials within the sinoatrial (SA) node of the heart initiate the excitation of the entire myocardium and drive the heart, via small currents created within the extracellular fluid. It is these small electrical differences in current which are measured using the ECG. At rest (i.e without the additional input of the nervous system) the automatic excitation by the SA will drive the heart at a rate of 100 beats per minute (bmp); however extrinsic nervous system inputs can cause both increases and decreases in the activation of the heart. ECG recordings are achieved using electrodes which are externally placed on the skin and measure the voltage difference between these electrodes using an amplifier or are internally placed on the cardic muscle itself (though this is only done during surgical procedures in which the heart is exposed). Electrode leads can be bipolar, measuring the difference between two active sites, or unipolar, measuring the difference between one active site and an earth electrode, which is maintained at a zero voltage. There are a number of commonly used electrode placements across the limbs and the chest. The component waves of the ECG represent the depolarisation of different areas of the heart and the depolarisation and repolarisation of the ventricles, the largest component is the R wave which appears as a positive deflection in the middle of the QRS complex (figure 4.1), due to the size of this component and the subsequent ease of detection, this wave is used to calculate the distance between the hearts contractions to create a measure of beats per minute (Pocock & Richards, 2006, pp. 262-273).

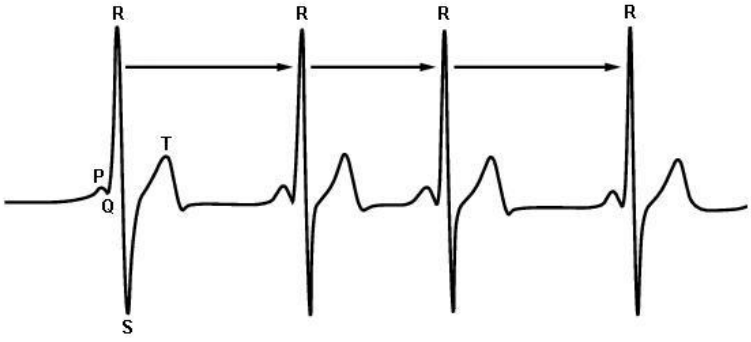


Figure 4.1: An example of an electrocardiogram (ECG) recording. Depicting the QRS complex and the determination of BPM as a measure of the distance between R waves.

Within this thesis bipolar stress test ECG electrodes where placed on the right coracoid process and the left of the xiphiod process and signals were recorded using shielded pinch leads. ECG data was recorded at a sampling rate of 250Hz and band-pass filtered offline from 0.5Hz-35Hz,

with 2000 coefficients. Offline data was peak corrected using a visually representative waveform as a template, and passed through a Peak detection algorithm to calculate QRS peaks. Visual inspection of the QRS peaks was carried out, channel offsets (caused by the peak correction) were corrected and missed beats were inserted by eye or using interpolation methods; interpolation of noisy beats was carried out on <5% of the QRS peaks within the analysis window of any file, if >5% of the QRS peaks were undetectable the respective data was marked as missing. The R wave (QRS peak), a large positive deflection of the QRS complex, was then used to create a HR channel in beats per minute (BPM), from which all further HR calculations were taken.

4.1.3.2.3 Electromyography (EMG)

Activation (i.e. contraction) of the skeletal muscle fibres is controlled by the production of muscle action potentials, resulting from nerve action potentials. Skeletal muscle action potentials are elicited by the action of voluntary control mechanisms which elicit chemical signals in the body such as neurotransmitters, hormones or local pH level changes (Tortora & Derrickson, 2006). A motor neuron can have a number of projections to different muscle fibres, which are activated via muscle action potentials; each neuron and its innervating fibres is known as a single motor unit. As mentioned earlier, the activation of muscle fibres occurs through voluntary effort. The higher the level of effort, the larger the number of motor units activated and the number of elicited action potentials, hence the greater the subsequent muscle contraction (Ganong, 2005). The time course of a single action potential is in the range of a few milliseconds, whereas the duration of the resultant muscle contraction and relaxation can be between 40-100ms (Pocock & Richards, 2006).

However not all muscle contractions are under voluntary control. The startle response is a fast activation of facial and bodily muscles which is elicited towards a range of acoustic, tactile and visual stimuli (Landis & Hunt, 1939). Startle responses have a more reflex like quality; although they have been shown to be modulated by internal and external factors, such as affect (for review see Grillon & Baas, 2003).Acoustic startle stimuli are the most common form of startle elicitation used within experimental studies, with sounds >80dB eliciting startle associated eye lid closure which can be measured from the obicularic occuli muscles below the eye. The pathways mediating the acoustic startle response include a number of neural processes, with research consistently illustrating the role of the caudal pontine reticular nucleus (for example Carlson & Willott, 1998; Koch et al., 1992), which has projections to the spinal cord, and cranial and facial nuclei (Martin et al., 1990).

It is possible to measure the activation of muscle tissue using electromyography (EMG), which records the electrical signals of multiple muscle action potentials, produced by numerous motor units. Intramuscular EMG recording require the insertion of a needle electrode into the individuals muscle, allowing for the recording of the activation for a single muscle fibre (Ganong, 2005). However, most commonly a pair of electrodes is placed externally on the skin over the muscle of interest and a differential detection technique is used, in which the signal at each site is subtracted from the signal at the paired sight, creating an amplified differential signal. Distant signals (such as electronic or ambient noise and motion artifacts) appear as common signals and will be removed, and local signals (such as EMG muscle activation) will be retained and amplified.

Within this thesis the startle reflex was measured using pairs of 0.5cm reusable bilateral orbicularis oculi EMG electrode placements (i.e. below the lower eye lids) with a sampling rate of 2000Hz. Startle EMG data was only analysed from the left orbicularis oculi electrode; in accordance with the findings of Morgan, Grillon, Lubin & Southwick (1997) that the startle response is greater in the left eye. Data was band-pass filtered offline from 28Hz-500Hz (the optimum bandwidth recommendations from van Boxtel, Borlhouwer and Bos, (1998)) and smoothed via a root mean square calculation with a 10ms time constant. Data was visually inspected and artifactual data was marked as missing. Trials were rejected if the peak occurred within the first 20ms following startle onset and the non response criterion was set as <0.1uV (untransformed); non response trials were set to 0 and included in the analysis, thus producing a measurement of reflex startle magnitude.

4.1.4 Computerised tasks

4.1.4.1 Virtual reality ('Iraq world') (Chapter 5, 6, 7 & 8)

The traditional analogue laboratory design for the investigation of risk factors in PTSD development is the trauma-film paradigm, which allows for longitudinal investigation of pre-, peri- and post-traumatic the risk factors (see Holmes & Bourne, 2008 for a review). Within such laboratory studies a film is shown to a participant that involves an event in which there is depiction of actual or threatened death or serious injury to other individual, thus meeting the criteria for a traumatic event in accordance with the DSM-IV A2 criteria for PTSD (APA, 2000). Despite the promising research outcomes associated with this paradigm, trauma-film exposures do not allow for the event to be experienced from an immersive first person

perspective or for the traumatic event depicted to involve threat of death or serious injury to the *self.* Virtual reality (VR) environments have the advantage of increasing immersion and presence within presented scenarios (Baumgartner et al., 2008) and allow for film viewing from a first person perspective, which has been shown to results in differential neural activations compared to third person perspective taking (Vogeley et al., 2004). A number of studies have illustrated the effectiveness of VR-exposure therapy in the treatment of PTSD, which is posited to be a consequence of the ability of VR to assist in engagement with trauma memories, with positive outcomes in individuals who resisted traditional exposure thearpies (for a review see Goncalves et al., 2012). As such, VR seems a promising tool for use within laboratory trauma designs, increasing the ecological validity of the findings, particularly when peri-traumatic processes are of interest.

Within the current thesis, the virtual reality ('IraqWorld') environment which was used as a trauma-analogue was designed by Hoffman and Miyahira, with input from Garcia-Palacios, Folen, Hollander & Rose, using virtools software (www.virtools.com). Prior to viewing the virtual reality (VR) scenario ('Iraq world'), participants were read a scene setting script (appendix 11) requiring them to imagine that they are on a university research placement in Iraq, driving through the city's streets trying to find and rejoin a military convoy who were escorting them through the wore torn city and from which their vehicle became separated during a sandstorm. Participants were instructed to pay careful attention to the scenario. The VR scenario was viewed from a first person perspective through table mounted VR goggles, in an unlit and sound proofed laboratory (Figure 4.2). During the VR scenario the participants watch as a Jeep they appear to be driving through an Iraq wartime city. At the end of the scenario an unidentified explosive device is detonated next to their vehicle; their jeep stops and appears to be seriously damaged, they see blood on their windscreen and hear the screams of a distressed woman nearby. As such, the VR 'Iraq world' scenario depicts scenes and events that would constitute a traumatic event within the 'real world', as categorised within DSM-IV-TR (APA, 2000). In addition, this VR Iraq world is currently being used within the Cornell University medical department, as an exposure treatment for servicemen with Iraq related PTSD, with successful reductions in symptomology (Gaylord et al., 2009).

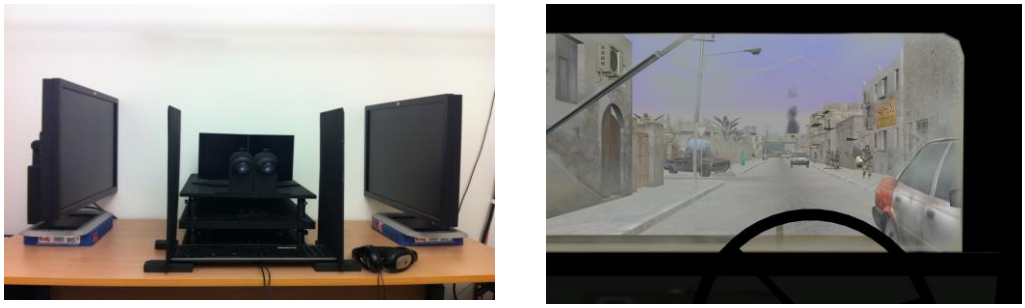


Figure 4.2: Virtual reality 'Iraq world'. Depiction of the table mounted VR viewing equipment and a screenshot from the 'Iraq World' VR scenario.

A pilot study was carried out to assess the impact of VR viewing on change in mood. Sixteen participants from the University of Exeter were recruited in return for course credits and were given visual analogue self-report mood measures immediately before and immediately after viewing the VR scenario, which was administered as described above. Pre-post measures showed that the VR caused a significant increase in sadness from pre (M=0.79, SD=1.06) to post (M=2.31, SD=2.26) (t(15)= -2.57, p= .021), depression from pre (M=0.84, SD=1.31) to post (M=2.08, SD=2.01) (t(15)= -2.14, p= .049), and anger from pre (M=0.58, SD=0.58) to post (M=1.83, SD=1.65)(t(15)= -3.47, p= .003),, and a significant reduction in happiness from pre (M=6.67, SD=1.19) to post (M=5.16, SD=2.11) (t(15)= 3.49, p= .003), and calmness from pre (M=6.21, SD=2.19) to post (M=4.57, SD=2.42) (t(15)= 2.34, p= .034),. There was a trend towards an increase in anxiety from pre (M=2.15, SD=2.06) to post (M=3.55, SD=2.97) VR viewing, although this difference failed to reach significance (t(14)= -1.54, p= .147); for this reason it was decided that a more sensitive measure of anxiety may be necessary, rather than simply requiring participants to rate how 'anxious' they are feeling on a visual analogue scale, as such the STAI state measure was included as a pre and post VR measure in all further experiments. The result of the pilot study provided preliminary proof of the efficacy of the VR Iraq world in inducing negative mood and reducing calmness. It was believed that within a larger sample change in self-reported anxiety would also become significant.

4.1.4.2 Neutral VR suburban city scenario (Chapter 7)

Although the neutral scenario (Figure 4.3) was presented through the VR equipment to increase immersion, the actual footage itself was a film rather than a computer generated scenario (as the trauma scenario was); however this scenario will be referred to as neutral VR

as it was presented through the same VR equipment. Prior to viewing the neutral scenario participants were read scene setting information (appendix 12) which told them to imagine that they were visiting a friend who had started a new university course near London and they had decided to visit them in the holidays and do some sightseeing around the town.

Figure 4.3: A depiction of the table mounted VR viewing equipment and a screenshot from the neutral suburban city scenario

4.1.4.3 Thought suppression task (Chapter 6)

Participants then completed a 3 minute thought suppression task, in order to assess rebound effects in the experience of intrusive memories. Psychophysiological measurements were recorded for the duration of this task. Participants sat at a computer and were instructed to 'try to not think about or picture any details relating to the VR Iraq scenario that you watched earlier and if any thought or picture relating to the VR Iraq scenario comes to mind, then every time this happens press the space bar on the key board'. The computer screen remained black for the duration of the thought suppression task; however E-prime computer software was used to register every time a participant pressed the space bar (i.e. had an intrusive VR-trauma related thought), allowing for later analysis of physiological responses time-locked at each key press (i.e. intrusion).

4.1.4.4 Startle paradigm: Counterbalanced block design (Chapter 5)

The acoustic startle habituation task was presented via a computer using E-prime software to control stimulus presentation. Startle stimuli consisted of 30 neutral and 30 traumatic 95dB (95dB sounds were selected following findings that this level of sound provides optimum startle response discrimination between PTSD patients and controls (Butler, Braff, Rausch, Jenkins, Sprock & Geyer, 1990)) 500ms tones which were presented bilaterally over sound attenuating headphones; neutral and trauma stimuli were presented in individual blocks,

counterbalanced across participants. Within each block the 30 startle tones were presented with randomised inter stimulus intervals of 18s to 32.5s, with a valence congruent foreground image (figure4.4); viewed through the VR table mounted goggle system so as to increase immersion. The trauma block consisted of a continuous background image of the VR scenario, with random acoustic presentation of a single gunshot (trauma startle tone). The neutral block consisted of a continuous background image of Exeter town centre, with random acoustic presentation of a single car horn (neutral startle tone). Picture congruent affective startle sounds were used within this paradigm following evidence that differentially valenced sounds modulate the physiological startle response in a similar manner to the effect shown when using white noise startle and modifying the valence of a background picture (Bradley & Lang, 2000); furthermore the use of real sounds increases the ecological validity of the paradigm. The sounds consisted of a 500ms car horn (neutral block) and a 500ms gunshot (trauma block).

Neutral foreground

Trauma foreground

Figure 4.4 Trauma and neutral pictures presented continuously during random startle sound presentation.

4.1.4.5 Startle paradigm: Randomised design (Chapter 7)

Participants were systematically allocated using a matched pairs, randomized block design to one of three groups: 'COPE' (Reappraise), 'SUPPRESS' or a 'VIEW' control group. Group allocations were matched according to gender and ASI scores (+/- 2) across each group, so as to ensure an equal split of males and females and levels of trait tendency to worry about the physiological concomitance of anxiety across the three groups. It was chosen to match groups on ASI rather than STAI-T scores, firstly due to the association between ASI and startle responses (and lack of STAI-T predictive relationships) found in Chapter 5, and secondly due to the physiologically arousing nature of the tasks which were to be carried out within this study.

Prior to the startle task participants were briefed by the experimenter, according to their group allocation, as to the general and group specific task instructions (appendix 13).

The startle task was presented in 4 blocks of 24 trials. 50% of the trials were neutral in nature and as such always received a VIEW' instruction, whilst 50% of the trials were traumatic in nature receiving a regulation instruction on half the trauma trials ('COPE'[6]/'SUPPRESS'/' VIEW') and a 'VIEW' instruction on the other half of the trauma trials. As such 50% of all trials were neutral (N), 25% trauma regulate (TR) and 25% trauma view (TV); having both TV and TR trials allowed for comparison of responses when regulating or not regulating emotions towards trauma stimuli, although this meant that for individuals in the control group both TV and TR trials were the same. Trials began with a rest period for 400ms in which the participants were shown the word "RELAX", during this period participants' were instructed to relax and get ready for the instruction. The instruction indicating the trial type ('COPE'/'SUPPRESS'/' VIEW') appeared for 2000ms and was followed by a fixation cross for 3000 or 400ms, randomly counterbalanced across the experiment. A trial congruent picture was presented (figure 4.5) and the correspondingly valenced startle sound was presented via headphones at a random delay of 450-5450ms post-picture-onset, randomly counterbalanced across the experiment. All foreground pictures were of a different part of the respective neutral or trauma scenario. The picture then remained on the screen for 5000ms post-startle onset- the critical period for electroencephalographic and psychophysiological measurements. The 96 picture stimuli consisted of a series of different still images of the stressor VR (48 pictures) and neutral VR (48 pictures) which had been viewed previously. Startle sounds which were presented concurrently were two 96dB 400ms valence specific sounds; a car horn (neutral trials) and a gunshot (trauma trials).

Neutral foreground

Trauma foreground

[6] The term COPE was presented on emotional acceptance based reappraisal trials as it was felt that this instruction would be clearer to participants and did not require reading such a long word as reappraise during the short instruction presentation phase.

Figure 4.5: Examples of the trauma and neutral foreground pictures presented during the startle task.

Participants were instructed to follow the trial specific task instruction for the entirety of the following picture presentation phase (with overlaid sound presentation) until they saw the 'RELAX' instruction for the next trial. The view (control) group received the 'VIEW' instruction for all trials; which consisted of responding to the pictures and sounds in any way that felt natural and not to try to alter their feelings or bodily responses in any way. As mentioned previously, participants in the two experimental groups received an instruction to use their emotion regulation strategy ('COPE'/'SUPPRESS') on 50% of the trauma VR trials and the 'VIEW' instruction on 50% of trauma VR trials and on all neutral trials. Stimulus presentation sampling was restricted so that the same stimulus type (trauma/neutral) and instruction pairing ('COPE'/'SUPPRESS'/'VIEW') could not appear more than three times sequentially, before a different trial type (stimulus valence and instruction combination) was sampled. The cope group were instructed that when the 'COPE' instruction preceded a stressor trial, they were to try to reappraise the way they viewed the picture and sound by normalising any negative emotions or reactions they experience and accepting the possibility of unwanted or unpleasant thoughts. Examples of the sorts of phrases which may assist this thought process were given such as "This feeling will pass." "I will get through this." "I am safe right now." "I have faced this situation and got through it", "I can cope". The behavioural suppression group were instructed that when the 'SUPPRESS' instruction preceded a stressor trial, they were to try to keep from showing any emotional reaction on their face or in their body.

Before the startle task began, a practice block of 12 trials was completed (without startle sounds played, in order to avoid habituation before the actual task). Participants were questioned on their task strategy following the practice block and any individuals who were not using the correct strategy for their group were given further explanations until it was clear to the experimenter that they understood the exact group instruction.

Between each trial block participants were asked to mark on a visual analogue scale their current mood, to assess any differences between groups in changes in mood across the task, as well as to write out the strategy they used for the last block as a second check for adequacy of understanding of group task instructions. Electroencephalographic potentials and psychophysiological measures were recorded during the startle response task, in order to monitor participant's autonomic responses and processing speeds.

4.2 METHODS: Participants, Procedure, Data pre-processing

4.2.1 Study one

4.2.1.1 Participants for Study 1

Eighty eight students from the University of Exeter, aged 18-32, expressed an interest in taking part in the study and were telephone-screened for eligibility. All participants underwent an initial screening interview (Mini International Neuropsychiatric Interview M.I.N.I) (Sheehan, et al., 2006), for current or past PTSD and current depression according to DSM-IV criteria. Candidates who meet the criterion for either mental health problem were excluded. Individuals currently taking psychopharmacological medication or with a history of brain surgery, epilepsy or prior exposure to a warzone were also excluded during the pre-screening as such factors could influence the data collected. Individuals with high blood pressure or a pacemaker were screened out due to the stress inducing nature of the VR-exposure and individuals with a skin condition affecting their scalp were excluded due to the potential for adverse skin reactions to the gel used for the set up and recording of EEG. Four students were excluded from the study as they did not meet the inclusion criteria, leaving a sample of 84 participants who took part in the laboratory study (52 females and 32 males). Participants were reimbursed for their time by a payment of £5 per hour or 1 course credit per hour (only psychology first year students could opt to received course credits, towards a compulsory research methods course module[7]). Participants were native English speakers, right handed, with normal or corrected to normal vision and hearing. Informed consent was obtained from all participants separately for the experimental study and the genetic sampling; although no individuals chose to opt out of the genetic sampling. The study received full ethical approval from the NHS South West Research Ethics Committee and the University of Exeter psychology ethics committee (appendix 14).

4.2.1.2 Procedure for Study 1(see Table 4.1)

A telephone pre-screening was carried out to assess EEG and VR exclusion criteria using the screening questionnaire and to assess current PTSD and depression using the trauma events checklist and Mini Mental State Examination (MINI); the presence of other psychiatric disorders, such as alcohol dependence, was not assessed during the pre-screening however they were assessed at the end of the laboratory session.

[7] Psychology students who were not eligible to take part in the laboratory study were given ½ a course credit for the time taken to complete the telephone screening.

All laboratory sessions began between the hours of 12:15 and 14:15, in order to retain consistency in the time of day of participation; with sessions lasting for 3 hours. Following informed consent participants filled out a demographic questionnaire assessing nicotine, caffeine, alcohol and drug intake as well as regularity of computer gaming, and completed initial mood ratings (STAI, visual analogue mood scale, SAM). Participants then watched the VR 'Iraq World' scenario, while psychophysiological measurements were recorded. A mood rating was taken following VR exposure, along with the VR peri-traumatic dissociation questionnaire.

A free recall test was administered 10 minutes after the VR-trauma, followed by a multiple choice cued recall test. Participants then completed a 3 minute VR-trauma thought suppression task, in order to assess intrusive memories and record psychophysiological responses towards intrusive VR-trauma memories. E-prime computer software was used for the recording of participant responses. As the final psychophysiological recording phase, participants completed an acoustic startle habituation task, presented via a computer using E-prime software to control stimulus presentation. At the end of the psychophysiological testing phase participants gave a saliva sample for genetic extraction. The experimenter then administered the final sections of the MINI which were not assessed during the telephone screening. Finally participants filled in a number of trait measures including ASI, HA, STAI_T, as well as the BDI and stressful life events questionnaires. As these measure assess trait styles and show strong test re-test reliability (see section 4.1.1.2) these questionnaires were carried out at the end of the 3 hour laboratory session in order to reduce fatigue effects within the experimental computer based sections of the study (i.e. VR, startle task, memory assessments).

Table 4.1: Study one variables. Summary of the risk and resilience factors pre- peri- and post-trauma and analogue symptom measures.

Pre-trauma	Peri-trauma	Phenotypic symptom Measures: 1. Startle response 2. Memory distortions
PERSONALITY: ▪ STAI-T ▪ ASI ▪ HA **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events **GENE POLYMORPHISMS:** ▪ 5HTTLPR ▪ BDNF ▪ D2 Taq1 ▪ NPS ▪ ADORA 2B **GENDER** *COVARIATES:* ▪ *Mini neuropsychiatric assessment (MINI)* ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)* ▪ *Drug use* ▪ *Computer gaming* ▪ *Beck depression inventory (BDI)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ SAM arousal difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**1. STARTLE (Neutral & Trauma trial types):** ❖ EEG ▪ PCA (P2 & P3 amplitude) ▪ Startle ERP onset latency ❖ EMG (make into t-score) ▪ Response magnitude ▪ Habituation ❖ HR ▪ Response amplitude ❖ SCR (range correct) ▪ Response magnitude ▪ Habituation **2. FREE RECALL:** ▪ Content inaccuracy ▪ Sequence ratio disorganisation **CUED RECALL:** ▪ Inaccuracy score (15 items) **INTRUSIONS (thought suppression):** ▪ Form ▪ Distress ▪ Frequency ▪ HR response ▪ SC response

4.2.1.3 Data pre-processing and reduction for genetic, electrophysiological (EEG, EMG,HR,SC) and free recall data in Study 1

4.2.1.3.1 Genetics

All genotype frequencies were within the Hardy-Weinberger Equilibrium (HWE): 5HTTLPR (x^2=1.00, df=1, p>0.05), BDNF (x^2=3.22, df=1, p>0.05), D2 Taq1 (x^2=0.06, df=1, p>0.05), NPS (x^2=0.00, df=1, p>0.05), ADORA 2B (x^2=0.69, df=1, p>0.05) (Rodriguez, Gaunt & Day, 2009). The HWE (Hardy, 1908) states that genetic distribution of allele frequencies will not vary across generations when random mating occurs, however due to evolutionary influences in populations will generally deviate from perfect HWE by small change amounts. As such a large deviation from the HWE is indicative of assays containing genotyping errors (i.e. laboratory error).

Composite allele risk groups were derived for each polymorphism by combining the homozygote and heterozygote risk allele carriers into a composite risk group. The risk group was then compared with remaining the homozygote carriers in further analysis (Table 4.2).

Table 4.2: Risk and resilience groupings of gene polymorphisms

Polymorphism	Risk allele Posited from literature	Combined risk group alleles		Homozygote Resilience alleles
5HTTLPR	s	s/s	s/l	l/l
BDNF	Met	Met/Met	Met/Val	Val/Val
D2Taq1	T	T/T	C/T	C/C
NPS	A & T	T/T	A/T	A/A
ADORA2B	s	s/s	s/l	l/l

4.2.1.3.2 EEG

EEG data was acquired as described in section 4.1.3 and further processed and analysed offline using Brain Vision Analyzer software (Brain Products, Munich, Germany).

EEG data were band-pass filtered offline from 1Hz-20Hz, and re-referenced to linked ears. Filtered data was then corrected for eye movements and EMG muscle tension and movement artifacts using manual artifact rejection and independent components analysis (ICA). ICA is a linear decomposition technique which allows for separation of artifacts from brain activity

patterns, by separating mixed signal sources with distinct patterns and topographies[8] (figure 4.6). Once ICA has separated statistically distinct signal components the experimenter can visually inspect the decompositions and make an informed decision about which constitute artefact signals, based on the respective signal composition and its topographical source (Viola, Debener, Thorne & Schnider, 2010). Signal components relating to ocular, muscle and other artifacts are then removed from the EEG, leaving the brain activation patterns. This artifact correction method allows for consistent removal of artifactual signals across the EEG and maximal data retention.

Following filtering and artifact correction the EEG was segmented into a 1000ms stimulus-locked (i.e. locked to startle sound onsets) epochs; consisting of a 200ms (-200 to 0ms) pre-stimulus baseline and a 800ms post-stimulus segment (beginning at startle sound onset). Segmented data was baseline corrected relative to the average during the 100ms prior to stimulus onset. Following baseline correction, and segments with errors or which still contained artifacts were discarded by means of visual inspection. The remaining EEG segments were averaged for every participant and experimental condition.

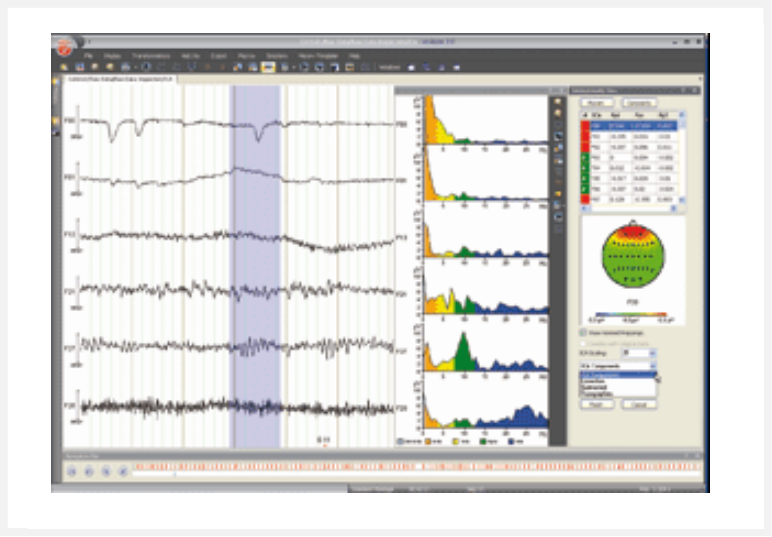


Figure 4.6: Example of independent components analysis (ICA); separating mixed signal sources and allowing for the removal of signal sources relating to ocular (as represented within the first component within the figure and the corresponding topographical map on the right), muscle and other artifacts.

[8] in a similar manner to the way factor analysis distinguishes latent variables or factors

4.2.1.3.2.1 Temporal Principal components analysis (PCA): Frequency domain

Data-driven temporal PCA (Donchin & Heffley, 1978; Weber & Lavric, 2008) ERP segmentation was carried out to identify temporally distinct components underlying the ERP waveform; in particular separation of the P2 and P3 waveforms was of interest. PCA is a data-driven procedure for determining more optimal and less biased distinction of temporal 'windows' within the ERP waveform; these distinct temporal components can then be subjected to statistical testing. ERP data from 0ms-800ms post-startle onset was extracted separately across subjects, electrodes and trial types. PCA was performed on the covariance matrix with time points (of which there where 400) as variables and subjects X electrodes X trial type as observations, using Varimax rotation with a component extraction criterion of eigenvalues ≥ 1. Factor loadings of the raw components which explained >1.5% of the total variance in the ERP response were plotted for inspection (see appendix 15, figure A15.1). Inspection of the factor loading plots showed two main components in the positive range whose time course was within the P2 and P3 time range of interest (figure 4.7). However it was apparent that that both the P2 and P3 component shared variance with an early negative component (N1), which occurred between 0-170ms post-startle onset; such N1-P2 and N1-P3 complexes have been previously documented in acoustic startle paradigms (Hirano, Russel, Ornitz & Liu, 1996; Cuthbert et al., 1998; Schupp et al., 1997, Amrhein et al., 2004). In order to separate the component scores of the components of interest (P2 & P3) from the negative component (N1) the PCA analysis was then re-ran on the ERP data re-extracted from 170ms-800ms. The topographical distribution of the 2 components within the P2 and P3 time-range within the 170-800ms PCA analysis was explored, illustrating a mid brain distribution over the posterior-frontal and parietal brain regions. This topographical distribution was confirmed for the same time windows within the grand average ERP, across both trial types, in the time domain (see figure 4.8). As such, across each participant and trial type, regions of interest were averaged for analysis of electrodes with a scalp topography over the frontal-posterior-mid region (FC1, FCz, FC2, C1, Cz, C2) and the parietal-mid region (CP1, CP2, P1, Pz, P2) (Figure 4.9) ; regional analysis with a focus on midline fontal-posterior and parietal electrodes is in line with previous startle literature (Hirano et al., 1996; Cuthbert et al., 1998; Schupp et al., 1997, Amrhein et al., 2004). Grouping of electrodes by hemispheric regions allows for a degree of anatomical validity and improves the signal-to-noise ratio by spatially smoothing.

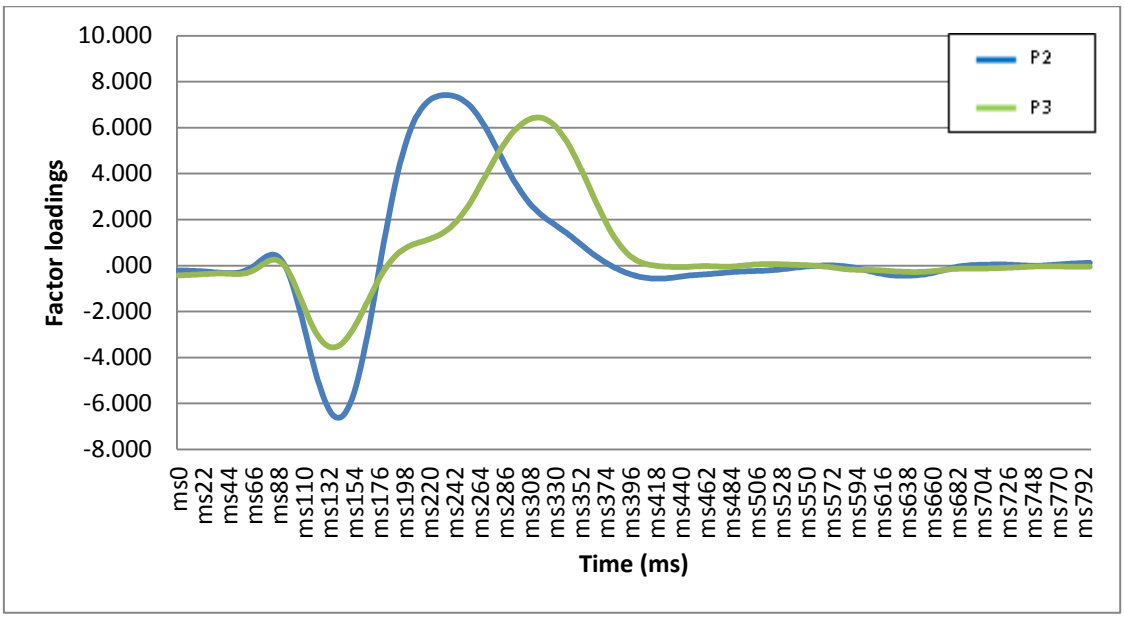


Figure 4.7: PCA analysis of startle ERP in study 1 in the frequency domain. Temporally independent components in the P2 and P3 time range, as derived from PCA analysis from 0-800ms across the startle ERP.

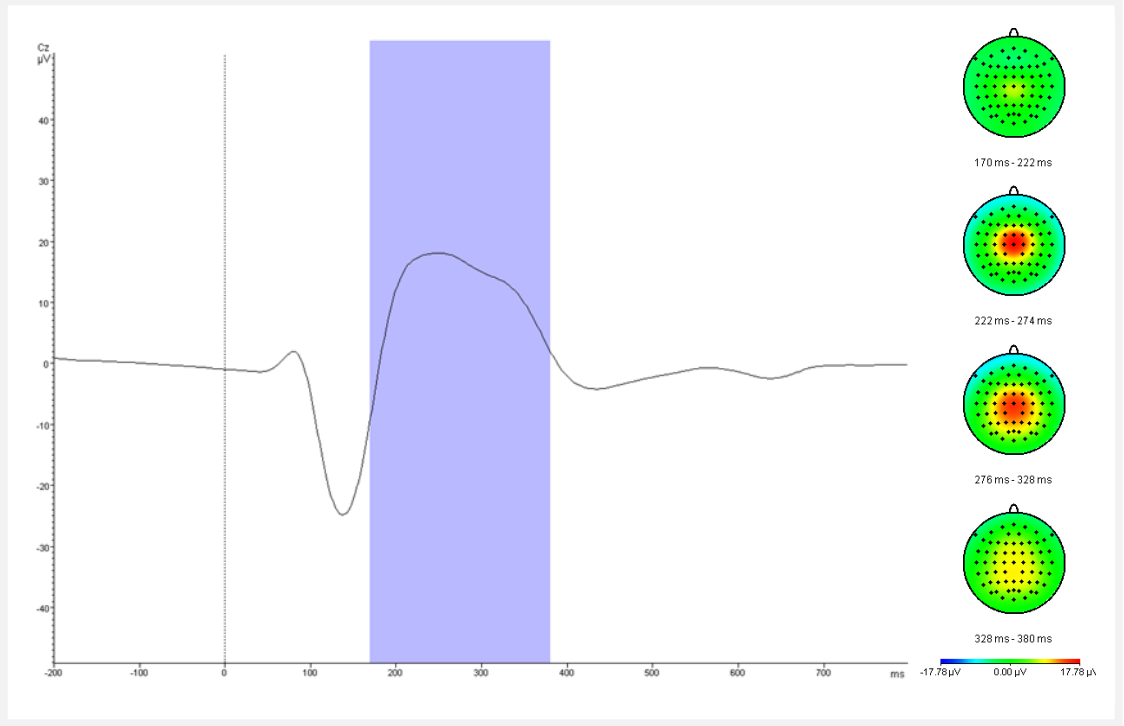


Figure 4.8: Grand average ERP startle response and topographies across the two time-windows of interest (P2 and P3 in the time domain).

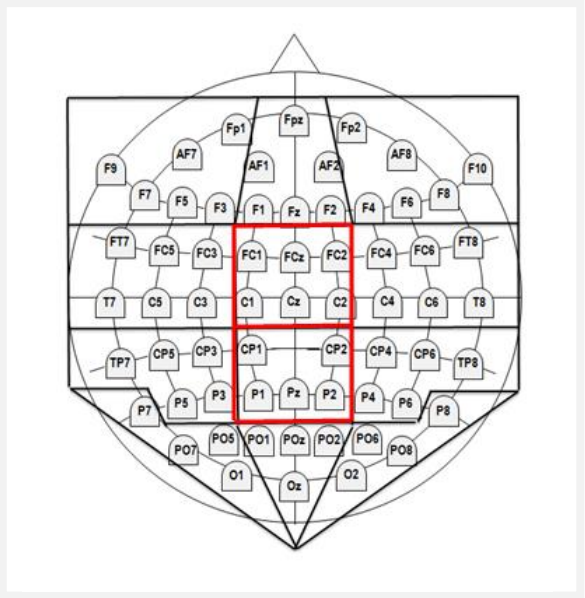


Figure 4.9: Topographical electrode groupings over the frontal-posterior-mid region (FC1, FCz, FC2, C1, Cz, C2) and parietal-mid region (CP1, CP2, P1, Pz, P2).

4.2.1.3.2.2 Startle ERP onset latency analysis: Time domain

In addition to analysis of individual differences in P2 and P3 amplitudes as obtained by the PCA procedure, this thesis was concerned with clarifying if individual differences were associated with change in the latency of brain processing responses towards startling sounds. However, as the P2 and P3 components could not be clearly defined within a number of subjects ERP responses, onset latency analysis was carried out across the whole startle ERP response to assess differences in latency of startle ERP responses in general. To determine startle ERP onset latencies the relative criterion technique was used. This technique defines the ERP onset as the time point at which the ERP amplitude reaches a pre-specified percentage of the overall ERP peak value. Simulations have been run to evaluate the effectiveness of this technique to assess onset latency at a variety of percentage specifications (30%, 50%, 70%) of various ERP components; all percentage specifications tested showed comparable results, with the relative criterion technique in general found to be one of the most desirable methods for determination of ERP latency (Kiesel, Miller, Jolicoeur & Brisson, 2008).

Within the current thesis startle ERP onset latency was determined as the time at which the ERP amplitude crossed a value of 75% of the overall maximum peak amplitude. Only onset latency scores which occurred after 170ms where included, so as to only include activity within the positive ERP range of interest and because early responses are more susceptible to eye-

blink artifact. However, if the ERP wave crossed the threshold at a number of different time points post 170ms, the earliest score was always taken.

4.2.1.3.3 Physiological measures

EMG, HR SCR response scores for parameters were computed offline. For startle stimuli all parameters were analysed, for thought suppression intrusion responses only HR and SC responses were analysed. EMG, HR and SC data was collected, filtered and cleaned as described in the measures sections above (EMG: 4.1.3.2.1, HR: 4.1.3.2.2, SC: 4.1.3.2.3).

4.2.1.3.3.1 Startle response scores

Startle Magnitude: EMG startle magnitude was taken as the time of maximum 21-150ms post tone onset, minus the mean during the 20ms post-stimulus BL; in accordance with published analysis guidelines for startle data (Blumenthal et al., 2005). Startle SC and HR response scores were calculated as the time of maximum within 1-5s post stimuli onset, minus the average level within 1s post stimuli. This response window was selected both via visual inspection of the data and in accordance with research indicating that phasic SC responses peak within 0.5-5s post stimulus (Boucsein et al., 2012) and that phasic HR responses last less than 30s (Jennings, Berg, Hutcheson, Obrist & Turpin, 1981), and previous research in the area (Griffin, 2008).

Startle habituation: Startle habituation scores were calculated as the number of trials before reaching a pre-defined non-response criterion on two successive trials. Non-response scores were set at <0.1uV for EMG data and <0.05uS for SC data (Shalev et al., 1997; Orr, 2003). SC responses were range corrected, to account for individual differences in range, using the following formula (Lykken & Venables, 1971):

1. $$\text{Range corrected SCR} = \frac{\text{Current SCR}}{\text{Overall SCR Max}}$$

Current SCR represents the average response to all startle stimuli of one trial type (i.e trauma or neutral trials) and overall SCR represents an individual's maximum SC value during the entirety of the laboratory session.

4.2.1.3.3.2 Intrusion response scores

HR and SC responses towards intrusive thoughts, during the thought suppression task, were calculated by subtracting the mean response in a 1s pre stimulus baseline period, from the maximum in a 1-4s response window post intrusion onset. Due to the minimal gap between some participants' intrusive thoughts, a reduced response window, compared to startle response data, was used for intrusion response calculations, to reduce the overlap of response scores across different intrusions. SC data was range corrected using Formula 1 above, where current SCR represented the average intrusion SCR.

4.2.1.3.3.3 VR scenario responses: SC and HR level

SC and HR levels were sub-divided into two time windows for analysis of the VR viewing period: data was split into a pre-explosion time window from 0-3.24s, during which individuals drove around the streets of the VR Iraq world, and a post-explosion 20s time window, from explosion onset and encompassing the immediate carnage following the explosion (whilst still immersed in the VR environment). SC level was range corrected, to account for individual differences in range, using the following formula (Lykken & Venables, 1971):

2. $$\text{Range corrected SCL} = \frac{\text{Current SCL} - \text{Overall SCL Min}}{\text{Overall SCL Max} - \text{Overall SCL Min}}$$

Where current SCL represents the SC level across a specific film segment (i.e. pre-explosion and post-explosion segments) and overall SCL Min and Max represents an individual's minimum and maximum SC values during the entirety of the laboratory session.

In order to compare responses towards the traumatic event, SC and HR trauma response change scores were calculated by subtracting the BL value from the post-explosion value. BL SC values were also range corrected using Formula 2 above, prior to change score calculation. SC and HR trauma response VR difference scores were calculated as the difference in response from the pre-explosion period to the post-explosion period, to allow for clearer separation of responses towards the Iraq VR exposure alone and to the VR traumatic event itself.

4.2.1.3.4 Free recall coding

A master listing of 96 items, which occurred during the virtual reality scenario, was compiled, and used by a single judge to score participants free recall scripts for content accuracy (as in

Wegner, Quillian & Houston, 1996). Items pertaining to general observational details and sounds, which continued over a prolonged period in the VR film, were omitted from the sequence master listing, leaving 67 items remaining in the sequence master listing. Inaccurate recall additions to free recall scripts were not analysed in content or sequence analysis, and as such, scores reflect only accurately recalled items.

4.2.1.3.4.1 Content accuracy

Free recall accuracy was scored as the number of items recalled by each individual from the master listing, where credit was given for a listed event, if the gist of the event was given in the participants free recall script. Content accuracy scores were expressed as a percentage of the total number of possible event items from the master listing (96 items), thus reflecting a measure of both recall accuracies and omissions. These scores were reversed to produce a measure of content inaccuracy.

4.2.1.3.4.2 Sequence recall

Sequence accuracy was credited where an event followed, in the film (and hence on the master listing), the event described immediately before it in the free recall script. Sequence errors were credited where an event actually occurred before, in the film, the event described immediately before it in the free recall script. A sequence-recall ratio percentage was calculated, as described in Wegner, Quillian & Houston (1996), by dividing the number of sequence accuracies by the total number of sequence accuracies and errors. Omitted events in the sequence of the free recall scripts where not analysed, so as to not confound the analysis of sequence accuracy with that of content accuracy (in accordance with the sequence analysis guidelines of Ferree & Cahill, 2009 and Wegner, Quillian & Houston, 1996). These scores were then reversed to create a measure of recall disorganisation.

4.2.1.3.5 Checks for normal distribution

All final variables (as illustrated in table 4.2) were tested for normality using Kolmorov-Smirnov and Shapiro Wilks tests, calculation of skewness and Kurtosis z scores and visual inspection of histograms and Q-Q plots. To correct for normality and the effect of extreme outliers, transformations were then run on all variables that departed from a normal distribution, as indicated by normality statistics or plots. One participant, who had a visible heart murmur in

earlier stages of psychological analysis, stood out in histograms and boxplots as an extreme outlier on a number of measures of HR response due to the small time windows from which BL and response data are calculated. As such their HR data was removed (marked as missing) on all HR response variables, but retained for measures of HR level across longer time windows (i.e. the VR) in which the heart murmur would not affect comparison with other participants; no further univariate outliers were removed at this stage of the analysis.

As none of the variables were severely skewed, square root transformations were applied first, if this did not improve the skewness of the variable then Log transformations were ran; if neither normalised the distribution, then inverse transformations were carried out (pp. 80-82 Tabachnick & Fidell, 2001). Square root transformation successfully normalised BDI scores, VR low mood difference scores, intrusion distress scores, startle EMG and SC magnitudes on N and T trials, startle HR amplitude response scores on N and T trials and onset latency ERP values on N and T trials. Log transformation successfully normalised the number of intrusive memories and free recall sequence ratio scores. Age retained a non-normal distribution with application of an inverse transformation, and as such 'age' was removed from further analysis; the removal of age was deemed appropriate as the non-normal distribution was driven by homogeneity of age values between 18 and 24 years (92.6% of the sample) and as meaningful analysis of age differences would not have been possible. Due to severely skewed distributions on the number of cigarettes and cups of coffee prior to the experiment, days since last drank and took substances, and the number of traumatic events experienced in the participants lifetime, these variables were all changed into dichotomies. Smoking or coffee drinking on the day of the experiment were given a value of one, drinking alcohol was scored if drank in the last 24 hours, substance use was scored if present, and traumatic events were scored if the participant had experienced at least one traumatic event in their lifetime.

4.2.2 Study Two

4.2.2.1 Participants

One hundred and ninety one participants completed the online screening questionnaire. Of these 123 students (44 male and 79 female) from the University of Exeter, between the ages of 18-37, right handed, fluent in English, with normal or corrected to normal vision and hearing were enrolled to take part in the laboratory study. One participant was excluded from all analysis due to equipment malfunction, leaving a sample of 122 individuals; 4 further

participants data were removed from analysis of startle responses and VR re-exposures (but retained for initial VR-trauma mood induction analysis), due to equipment malfunctioning during the startle task resulting in these individuals not hearing all the startle sounds. See appendix 16 figure A16.1 for a flowchart depiction of participant recruitment and subsequent allocation to the manipulation conditions. Participation was in return for a payment of £5 per hour or one course credit per hour; course credits were also available to first year psychology undergraduates, towards a compulsory research methods course module. Candidates were pre-screened online and those with a tentative diagnosis of current depression or PTSD, taking psychopharmacological medication, with a history of brain surgery, epilepsy or prior exposure to a warzone were excluded. Written informed consent was gained from all participants and the study was approved by the University of Exeter, School of Psychology Ethical committee (appendix 17).

4.2.2.2 Procedure for Study 2 (see Table 4.3)

Pre-screening and collection of demographic and trait measures werecarried out via an online questionnaire. The trauma events checklist from the clinician administered PTSD scale (CAPS), together with the Primary Care PTSD screen, were used as a pre-screening tool for current PTSD. Whilst the PHQ9 was used as a pre-screening for current depression and the EEG and VR exclusion criteria were assessed using the screening questionnaire. Eligible candidates were then invited to take part in the experimental laboratory study and asked to fill out a number of pre-laboratory measures online. A battery of trait measures which have been previously associated with PTSD and anxiety were completed. The STAI-T and ASI were used to measure anxious tendency and fear relating to the bodily sensations of anxiety, respectively. The ERQ was measured to ascertain the level of trait reappraisal and suppression, in order to control for this within the analysis of experimental group differences. The Social Readjustment Rating Scale (SRRS) was completed on the day of the laboratory assessment to account for the effects of previous exposure to stressors in the last year of participants lives; based on the findings of study 1 the decision was made to focus attention on the events within the last year instead of lifetime stress exposure, as this was the only predictive factor of analogue symptomology.

Informed consent was gained separately for the online questionnaire and laboratory study. The laboratory sessions took place across the entire day, with sessions beginning at 9:00, 12:00 and 15:00. Information pertaining to nicotine, caffeine, alcohol and drug intake as well as regularity of computer gaming was gathered at the beginning of the laboratory session during equipment set up. The laboratory study took a total of three hours to complete and began

with exposure to a virtual reality Iraq world stressor with concurrent recording of SC and HR. State mood (STAI, visual analogue mood scale) was recorded immediately before and after each VR exposure and the dissociation questionnaire was completed following each VR exposure. Prior to the startle task participants were allocated to group manipulation conditions (acceptance and coping based reappraisal, behavioural suppression and a control group instructed to view normally), and completed the startle task in line with their group instructions as described in section 4.1.4.5 and appendix 13.

Following completion of the startle task participants were given a 10 minute break and then asked to re-view the stressor Iraq VR twice more, whilst SC and HR were recorded. During both viewings participants were instructed to watch the VR again from a first person perspective and given the briefing that they were back in the same Iraq city on a different day. With each Iraq VR viewing the IED went off at an earlier position in the scenario to prevent a conditioning effect from occurring. During the first re-viewing only the initial VR scene setting information was given, this re-viewing assessed carry over effects from the emotion regulation manipulation within the preceding startle task. For the second re-viewing participants in the two experimental groups (reappraise/suppress) were instructed to use their group specific emotion regulation strategy that they used earlier on regulate trials in the startle task ("COPE"/"SUPPRESS"), whilst the control group were only read the initial VR scene setting information. A gap of 10 minutes was left between the two VR re-viewings, in which participants filled out the SRRS stressful events measure. State mood measures were taken before and after both VR re-viewings and peri-VR dissociation was measured immediately after each VR.

All psychophysiological measures (EEG, EMG, SC, HR) were recorded during the startle task and SC and HR measures were recorded during all VR viewings (both neutral and trauma). The experimenter left the room while all questionnaires and computer tasks were completed and all tasks involving psychophysiological recording were carried out in darkness, following the finding that physiological startle responses are facilitated by darkness, and this facilitation effect is greater for PTSD patients compared to controls (Grillon, Charles, Morgan, Davis & Southwick, 1998).

Table 4.3: Study two variables. Summary of the risk and resilience factors pre- peri and post-trauma and analogue symptom measures.

Pre-trauma	Peri-trauma	Post-trauma	Phenotypic symptom measures of Stress sensitization
PERSONALITY: ▪ ASI ▪ STAI-T **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events checklist **GENDER** *COVARIATES:* ▪ Computer gaming ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**EMOTION REGULATION MANIPULATION:** ▪ Suppression vs. Reappraisal vs. Control (No manipulation)	**1. STARTLE (N/TV/TR trial types):** ❖ VAS Mood (positive and negative) ❖ ERP ▪ PCA (P2 & P3 amplitude) ▪ Startle ERP onset latency ❖ EMG (make into t-scores) ▪ Response magnitude ▪ Habituation ❖ HR ▪ Response amplitude ❖ SCR (range correct) ▪ Response magnitude ▪ Habituation **2. VR2 AND VR3 RE-EXPOSURE:** ▪ HR 0:00-1:08 & 20s post-explosion ▪ SCL 0:00-1:08 & 20s post-explosion

4.2.2.3 Data pre-processing

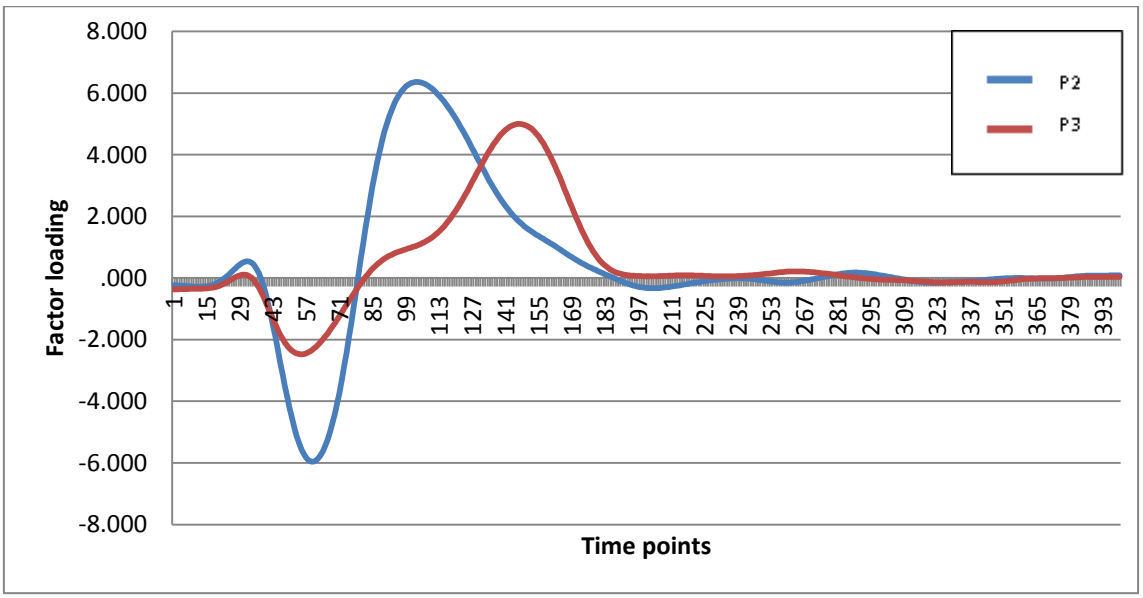
4.2.2.3.1 EEG

EEG data recorded during the startle task was segmented separately by group (cope, suppress, view) and trial type (i.e stimulus and instruction pairing: Trauma + Reappraise/ Trauma + View/ Neutral) into a 1000ms epochs, from 200ms prior to startle sound onset, and baseline corrected relative to the average during the 100ms prior to stimulus onset. EEG data was

filtered offline and artifacts were removed prior to the summation of the data into startle response ERPs, as described in EEG section 4.2.1.3.2.

4.2.2.3.1.2 Temporal Principal components analysis (PCA): Frequency domain

Temporal PCA (Donchin & Heffley, 1978) was run on the entire ERP epoch in order to decompose the ERP waveform into its temporally unique components; with particular interest in separation of the P2 and P3 waveforms (see section 4.2.1.3.3 for an explanation of PCA methodologies and its advantages in the separation of distinct temporal 'time-windows'). Due to the fact that trauma regulate and trauma view trials were the same for the control goup, who received no task manipulation instructions, PCA analysis was run and analysed separately for comparisons of N & TR trials and N & TV trials across all 3 groups (suppress, reappraise, control), and for TR & TV trials across the 2 manipulation groups (suppress & reappraise).ERP data from 0ms-800ms post-startle onset was extracted separately across manipulation conditions, subjects, electrodes and trial types. PCA was performed on the covariance matrix with time points (of which there where 400) as variables and manipulation group X trial type X subjects X electrodes as observations, using Varimax rotation with a component extraction criterion of eigenvalues $\geq$ 1. Factor loadings of the raw components which explained >1.5% of the total variance in the ERP response were plotted for inspection (for an example see appendix18 figure A18.1). As in Study 1, two unique positive components within the P2/P3 time range were apparent which illustrated shared variance with an earlier negativity in the N1 time range (Figure 4.10). In order to concentrate further analysis on only the positive waveforms of the two components of interest, the PCA was then re-ran from 158ms - 800ms. The component scores for the 2 positive components from the 158-800ms PCA analysis were extracted to SPSS and regions of interest were created in accordance with inspection of the topographical distribution of the startle ERP across the positive time windows of interest (figure 4.11). These were also in accordance with Study 1 (see section4.2.1.3.3; i.e. analysis of electrodes with a scalp topography over the Frontal-posterior-mid region (FC1, FCz, FC2, C1, Cz, C2) and the Parietal-mid region (CP1, CP2, P1, Pz, P2) (figure 4.9)).



Note: 1 time point = 2ms

Figure 4.10: Example of PCA analysis of startle ERP in study 1 in the frequency domain: comparison of neutral and trauma regulate trials. Temporally independent components in the P2 and P3 time range, as derived from PCA analysis from 0-800ms across the startle ERP.

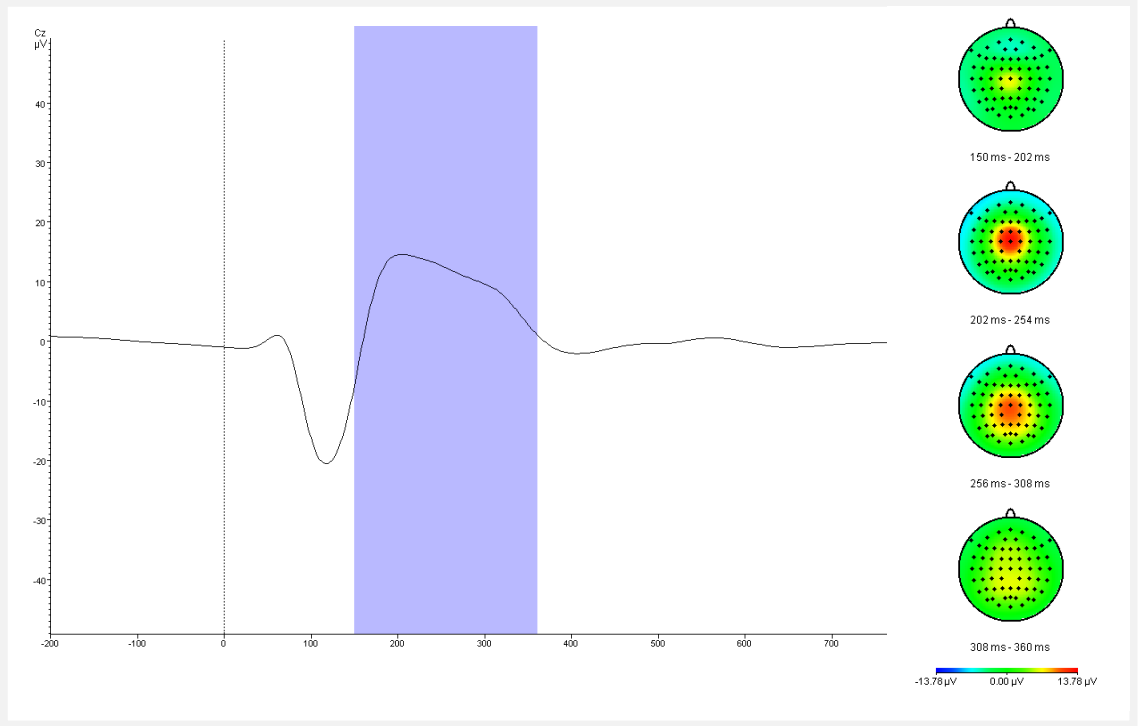


Figure 4.11: Grand average ERP startle response and topographies across the two time-windows of interest (P2 and P3) in the time domain.

4.2.2.3.1.3 Startle ERP onset latency analysis: Time domain

Onset latency analysis was as described in section 4.2.1.3.2.2; however within study 2 the cut off point from which onset latency scores were included in analyses was 150ms, so as to only include activity within the positive ERP range of interest and because early responses are more susceptible to eye-blink artifact.

4.2.2.3.2 Physiological measures of autonomic nervous system activation

EMG, HR SCR response scores for parameters were computed offline. For startle stimuli all parameters were analysed, for VR scenario responses only HR and SC responses were analysed. EMG, HR and SC data was collected, filtered and cleaned as described in the measures sections above (EMG: 4.1.3.2.1, HR: 4.1.3.2.2, SC: 4.1.3.2.3).

4.2.2.3.2.1 EMG, SC and HR response scores: Startle data

Startle data analysis was as described in study 1 section 4.3.4.4. Correlational analysis of peri-traumatic HR and SC responses indicated that trauma HR/SC responses calculated as change from BL responding (i.e. trauma response minus BL) and trauma HR/SC calculated as change from the pre-trauma VR film section, both were illustrating a comparable measure (HR: $r(117)=.76$; SC: $r(117)=.63$) as confirmed by Cronbach'sCronbach's alpha values of .69 on SC variables and .85 on HR variables. It was therefore decided to only include peri-traumatic physiological change from BL scores within further analyses; due to the fact that in study 1 analyses, BL change scores showed stronger predictive relationships than the change scores calculated from differences within the VR itself.

4.2.2.3.2.2 SC and HR levels: Neutral and trauma VR scenarios

SC data was first corrected for individual difference using the range correction calculation described in section 3.3.4.4.3. The analysis windows for SC and HR levels across VR viewings were sub-divided into comparable time bins, taking the first 0:00 – 1:18 minutes of the VR driving around the wartime city and the 20 seconds during which the 'traumatic' explosion occurs, these time windows were chosen in order to retain consistency in the portion of the VR scenario which was analysed across each of the VR-viewing.

4.2.2.3.3 Checks for normal distribution

All variables were tested for normality using Kolmorov-Smirnov and Shapiro Wilks tests, calculation of skewness and Kurtosis z scores and visual inspection of histograms and Q-Q

plots. To correct for normality and the effect of extreme outliers, transformations were then run on all variables that departed from a normal distribution, as indicated by normality statistics or plots (pp. 80-82 Tabachnick & Fidell, 2001). Square root transformation successfully normalised SRRS, STAI and low mood difference scores across all VR exposures, and negative mood, SC and EMG magnitude and HR amplitudes across the startle task. Log transformation normalised ASI scores and inverse transformations did not improve normality of any of the variables tested. As in study 1 analyses, age retained a non-normal distribution with application of an inverse transformation due to homogeneity of age values between 18 and 24 years (93.4% of the sample). As such meaningful analysis of age differences would not have been possible and 'age' was therefore removed from further analysis. In accordance with study one analysis, coffee drinking, smoking and drug taking were dichotomized. A number of variables were not altered using the above transformations. Startle habituation scores were slightly negatively skewed due to the high number of participants failing to habituate across all physiological response measures and ERP onset latency scores were slightly positively skewed reflecting a predominance of earlier ERP startle response amplitudes; as skewness was an expected and inherent feature of these variables they were retained for further analysis. Non-normal distribution was driven by outlying cases on experience of traumatic life events, ERQ reappraisal, HR responses during the second and third exposure to the Iraq VR and SC responses during the explosion on the third Iraq VR exposure. Outlying cases on these variables were replaced with a value one unit larger or smaller than the next score in the distribution (Tabachnick & Fidell, 2001) to improve normality; univariate outliers on other variables were not addressed at this stage of analysis and instead multivariable outliers were sought and addressed only if they unduly influenced the fit of later regression models containing these variables.

5 PRE- AND PERI-TRAUMATIC RISK AND RESILLIENCE FACTORS IN THE DEVELOPMENT OF PTSD-LIKE HYPERAROUSAL SYMPTOMS IN AN ANALOGUE SAMPLE EXPOSED TO A VIRTUAL REALITY TRAUMA

5.1 ABSTRACT

PTSD is believed to develop when fear responses conditioned during trauma exposure fail to extinguish naturally. As such, PTSD is associated with increased reactivity to emotional stimuli and altered startle responses. Research suggests that the amplification or extinction of conditioned fear responses over time could depend on premorbid traits and peri-trauma factors. This research explores, in a healthy sample, how individual differences in pre-trauma characteristics and peri-trauma reactions affect emotional processing and physiological reactivity, towards ecologically valid startling sounds, following exposure to a virtual reality (VR) trauma. Findings showed that although individual differences in ERP startle processing are apparent, pre- and peri-trauma risk factors explain greater variance in reflex and peripheral startle responses. Biological pre-trauma risk factors (gender and genetic polymorphisms previously related to pathological anxiety) and peri-trauma heart rate (HR) responses were important factors in predicting exaggerated post-trauma startle eye blink, HR and skin conductance. These findings suggest that although pathological levels of startle responding may develop in line with PTSD, biological and peri-traumatic factors can predict responding in the immediate post trauma phase and may provide insight into those at risk of full symptom development. This study highlights the ability of VR technology, electrophysiology and stress activation to broaden our understanding of the dynamic relationship between predisposing factors and phenotypic PTSD symptomology.

5.2 INTRODUCTION

Posttraumatic stress disorder (PTSD) is a highly debilitating mental health condition, associated with exposure to a traumatic event. Interestingly however, following trauma exposure, the conditional probability of PTSD development is found to be around 9-10% (McManus et al., 2009; Breslau et al., 1991; Breslau et al., 1998; Davidson et al., 1991; Helzer, Robins, & McEvoy, 1987; Kessler et al., 1995). The fact that PTSD is the minority response clearly illustrates the important role of individual differences in PTSD development. Indeed, evidence suggests that individual variation in a number of pre-, peri- and post- trauma risk factors are predictive of subsequent PTSD diagnosis and symptomology. In addition to symptomatic

avoidance behaviours, memory impairments and intrusions, PTSD is characterised by a profile of hyperarousal, commonly expressed in an exaggerated emotional and physiological response to startling stimuli. The reflex eye-blink response towards startling stimuli is an automatic defence response, which has been found to be augmented by negative foregrounds and inhibited by neutral and positive foregrounds (Bradley, Cuthbert & Lang, 1990) in accordance with the emotional hypothesis of startle modulation proposed by Lang, Bradley & Cuthbert (1990). Whilst emotional modulation has been differentially associated with PTSD related traits, generalized hyperarousal towards startle stimuli has commonly been investigated in PTSD population studies.

Exaggeration of physiological startle responding in PTSD has been found in reflex eye-blink EMG magnitudes, HR amplitudes, and increases in the latency of SC response habituation (Shalev et al., 1992; Orr et al., 1995; Rothbaum et al., 2001); with some literature additionally illustrating enhancement of SC response magnitudes (Shalev et al., 1992; 1997) and impairment in reflex EMG habituation (Shalev et al., 2000). A meta analysis carried out by Pole (2007) found exaggerated HR startle responses, trauma-modulated[9] startle EMG enhancement and slower SC startle habituation to be the strongest correlates of PTSD specific responding. As well as the general enhancement of startle responding, individuals with PTSD show increased emotional-modulation of the startle response towards negative and trauma valenced startle foregrounds (Pole, 2007; Jansen & Frijda, 1994) and sounds (Casada et al., 1998); which may be explained by the augmentation of emotionally consistent reflexes (Lang et al, 1990). Heightened fear potentiation (i.e. within the context of danger) of the startle response (Morgan et al., 1995) and deficits in learning and inhibiting responses to safety cues, have been associated with heightened PTSD symptom expression (Jovanovic et al., 2009).

Compared to other PTSD symptomology, the contribution of individual differences as vulnerability factors in the development of an exaggerated startle response post-trauma has been relatively under investigated, despite evidence that an enhanced startle response profile is highly associated with PTSD (Pole, 2007) and research showing support for its utility as a research tool (Grillion & Baas, 2003). In order to accurately assess the influence of potential vulnerability factors on symptomatic startle responses, longitudinal patient studies collecting individual difference variables pre-trauma, or longitudinal laboratory research exposing individuals to an analogue trauma experience, are required. The lack of patient studies addressing this area may be in part due to the financial and time expense involved in such

[9] Trauma related contexts and stimuli as opposed to neutral or otherwise valenced contexts and stimuli.

investigations and the lack of analogue research may stem from the mixed evidence as to the categorisation of the exaggerated startle response as either a predictor of pathological vulnerability, preceding diagnosis (Guthrie & Bryant, 2005), or a pure symptom, developing only in line with pathological symptom development (Shalev et al., 2000; Orr et al, 2003; Griffin, 2008). This body of work has shown that pre-trauma SC startle responses and baseline physiological reactivity can predict later PTSD symptom development in the acute post trauma phase (Guthrie & Bryant, 2005), while HR and eye-blink EMG startle responses may develop in line with diagnosis rather than representing a vulnerability factor (Shalev et al., 2000; Orr et al, 2003; Griffin, 2008). Although measurement parameters may affect the pathologically predictive capacity of the post-trauma startle response, differential findings could also be produced by variable study design; with support for startle as a vulnerability factor coming from a longitudinal retrospective design (Guthrie & Bryant, 2005) and evidence for startle as a pure symptom coming from prospective investigations (Shalev et al., 2000; Orr et al, 2003; Griffin, 2008).

Recent phenotypic rat-models may cast further light on the inconsistencies in the startle literature. These models suggests that a profile of anxiety behaviours and an exaggerated startle response is predictive of later phenotypic PTSD symptom development, but only when this pre-trauma vulnerability profile is activated by a non-pathological mild stress exposure (Nalloor et al., 2011). The rats which later went on to express phenotypic behaviours following a traumatic event which produced a conditioned fear response, showed a prior vulnerability profile of elevated startle and anxiety behaviours following exposure to a mild stressor event which produced no conditioned fear response. This new evidence from rodent modelling implies that non-traumatic stress activation may be a necessary prerequisite to assessing startle response as a predictor of later PTSD development, a condition that could only be met by a longitudinal design. Support for the validity of this animal model within human populations comes from literature illustrating that stressful life events can induce as many PTSD like symptoms as traumatic events (Mol et al, 2005). This evidence suggests that longitudinal patient studies assessing startle as a vulnerability variable should do so following exposure to a mild stressor. Indeed Grillon, Morgan, Davis & Southwick (1998b) found that group differences in startle magnitudes were only apparent, in PTSD patients compared to trauma-controls and non-exposed controls, when tested in a stressful threat of shock context and were not apparent in the absence of experimental stress. Furthermore, these findings support the investigation of phenotypic startle responses in an analogue design in which mild stress exposure (i.e. analogue trauma exposure) prior to measurement of startle response is a

necessary prerequisite of the design, and suggest that exaggerations in measured phenotypic startle responses could in themselves be important predictors of pathological vulnerability.

Genetic polymorphisms including BDNF, 5HTTLPR, D2 Taq1, ADORA2B and NPS have been highlighted in the literature as additional pre-trauma risk factors associated with PTSD symptom expression and pathology (see literature review, section 2.3 for a full summary of findings). Although twin studies have shown high heritability rates of startle response magnitude, they do not support a genetic basis of the affect-modulation of the startle response (Anokhin, Golosheykin & Heath, 2007); although support for emotion modulated startle constituting a genetic or trait measure is illustrated by research showing individual stability of emotion-modulated startle response magnitudes across multiple testing (Larson, 2000). Evidence for the genetic basis of the startle response comes from studies investigating NPS, BDNF and 5HTTLPR; however inconsistencies exist in findings pertaining to the role of BDNF and NPS alleles. NPS knock-out mice show a reduction in the magnitude of the acoustic startle response (Fendt et al, 2011), NPS receptor T allele showing a strong association to amygdala activation to fearful faces (Dannlowski et al, 2011) and NPS T allele expression increased in female panic disorder patients (Domschke et al., 2010); whilst in other studies NPS and the NPS receptor have been shown to have stress and anxiety reducing effects (Reinscheid, Xu & Civelli, 2005), improve memory consolidation and retention in animals (Han, 2013; Lukas and Neumann, 2012) and humans (Fendt et al., 2010; Lennertz et al, 2012) and block fear potentiated startle responses (Okamura, et al., 2011; Lennertz et al, 2012); thus implicating the NPS A allele in elevated hyperarousal and memory impairments associated with PTSD. Furthermore, the BDNF Met allele has both been associated with a deficit in the fear potentiated startle response (Londsdorf et al., 2010) as well as showing positive relationships with PTSD vulnerability traits such as harm avoidance (Montag, Basten, Stelzael, Fiebach, & Reuter, 2010; Jiang et al., 2005). Adversive enhancement of amygdala activation has been found to occur in carriers of the 5HTTLPR s allele (Cali, Ferri & Duman, 2009); the amygdala is believed to serve as a command centre for startle response facilitation (Koch, 1999) and both amygdala activation and the 5HTTLPR s variant have been implicated in PTSD. 5HTTLPR s allele expression may therefore predict hyperarousal and exaggerated startle responses in a fearful context.

Individual differences are clearly important in the expression of enhanced startle responding and a number of pre-trauma traits and peri-trauma responses have been implicated in predicting PTSD risk more generally (see literature review, sections 2.3 and 2.4 for a summary

of these findings). Increased startle reflex magnitudes have been found in females compared to males (Quevedo et al., 2009). Affect-modulated adversive enhancement of startle response magnitudes are potentiated by pre-trauma individual differences in trait fearfulness (Vaidyanathan, Patrick & Bernat, 2009), depression and anger (Cook, Hawk & Davis, 1991); with evidence illustrating that the negative-potentiation effect is solely restricted to individuals high on harm avoidance (Corr, Kumari, Wilson, Checkley & Gray, 1997; Corr et al., 1995). However, to the best of the authors knowledge, there have been no studies looking at association between peri-traumatic responses and subsequent startle responding specifically. Interestingly, a profile of exaggerated startle reactivity has not however been found across the board in PTSD patients; Medina, Mejia, Schell, Dawson and Margolin (2001) found that females with PTSD relating to Type II stressors illustrated reflex startle suppression, even though startle response testing followed a trauma related task. This finding is line with studies illustrating that there is a sub-group of PTSD patients with dissociative symptom profiles which do not include the typical hyperarousal symptomology (Lanius et al., 2010; Ginzburg et al., 2006) and evidence that dissociation is associated with a reduction in physiological reactivity (Griffin et al., 1997).

In accordance with evidence from rat modelling that phenotypic vulnerability to PTSD can be assessed via examination of anxiety behaviours and startle responding following mild stress exposure, an investigation will be carried out to examine how pre- and peri-trauma individual difference variables, which have been previously implicated in PTSD risk generally or startle responding specifically, can predict differential startle responding following a VR-trauma ('Iraq world') experience. In this sense, VR-trauma exposure will serve as both a mild stressor and an analogue trauma experience. The use of an analogue design allows for longitudinal assessment of individual differences and peri-trauma physiological responses, and unlike the typical trauma-film paradigm (Holmes & Bourne, 2008), VR trauma exposure allows for a more immersive and realistic analogue experience (Bowman & McHahan, 2007); this is important in light of findings showing that the level of presence experienced is associated with level of induced emotional state (Riva et al, 2007). During the post-trauma startle testing phase, in addition to immersive sound-valence-congruent foregrounds, ecologically valid startle sounds of trauma (gun-shot) and neutral (car horn) valence will be used to investigate the emotion-modulation of the startle response. The measurement of startle responding will act as an analogue to PTSD symptomology, elucidating risk factors which could be key to differential expression of startle responding post-trauma.

In order to assess the attentional afferents of startle responding, and how such processes may be affected by emotional content of the startle stimuli, simultaneous measurement of ERP components is required. The constituting ERP components in typical startle responsesinvolve a negative deflection around100ms (N1) and positive deflections at 200ms (P2) and 300ms (P3). Although previous research has illustrated emotional and arousal dependent modulation of the positive startle ERP components (Cuthbert, Schupp, Bradley, McManis & Lang, 1998; Schupp, Cuthbert,Bradley, Birbaumer & Lang, 1997) and ERP components occurring within similar time frames towards visual stimuli have been found to be modulated by PTSD pathology (Karl et al., 2006), little research has explicitly explored startle ERP responses in PTSD patients. One study which investigated PTSD dependent modulation in startle ERP components has illustrated that carriers of the s allele of the 5HTTLPR polymorphism showed increased P2 startle ERP amplitude compared to l allele carriers (Karl et al., 2007). These findings highlight the role of the serotonin transporter s allele startle ERP modulation but illustrate that within clinical populations there are individual differences in ERP startle processing which may be associated with the development of different symptomology and associated with different pre-trauma genetic risk factors.

This research will not only investigate the utility of VR-trauma analogue designs and the emotion-modulation of startle responding, but will prospectively investigate the predictive capacity of risk factors within the pre- and peri-trauma phases in the explanation of electrophysiological and peripheral startle responses. It is hypothesised that individual differences in PTSD risk factors pre-trauma (anxiety traits, previous stressful and traumatic life events, risk allele gene expression, gender) and peri-trauma reactivity (anxious emotional and physiological (SC, HR) responding) will predict enhancement of physiological startle responses and a delayed latency of ERP components, following exposure to a VR-trauma. Such findings would suggest that studies failing to find evidence of startle as a pre-trauma PTSD vulnerability factor may be the result of the exclusion of a mild stress activator from the study design.

5.2.1 Research questions and hypothesis

Q1: Are affective and electrophysiological startle mechanisms sensitive to trauma versus neutral valence effects following exposure to a virtual reality trauma?

> *H1: Affective and reflex EMG startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli.*

Q2: What are the predictive effects of pre-trauma individual differences on startle responses?

H2: Pre-trauma anxiety related personality traits and stressful life events will be associated with elevated autonomic physiological startle responses

H3: NPS A allele will be associated with increased startle eyeblink responses

Q 3: What are the predictive effects of peri-trauma individual differences on startle responses?

H4: Peri-traumatic dissociation will be negatively associated to startle responding

5.3 METHOD

5.3.1 Participants

See Chapter 4 Study 1 participants section 4.2.1.1.

5.3.2 Measures

See the following sections within Chapter 4 Measures section (4.1.1):

Screening questionnaires section 4.1.1.1: EEG and VR screening questionnaire, MINI, BDI-II

Trait questionnaires section 4.1.1.2 : ASI, STAI, HA,

Life events questionnaires section 4.1.1.3: SRRS, traumatic life events checklist,

State questionnaires section 4.1.1.4: SAM mood manikin, VAS mood scale and peri-trauma dissociation measure.

Genotyping section 4.1.2.

Psychophysiological responses section 4.1.3: EEG, SC, ECG (i.e. HR) and EMG.

Computer tasks sections 4.1.4: VR Iraq world, Startle paradigm counterbalanced block design.

5.3.3 Procedure

See Methods Chapter 4 Procedure section 4.2.1.2 for an overview of the full study design from which the data within this chapter were collected. The same set of pre- and peri-trauma factors will be analysed across this and the proceeding Chapter 6; however the outcome measures covered within this chapter relate only to the startle response analogue symptom measurement.

As a brief re-cap, the data within this chapter explored the influence of pre- and peri-trauma individual differences on the emotion modulated startle response, following exposure to a

virtual reality trauma (Iraq world). Within the startle paradigm participants were exposed to 95 dB startle stimuli with trauma (gunshot) and neutral (car horn) contents within separate blocks. Blocks were counterbalanced across participants. Startle blocks were presented with valence congruent foreground pictures, which remained throughout the entire block. The trauma foreground was a still from the earlier VR-trauma Iraq city scenario, whilst the neutral foreground was a picture of the local city. SC and HR responses were recorded during VR-trauma exposure and EEG, eye-blink EMG, SC and HR responses were recorded during the thought suppression task. The startle response outcome variables and individual difference predictor variables are depicted in table 5.1.

Table 5.1: Variables assessed within Chapter 5. Summary of the pre- and peri-trauma risk and resilience factors, and analogue symptom measures.

Pre-trauma	Peri-trauma	Phenotypic symptom Measure: Startle response
PERSONALITY: ▪ STAI-T ▪ ASI ▪ HA **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events **GENE POLYMORPHISMS:** ▪ 5HTTLPR ▪ BDNF ▪ D2 Taq1 ▪ NPS ▪ ADORA 2B **GENDER** *COVARIATES:* ▪ *Mini neuropsychiatric assessment (MINI)* ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)* ▪ *Drug use* ▪ *Computer gaming* ▪ *Beck depression inventory (BDI)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ SAM arousal difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**STARTLE (Neutral & Trauma trial types):** ❖ EEG ▪ PCA (P2 & P3 amplitude) ▪ Startle ERP onset latency ❖ EMG (make into t-score) ▪ Response magnitude ▪ Habituation ❖ HR ▪ Response amplitude ❖ SCR (range correct) ▪ Response magnitude ▪ Habituation

5.3.4 Pre-processing

See the following sections within Methods Chapter 4 pre-processing section (*4.2.1.3*):

Genetics section 4.2.1.3.1.

EEG section 4.2.1.3.2: Temporal PCA, Startle ERP onset latency

Physiological measures section 4.2.1.3.3: Startle response scores, VR scenario responses

Checks for normal distribution section 4.2.1.3.5.

5.3.5 Statistical analysis

Analysis of the emotion modulation of the startle response was carried out using paired sample t-tests and repeated measures analysis of variance. Prior to analysis of the prediction of startle responding, zero order correlations were carried out across all predictor and outcome variables, illustrated in table 5.1, to check for multicolliniarity between predictor variables and very high correlations among outcome variables; outcome measures with correlations >.7 were tested using Cronbach's alpha. Cronbach's alpha values of >.7 were concluded to represent the same theoretical dimension and were therefore summed to create a single item. Zero order correlations were re-ran using the final outcome variables, to inform as to the strongest set of predictor variables for each regression model. However, due to problems of multiple comparisons which are associated with running a large number of correlations, although all correlated variables are reported, results which are not evident across a number of different outcome measures should be interpreted cautiously and, as such, patterns in the data will be sought and highlighted within the chapter conclusion. Regression analysis, using a hierarchical forced entry method as illustrated in table 5.2, was carried out on all predictor variables that showed significant zero order correlations with phenotypic outcome measures, in order to explore their predictive capacity. Where multivariate outlying cases changed the regression model qualitatively, the model with these cases replaced with a value one unit larger or smaller than the next score in the distribution (Tabachnick & Fidell, 2001) is reported.

Table 5.2: Blockwise hierarchical regression analysis structure applied in predictive analysis of startle response outcome variables

Block 1:	Gender
Block 2:	Life events
Block 3:	Personality
Block 4:	Genes
Block 5:	Peri-trauma responses
Block 6:	Covariates

5.4 RESULTS

5.4.1 Utility of VR-trauma induction: Manipulation check

Across all mood reports, negative mood was found to significantly increase, whilst positive mood was found to significantly reduce. Furthermore whilst anxiety significantly increased post-VR, calmness reduced; illustrating that the VR-trauma induced negative mood change and arousal induction (See table 5.3).

Correlations between physiological and self-report (change scores) peri-traumatic measures showed that increased HR response during the traumatic sequence of the VR film, compared to the preceding portion of the VR scenario, was associated with an increased self-report of STAI ($r(77)=.28$, $p=.012$), anxiety($r(79)=.42$, $p<.001$)and low mood ($r(79)=.31$, $p=.005$). Dissociation during the VR film was associated with a reduced HR during the traumatic sequence of the VR film, compared to the preceding portion of the VR scenario ($r(78)=-.25$, $p=.028$) and in the trauma sequence compared to BL response ($r(78)=-.34$, $p=.002$). These findings provide support for the validity of the self-report measures used within this VR paradigm.

Table 5.3: Mean change in mood ratings from pre-VR to post-VR exposure

Mood variable	Pre-VR	Post-VR	*t*	*df*
Sad	.92 (1.26)	2.8 (2.38)	-7.42***	83
Happy	7.4 (1.56)	5.49 (2.08)	9.46***	83
Anxious	1.99 (2.14)	3.87 (2.63)	-6.9***	83
Depressed	.61 (1.09)	1.58 (1.78)	-5.29***	83
Calm	7.54 (1.80)	5.47 (2.17)	9.15***	83
Hopeless	.69 (1.05)	1.68 (2.03)	-4.51***	83
Angry	.51 (0.90)	1.72 (2.01)	-5.55***	83
STAI-S	30.04 (7.24)	40.7 (10.81)	-10.8***	82

Note. ***= p<.001. Standard deviations appear in parenthesis below means

5.4.2 Emotion modulation of startle responses

The following analysis will investigate the effects of emotional valence of startle stimuli and startle foreground images on startle responses, addressing research question 1 and hypothesis 1:

Q1: Are affective and electrophysiological startle mechanisms sensitive to trauma versus neutral valence effects following exposure to a virtual reality trauma?

> *H1: Affective and reflex EMG startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli.*

No significant trial effect was found for startle related SC magnitude (F(1,81)=1.7, p=.196), SC habituation (F(1,81)=.083, p=.774), HR amplitude (F(1,79)=.032, p=.859), EMG magnitude

(F(1,81)=1.68, p=.199) and EMG habituation (F(1,81)=0.027, p=.871); illustrating that physiological and reflex eye-blink startle responses showed no emotion related modulation.

Analysis of EEG responses showed a significant trial type effect for startle specific PCA components (F(1,82)=5.91, p=.017) and ERP onset latency (F(1,82)=3963.83, p<.001). These effects were superseded by significant interaction effects of component by trial type on startle PCA components (F(1,82)=3548.01, p<.001) and region by trial type for ERP onset latencies (F(1,82)=5.78, p=.018). Post hoc analysis illustrated increased P2 amplitudes were higher in response to trauma startle (M=1.06, SE=.097) compared to neutral startle (M=0.83, SE=.103) (F(1,82)=10.93, p=.001), whilst P3 amplitudes did not differ across neutral startle (M=0.75, SE=.09) and trauma startle stimuli (M=0.70, SE=.096) (F(1,82)=0.45, p=.505). An earlier time of startle ERP onset latency was found on trauma startle (M=15.15, SE=.112) compared to neutral startle (M=15.38, SE=.125) in both the frontal-posterior region and the parietal region (Trauma: M=315.03, SE=.282; Neutral: M=334.63, SE=.285); although the effect was found to be stronger in the parietal region (F(1,82)=4017.95, p<.001) than the frontal region (F(1,82)=7.58, p=. 007).

The order of the counterbalancing of trial type across blocks was found to have no effect on any of these measures apart from on SC habituation (F(1, 81)=4.36, p=.040) and HR amplitudes (F(1,79)=4.47, p=.038) for which a significant effect of order was present, hence prohibiting the interpretation of these measures in regards to the trial effects described above.

Post hoc analysis to explore significant order by trial interactions revealed that carryover effects across blocks were in the expected direction (see appendix 19 for means and F values), with higher responses on the trial type which constituted the first block and lower responses on the trial type which constituted the second block (i.e. natural habituation independently of trial effects), on all measures expect for HR amplitude. Heightened neutral HR responses (M=2.74, SD=.572) compared to trauma HR responses (M=2.57, SD=.547) were found when the neutral startle block was presented before the trauma block (F(1,41)=7.54, p=.009) and no differences in HR responses across neutral (M=2.36, SD=.517) and trauma (M=2.51, SD=.455) blocks were found when the trauma startle block was presented before the neutral block (F(1,38)=3.05, p=.089).

5.4.3 Prediction of startle responses by individual differences

The following analysis will investigate the predictive influences of individual differences on startle responses, addressing the following research questions and hypothesis:

Q2: What are the predictive effects of pre-trauma individual differences on startle responses?

H2: Pre-trauma anxiety related personality traits and stressful life events will be associated with elevated autonomic physiological startle responses

H3: NPS A allele will be associated with increased startle eyeblink responses

Q 3: What are the predictive effects of peri-trauma individual differences on startle responses?

H4: Peri-traumatic dissociation will be negatively associated to startle responding

5.4.3.1 Data reduction: Zero order correlations

Exploratory correlations, run on the variables illustrated in table 5.4, showed that there were no problems with multicollinearity between the predictor variables, with all pre- and peri-trauma predictors showing inter correlations of <0.7. A number of outcome measures showed inter-correlations and Cronbach's alphas of >.07 and reduced to core outcome variables as follows:

PCA startle component scores in the frontal posterior mid region were found to be moderately negatively correlated with one another on trauma ($r(82)=.56$, $p<0.001$) and neutral trials ($r(82)=-.666$, $p<0.001$). Further analysis of Cronbach's alpha illustrated that both components tap one unified, but opposing, factor; with Cronbach's alpha values of .72 on trauma trials and .79 on neutral trials. As such, component difference scores were calculated by taking away the late component from the early component; higher difference scores therefore represent greater responses on the late component compared to the early component (i.e. a generally later response to the startle stimuli). Component scores in the parietal mid region had moderate negative correlations, however Cronbach's alpha values were <.7 for neutral ($r(82)= .5$, $p<0.001$; $\alpha = .66$) and trauma sounds ($r(82)= .49$, $p<0.001$; $\alpha = .65$), therefore the individual component scores (early and late) were retained in this form for further analysis of potentially differential predictor variables.

In addition inter-correlations and Cronbach's alphas of >.07 were found across valence types for EMG responses across neutral and trauma sounds on both magnitude (r(81)= .8, p<.001; α = .89) and habituation scores (r(81)= .71, p<.001; α = .83), parietal PCA component scores across the neutral and trauma conditions, for both the early (r(82)= .78, p<.001; α = .88) and late component (r(82)= .76, p<.001; α = .86), frontal PCA component difference scores across the neutral and trauma conditions (r(82)= .73, p<.001; α = .84) and frontal ERP onset latencies across the neutral and trauma conditions (r(82)= .74, p<.001; α = .85). Interestingly, although peripheral measures of HR and SC were differentially influenced by sound valence, these results show that, at the neurological level and in terms of startle eye blink responding, sound valence has little effect. As such, these EMG and neurological outcome measures were averaged to create single items independently of valence, thus representing general electromyographic and electrophysiological responding to startle sounds.

EMG habituation and magnitude scores also showed high correlations across neutral trials (r(81)= .9, p<.001), trauma trials (r(81)= .9, p<.001), indicating that, as expected, the greater the magnitude of responding the longer it takes to desensitize to the startle probes. Both habituation and Magnitude scores were retained for regression analysis as individual items, but similar patterns of predictive associations were expected.

Exploratory zero order correlations were ran on the final variables illustrated in table 5.4.

Table 5.4: Chapter 5 variables of interest. Summary of the risk and resilience factors pre- peri- and post-trauma and analogue symptom measures.

PREDICTORS: Pre-trauma	PREDICTORS: Peri-trauma	OUTCOME: Phenotypic symptom Measures Stress sensitization: Startle
PERSONALITY: ▪ STAI-T ▪ ASI ▪ HA **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events **GENE POLYMORPHISMS:** ▪ 5HTTLPR ▪ BDNF ▪ D2 Taq1 ▪ NPS ▪ ADORA 2B **GENDER** *COVARIATES:* ▪ *Mini neuropsychiatric assessment (MINI)* ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)* ▪ *Drug use* ▪ *Computer gaming* ▪ *Beck depression inventory (BDI)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ SAM arousal difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**VALENCE INDEPENDENT STARTLE RESPONSE:** ❖ ERP ▪ FrPm Component difference waves ▪ Prm early Component ▪ Prm late Component ▪ FrPm onset latency ❖ EMG ▪ Response magnitude ▪ Habituation **NEUTRAL STARTLE RESPONSE::** ❖ ERP ▪ Prm onset latency ❖ HR ▪ Response amplitude ❖ SCR (range correct) ▪ Response magnitude ▪ Habituation **TRAUMA STARTLE RESPONSE:** ❖ ERP ▪ Prm onset latency ❖ HR ▪ Response amplitude ❖ SCR (range correct) ▪ Response magnitude ▪ Habituation

P3 component scores in the parietal-mid region showed no zero order correlations with the predictor variables; neither did HR amplitudes on trauma trials or SC magnitudes on neutral trials. These findings suggest that individual differences risk factors may be better differentiators of HR responses when observing over-generalized responses to non-trauma related sounds/stimuli, rather than responses to trauma related stimuli themselves; with the inverse true for SC responses, which were only predicted on trauma trials.

5.4.3.2 EEG: PCA components

5.4.3.2.1 Correlations

In the parietal-mid region, P2 component amplitudes were associated with increased HR during the trauma sequence (compared to the preceding VR sequence) ($r(79)=.22$, $p=.046$). In the frontal posterior-mid region, P3 component amplitudes compared to P2 component amplitudes, were associated with increases in the number of stressful life events experienced in the last year($r(75)=.25$, $p=.032$).

5.4.2.1.2 Regressions

Although HR response to the VR trauma was associated with P2 ERP component amplitudes in the parietal-mid region, a predictive model of this association failed to reach significance once an outlying case was brought down to the one unit above the next smallest value in the distribution (Table 5.5).

Table 5.5 Regression analysis predicting P2 ERP component amplitudes in the parietal-mid region

	B	*SE B*	β
Constant	1.08	0.17	
HR change VR	0.07	0.04	.21

Note R^2= .045 (p=.058). *p<.05. **p<.01. ***p<.001

Component scores in the Fontal posterior-mid region, were predicted by stressful life events in the last year, however the amount of variance explained was low (6%). Increased P3 ERP responses compared to P2 ERP responses towards startling sounds was predicted by a higher number of stressful life events in the last year (Table 5.6).

Table 5.6 Regression analysis predicting P3 compared to P2 ERP component amplitudes in the frontal-posterior-mid region

	B	*SE B*	β
Constant	-2.81	0.77	
SRRS	0.007	0.003	.245*

Note R^2= .06 (p=.03). *p<.05. **p<.01. ***p<.001

5.4.3.3 ERP: Onset latency

See chapter 4 section 4.2.1.3.2.1 for the rationale behind this analysis approach and see figure 4.8 for an illustration of the startle ERP.

5.4.3.2.1 Correlations

In the parietal-mid region ERP onset latency values on trauma trials were associated with NPS ($r(82)=.22$, $p=.043$), reduced state anxiety during VR ($r(80)=-.237$, $p=.032$), and playing computer games ($r(62)=.25$, $p=.045$), and ERP onset latency values on neutral trials were associated with a reduction in state anxiety during the VR film.

In the frontal posterior-mid region ERP onset latency values were associated with increases in the number of stressful life events experienced in the last year($r(75)=.34$, $p=.003$, respectively).

5.4.2.1.2 Regressions

A model of ERP onset latency in the parietal mid region on trauma startle trials, including computer games as a predictor was not found to be significant, with computer gaming not contributing significantly to the model. A model containing NPS and state anxiety towards VR exposure explained 8% of the variance in parietal mid ERP onset latency scores, however both NPS and state anxiety failed to individually contribute significant predictive value (Table 5.7); although NPS approached significance (p=.051) when entered into the model alone at step one, suggesting a possible association between homozygote A allele expression and an earlier startle processing in the parietal mid brain region.

Table 5.7 Hierarchical regression analysis for biological and ecological pre-trauma factors predicting ERP onset latency in the parietal mid region on trauma trials

	B	*SE B*	β
Step 1			
Constant	314.33	0.48	
NPS	1.17	0.59	.22
Step 2			
Constant	315.11	0.66	
NPS	0.87	0.61	.16
STAI_S	-0.05	0.03	-.19

Note R^2= .047 for Step1 (p=0.51); ΔR^2 =.033 for Step 2 (p=.094). Final model: R^2 =.08, p= .037 *p<.05. **p<.01. ***p<.001

The ERP onset latency in the parietal mid region on neutral trials were predicted by state anxiety during VR scenario, explaining 9.4% of the variance. An increase in anxiety during the VR predicted earlier startle processing in the parietal-mid region on neutral trials (Table 5.8).

Table 5.8 Regression analysis predicting ERP onset latency in the parietal mid region on neutral trials

	B	*SE B*	β
Constant	335.62	0.43	
STAI_S	-0.09	0.031	-.31**

Note R^2= .094 (p=.01). *p<.05. **p<.01. ***p<.001

A smaller number of stressful life events in the last year also predicted onset latency in the frontal posterior-mid region, explaining 11.2% of the variance (Table5.9).

Table 5.9 Regression analysis predicting ERP onset latency in the frontal-posterior mid region

	B	*SE B*	β
Constant	29.5	0.42	
SRRS	0.006	0.002	.34**

Note R^2= .112 (p=.003). *p<.05. **p<.01. ***p<.001

5.4.3.4 EMG: Magnitude and Habituation

5.4.3.4.1 Correlations

NPS was negatively associated with EMG magnitude (*r*(81)= -.23, *p*=.038) and habituation (*r*(81)= -.29, *p*=.008) and peri-traumatic HR during the trauma sequence was positively associated with magnitude(*r*(79)= .36, *p*=.001) and habituation scores (*r*(79)= .34, *p*=.002).

EMG magnitudes were additionally negatively associated with cigarette smoking prior to the experiment (*r*(81)=-.24, *p*=.031) and with drinking alcohol in the last 24 hours(*r*(81)=-.24, *p*=.032). Contrary to expectations EMG habituation scores were negatively associated with self-report peri-traumatic arousal (*r*(79)=-.225, *p*=.044).

5.4.3.4.2 Regressions

Startle EMG magnitudes were predicted by NPS and HR Change from BL to VR trauma exposure, with models accounting for recent cigarette smoking and alcohol use not adding significant predictive value to the model; therefore the final model does not include these covariates (Table 5.10). The NPS A allele together with an increase in HR during the VR, predicted increase EMG startle responses on all trials; with the overall model explaining 16.5% of the variance in EMG magnitudes.

Table 5.10: Hierarchical regression analysis for biological pre-trauma factors and peri-traumatic responses predicting reflex EMG startle magnitudes

	B	*SE B*	β
Step 1			
Constant	00.83	0.06	
NPS	-0.18	0.08	-.25*
Step 2			
Constant	0.81	0.06	
NPS	-0.14	0.08	-.20
HR diff	0.02	0.01	.32**

Note R^2= .063 for Step1 (p=.024); ΔR^2 =.102 for Step 2 (p=.003). Final model: R^2 =.165, *p*= .001 *p<.05. **p<.01. ***p<.001

The number of trials to startle EMG habituation was also predicted by NPS and BL to VR HR change, together with VR self-reported arousal (Table 5.11). The model accounted for 26.2% of the variance in EMG habituation, with individuals expressing the NPS A allele, showing an increased HR response to the VR trauma and reduced self-reported arousal showing slowest habituation of EMG startle responses.

Table 5.11: Hierarchical regression analysis for biological pre-trauma factors and peri-traumatic responses predicting reflex EMG startle habituation

	B	*SE B*	β
Step 1			
Constant	40.77	3.88	
NPS	-13.83	4.73	-.32**
Step 2			
Constant	46.68	4.31	

NPS	-11.69	4.42	-2.7**
HR difference	1.12	0.34	.33**
SAM arousal	-3.92	1.36	-.29**

Note R^2= .10 for Step1 (p=.005); ΔR^2 =.162 for Step 2 (p=.001). Final model: R^2 =.262, p< .001 *p<.05. **p<.01. ***p<.001

5.4.3.5 HR Amplitude

5.4.3.5.1 Correlations

HR amplitudes were found to be predicted by predicted by individual difference variables only on neutral trials, suggesting that over-generalised HR responding is a better differentiator of risk. HR amplitudes on neutral trials were predicted by a number of pre and peri-trauma factors including negative associations with drug use (r(79)=-.282, p=.011) and HA (r(79)=-.230, p=.039), and positive relationships with ASI (r(78)=.238, p=.033), ADRA2B (r(79)=.225, p=.043) , peri-traumatic HR during the trauma sequence compared to BL (r(78)=.375, p=.001) and compared to the preceding VR sequence (r(78)=.227, p=.043).

5.4.3.5.2 Regressions

The model accounting for the largest amount of variance in HR startle responses, on neutral trials, included ASI, ADORA2B and HR during VR trauma compared to BL responding; this model explained 21.8% of the variance in startle HR responses (Table 5.12). Carrying the s allele on ADRA2B and experiencing increased HR responses towards the VR trauma sequence predicted increased HR responses on neutral startle trials. Although ASI did not predict startle HR responding at any stage of the model, peri-traumatic HR added significantly to the predictive power of the model in the final block, with pre-trauma individual differences alone not illustrating predictive associations.

Table 5.12: Hierarchical regression analysis for ecological and biological pre-trauma factors and peri-traumatic responses predicting HR startle amplitudes

	B	*SE B*	β
Step 1			
Constant	2.07	0.26	
ASI	0.12	0.01	.21

Step 2			
Constant	1.81	0.31	
ASI	0.01	0.01	.20
ADRA2B	0.18	0.12	.17
Step 3			
Constant	1.73	0.29	
ASI	0.01	0.01	.19
ADRA2B	0.27	0.11	.25*
HR change	0.03	0.01	.39***

Note R^2= .043 for Step1 (p=.068); ΔR^2 = .030 for Step 2 (p=.118); ΔR^2 = .145 for Step 3 (p<.001). Final model: R^2 =.218, *p*< .001 *p<.05. **p<.01. ***p<.001

5.4.3.6 SC: Magnitude and habituation

5.4.3.6.1 Correlations

On neutral trials SC habituation was related to peri-traumatic HR during the trauma sequence(*r*(79)=.24, *p*=.034).

On trauma trials SC habituation was associated with gender(*r*(81)=.3, *p*=.006), peri-traumatic SC in the trauma sequence (*r*(81)=.28, *p*=.011) and change in SC from VR viewing to trauma specific sequence (*r*(81)=.23, *p*=.04). Magnitude was positively associated to gender (*r*(81)=.42, *p*<.001), peri-traumatic SC in the trauma sequence compared to BL (*r*(81)=.3, *p*=.006) and change in SC from VR viewing to trauma specific sequence (*r*(81)=.23, *p*=.037), and negatively associated with ASI (*r*(80)=-.26, *p*=.019).

5.4.3.6.2 Regressions

SC habituation on neutral trials was predicted by HR responding in the VR trauma sequence compared to BL (Table 5.13). An increase in HR trauma responding predicted a greater number of trials to habituation of SC responding on neutral startle trials, however the total amount of variance explained was low (5.5%).

Table 5.13: Regression analysis predicting SC startle habituation on neutral trials

	B	*SE B*	β
Constant	12.71	1.19	
HR change	0.41	0.19	.24*

Note R^2= .055 (p=.034). *p<.05. **p<.01. ***p<.001

Gender and peri-traumatic SC responding (compared to BL and to pre-VR immersion) explained 17.2% of the variance in SC habituation on trauma trials. Blockwise modelling, however, illustrated that peri-traumatic SC responding did not predict slower habituation of SC on trauma startle trials, over and above that already predicted by male gender. As such gender was the only significant predictor of SC habituation profiles (Table 5.14).

Table 5.14: Hierarchical regression analysis for biological pre-trauma factors and peri-traumatic responses predicting SC startle habituation on trauma trials

	B	*SE B*	β
Step 1			
Constant	3.88	3.24	
Gender	6.21	2.21	.30**
Step 2			
Constant	1.45	3.27	
gender	6.35	2.17	.31**
SC change	5.76	4.81	.16
SC difference	9.66	7.61	.17

Note R^2= .089 for Step1 (p=.006); ΔR^2 =.082 for Step 2 (p=.024). Final model: R^2 =.172, *p*= .002 *p<.05. **p<.01. ***p<.001. Gender = females coded '0' and males coded '1'

30.8% of the variance in startle SC magnitudes on trauma trials was predicted by gender, ASI and peri-traumatic SC responding. Male gender, lower ASI scores and larger SC responses during the VR trauma sequence compared to the pre-trauma VR sequences, all significantly predicted greater SC magnitudes towards trauma related startling sounds (Table 5.15).

Table 5.15 Hierarchical regression analysis for biological and ecological pre-trauma factors and peri-traumatic responses predicting SC magnitudes on trauma trials

	B	*SE B*	β
Step 1			
Constant	0.09	0.23	
Gender	0.07	0.02	.43***
Step 2			
Constant	1.62	0.04	
Gender	0.06	0.02	.40***
ASI	-0.002	0.001	-.21*
Step 3			
Constant	0.14	0.04	
Gender	0.07	0.02	.43***
ASI	-0.002	0.001	-.22*
SC difference	0.13	0.04	.29**

Note R^2= .18 for Step1 (p<.001); ΔR^2 = .045 for Step 2 (p=.036); ΔR^2 = .082 for Step 3 (p=.003). Final model: R^2 =.308, *p*<.001. *p<.05. **p<.01. ***p<.001. Gender = females coded '0' and males coded '1'

5.5 DISCUSSION

This exploratory investigation aimed to elucidate the individual difference factors which predict differential electrophysiological emotion-modulated startle responses following VR-trauma exposure, with the hope that this may illuminate potential risk and resilience factors in the development of hyperarousal PTSD symptoms. Importantly, the VR-trauma exposure was shown to induce negative mood and arousal and as such act as an effective stressor analogue of trauma exposure.

No evidence was found for the emotion-modulation of physiological startle responses, illustrating a lack of support for hypothesis 1. Across reflex eye-blink EMG magnitude and habituation and SC magnitude no significant differences were found between responses on N and T blocks. However, significant effects of the order of block presentation on HR amplitudes and SC habituation prohibited the interpretation of the non-significant trial effects on these measures. These results do not support the hypothesis that startle responding would be

facilitated by trauma picture contexts and trauma sound contents. Furthermore, they are inconsistent with the emotional hypothesis of startle modulation proposed by Lang, Bradley & Cuthbert (1990) that neutral and positive foregrounds inhibit the startle response, whilst negative foregrounds augment (Bradley, Cuthbert & Lang, 1990). There are a number of possible interpretations of these findings, first the VR-trauma may not have induced sufficient negative affect to differentiate it from the neutral town city context; however self-reported mood change did illustrate significant negative mood induction as a result of Iraq VR exposure making this interpretation unlikely. Secondly due to the neutral context photograph being a picture of the local town centre, it is possible that some participants had non-neutral, or even negative, associations with the 'neutral' foreground photograph. However in light of the fact that the gunshot and car horn sounds themselves differ in their inherent associations[10], independently of individuals associations with the foreground pictures, emotion-modulation of the startle responses would have been expected for Lang et al's (1990) hypothesis to hold true. Interestingly however a recent study of amygdala activation towards emotional stimuli found that whilst activation is increased towards negative picture compared to neutral ones in control subjects, no difference in activation were apparent for individuals with PTSD (Brunetti et al., 2010). Therefore it is possible that the VR-trauma exposure, prior to the startle task, resulted in an emotionally independent general excitation of the startle response.

However early (i.e P2) startle ERP components and startle ERP onset latency times were shown to be emotionally modulated. Analysis of startle components showed that P2 amplitudes were increased for trauma sounds than neutral sounds and P3 amplitudes showed no emotional modulation; such early ERP effects have been posited to reflect the sensory encoding by implicit selective attention mechanisms (Schupp, Markus, Weike & Hamm, 2003). However early (i.e P2) startle ERP components and startle ERP onset latency times were shown to be emotionally modulated. Analysis of startle components showed that P2 amplitudes were higher for trauma sounds than neutral sounds and P3 amplitudes showed no emotional modulation; such early ERP effects have been posited to reflect the sensory encoding by implicit selective attention mechanisms (Schupp, Markus, Weike & hamm, 2003). Although these findings do not support previous arousal related modulation of the startle P3 (Cuthbert et al., 1998; Schupp et al., 1997), the current findings of trauma enhanced P2 are in line with research showing that early positive ERP waveforms with a peak latency of <250ms are augmented towards negative stimuli (Carretie, Hinojosa, Martin-Loeches, Mercado & Tapia,

[10] A gun-shot is an unusual sound, which is likely to be associated with imminent threat and mortality; whereas a car-horn is a more everyday occurrence generally associated with more routine events.

2004; Smith, Cacioppo, Larsen & Chartrad, 2003) and findings that P2 amplitudes specifically are enhanced towards negative pictures compared to neutral or positively valenced pictures (Olofsson & Polich, 2007); although it should be noted that some studies have found enhanced P2 towards positive pictures compared to negative and neutral pictures (Amrhein, Muhlberger, Pauli & Wiedermann, 2004), suggesting that arousal or other cognitive processes may also be implicated. In addition the current findings are of interest in light of meta-analytic findings that acoustic P2 amplitudes correlate with PTSD symptom severity (Karl et al., 2006) and PTSD patients carrying the 5HTTLPR s allele illustrate increased startle P2 responses; the s allele is related to low serotonin receptor transcription efficiency and has been implicated in increased amygdala activation towards emotional and fearful stimuli (Hariri et al., 2002; Wurman, 2005; Munafo, Brown & Hariri, 2008).

Interestingly whilst previous studies have found no regional differences in the emotional-modulation of positive ERP amplitudes (Cuthbert et al., 2000; Amrhein et al., 2004), within the current study the onset latency of startle ERP responses occurred earlier towards trauma startle than neutral startle in both regions of interest, with a stronger emotional effect in the parietal region; suggesting that onset latency ERP analysis may be more sensitive to regional differences in emotional processing. These findings support the assumption that the emotional content of stimuli are processed to a greater extent in the parietal region, in line with Heller's model of the neural substrates of emotional functions (Heller, 1986; 1990; 1993; 1998). Within this model the right parietotemporal region is held as responsible for processing and interpreting emotional information and controlling the level of autonomic arousal, with the frontal region posited to respond to the experiential aspects of emotion and emotional valence; such findings have been experimentally supported (Heller, 1997) and are consistent with clinical findings in depression and anxiety (for review, see Heller, 1998). The current finding of earlier processing and implicit attention allocation towards trauma stimuli, especially in the parietal region, adds support to Heller's model implicating the parietal cortex in early emotional processing.

Correlation analysis, across valences within measurements, illustrated that eye-blink startle, and electroencephalographic responses (with the exception of parietal time of onset latency scores), produced highly comparable[11] startle responses across different emotional picture and sound contexts. HR and SC responses, and response habituation, however were not highly correlated. These findings show that HR and SC startle responses, although not significantly

[11] Tapping one unified factor, as illustrated by high correlations and internal consistency across valences

emotionally-modulated, do result in inherently different responses towards neutral and trauma sounds. Regression analysis highlighted both pre-trauma and peri-trauma individual difference factors as important factors in the prediction of a range of electrophysiological startle responses, following exposure to a VR-trauma. Peri-traumatic HR response was the only consistent predictor across a number of different startle measures, with increased peri-traumatic HR showing associations with increases in startle related reflex eye-blink, HR response and SC habituation. The importance of peri-traumatic HR supports previous findings that suggest peri-trauma variables are key in the prediction of PTSD symptom development (Brewin et al., 2000; Ozer et al., 2003; Trickey et al., 2012).

Earlier parietal ERP responses on neutral trials were predicted by increased peri-traumatic anxiety. Whilst later frontal ERP responses and increased P3 ERP compared to P2 ERP component amplitudes were predicted by a higher number of stressful life events in the last year. This profile of predictive associations adds further support for the applications of Heller's model to the modulation of ERP startle responding, illustrating that faster parietal processing of neutral startle sounds is predicted by increased arousal related peri-traumatic responses; highlighting the role of arousal in parietal responding. The association between stressful life events and slower startle processing suggests a role of stress inoculation processes in startle attentional allocation and encoding, where individuals who have experienced a high number of stressful life events in the last year appear to allocate reduced early attentional resources to the processing of startling stimuli suggesting that such stimuli carry a reduced emotional or arousal evaluation (Cuthbert et al., 2000), compared to individuals who have experienced a low number of prior stressful events, who show earlier allocation of attentional processes for startle stimulus encoding suggesting a heightened emotional or arousal evaluation. Furthermore, the current study, and previous studies (Madina et al., 2001), failed to find an association between chronic stressors and startle reflex modulation in measures of reflex eyeblink responding; suggesting that more neutrally sensitive measures of attention and encoding are needed to illustrate and investigate the effects of stress inoculation on startle modulation. Interestingly, cortisol (a stress related hormone) is believed to weaken the trauma memory trace, with low dose administration of glucocorticoids showing improvements in memory re-experiencing symptoms in PTSD (Aerni et al., 2004; Schelling et al., 2006; de Quervain & Margraf, 2008). These findings support the current stress inoculation effects, illustrating that the speed of attentional allocation and encoding towards adversive startle stimuli is reduced when a higher number of prior stressful life events have been experienced in the last year and suggesting that glucocorticoids could also have adaptive effects on startle

processing in PTSD treatment; although stress inoculation effects appear to only be at a neural level with no effects on reflex EMG startle responses.

Increased reflex eye-blink magnitudes and slower habituation were predicted by both carrying the neuropeptide-S (NPS) A allele and experiencing heightened peri-traumatic autonomic responding (as measured by HR). Surprisingly EMG habituation profiles were additionally predicted by a reduction in peri-traumatic arousal, illustrating a de-coupling between self reported arousal and HR responses; such a de-coupling has been previously associated with alexithymic traits (Martinez-Sanchez, Ortiz-Soria & Ato-Garcia, 2001). These results are consistent with previous findings illustrating that individual differences influence eyeblink startle potentiation (Cook, Hawk, Davis & Stevenson, 1991; Corr et al., 1997); although pre-VR-trauma personality traits were not found to be associated with eyeblink startle response modulation in this study, other studies have also failed to find associations with personality variables (Nitschke et al., 2002). The current results also support the genetic relationship with startle response facilitation (Zhang et al., 2011) and extend previous reports that the NPS T allele blocks startle eyeblink responding (Fendt et al., 2010; Okamura et al., 2011; Lennertz et al, 2012), by illustrating that inversely the NPS A allele augments startle eyeblink responding. The current findings support hypothesis 3 and implicate the NPS A allele with increased reflex startle responses and the T allele with reductions in reflex arousal responses, further investigation of the exact nature of this is warranted in light of the previous research implicating the T alelle as a risk factor for panic disorder (Domschke et al., 2010).

Startle HR responses were not found to be predicted by individual differences on trauma startle stimuli, however neutral startle responses were associated with trait, genetic and peri-traumatic factors. This is in line with findings that generalised fear potentiation (i.e. in neutral contexts), as illustrated by increased amygdala activation, is more predictive of PTSD symptomology (Brunetti, 2010).The final model explaining the highest amount of variance in HR startle responding, illustrated a predictive relationship between increased anxiety sensitivity, carrying the ADRA2B s allele and heightened peri-traumatic HR responses. Findings support previous research showing an association between ASI and PTSD symptomology (Feldner, Lewis, Leen-Felder, Schnurr, Zvolensky, 2006; Feldner, Zvolensky, Schmidt & Smith, 2008), although as ASI failed to reach significance within the model it lacks a predictive relationship in itself. Interestingly only after adjusting for the strong effects of peri-traumatic HR responses was it possible to see the smaller genetic influences of ADRA2B on startle HR magnitudes. The influences of peri-traumatic HR responding on later startle HR responses are less noteworthy that its associations with other startle response measures, as it seems logical

that individuals who have elevated HR responses in an adversive trauma encounter would also have elevated HR responses in an adversive startle paradigm. Previous work has as yet only implicated ARDA2B s allele in enhanced emotional memory formation (Rasch et al, 2009) with no effects on arousal (de Quervain et al., 2007), the findings of the current study illustrate that the s deletion variant of this gene may also impart risk for increased defence responding (elevated cardiovascular responding) towards contextually threatening stimuli (neutral startle). However, as effects of the order of counterbalanced valence presentation were apparent on HR amplitude analysis, in line with previous studies showing cardiac order effects in startle responses, the current cardiac predictive effects and subsequently described SC habituation regression models (which also illustrated order effect) must be interpreted with caution, and replication in a within subjects design is called for.

Increased SC magnitudes and habituation on trauma trials were both predicted by male gender and having increased peri-traumatic HR responses. These findings illustrate that an increased cardiac defence response peri-traumatically predicts increased arousal towards startling stimuli post trauma. The finding that male gender predicts increased SC startle responding is in contrast to previous literature illustrating increased reflex startle responses in females (Quevedo et al., 2009). Interestingly however, in the 2007 Adult psychiatric morbidity in England survey (McManus, Meltzer, Brugha, Bebbington, Jenkins, 2009), although overall prevalence rates of adulthood PTSD were greater in women than in men, assessment of current PTSD based on lifetime prevalence showed an increased occurrence of current PTSD in males over females, in the 16-24 age range only (although it is not reported whether this difference is significant). The age range of the current sample was between 18-32 years, with a mean age of 20.5 years. It is possible that the age of the population sampled resulted in the findings of a male risk towards increased SC startle responding. Furthermore, the current finding of reduction in SC startle responses in females is interesting in light of the previously reviewed study of female PTSD patients with Type II traumas who showed inhibition of reflex startle responding (Medina et al., 2001). An additional predictor of SC habituations within the current study was found to be reduced trait anxiety sensitivity. Although ASI was expected to be associated positively with PTSD symptomology (Feldner et al., 2006, 2008; Leen-Feldner et al., 2008), previous studies have shown that trait ASI scores may alter in accordance with PTSD symptom development (Marshall et al., 2010). The current findings therefore suggest, that whilst post-trauma ASI scores may be predictive of PTSD development (Olatunji & Wolitzky-Taylor, 2009; Naragon-Gainey, 2010), pre-pathology ASI scores appear to be associated with improvements in startle SC habituation speeds.

The finding that individual difference variables including genetic factors and peri-traumatic responses, predict the exagerated startle responding supports the view of startle responses as a stable and robust characteristic (Fendt & Koch, 2013) and implies that individual differences, which can be seen following a mild stressor (VR-trauma), may increase susceptibility to the development of a PTSD like hyperarousal symptom profile post-trauma. The variety of individual difference variables that predicted different electophysiological startle responses, illustrates the need to include and measure a range of outcome measures when investigating startle modulation. Although a number of individual difference variables were found to be predictive of startle response profiles the results do not fully support hypothesis 2, with stressful life event exposure predicting slower electrophysiological responses towards startling sounds; such findings are indicative of a stress inoculation mechanism as discussed previously. In addition, whilst peri-traumatic HR responses were consistently associated with exaggerated startle responses, hypothesis 4 was not supported with a lack of evidence for an association between peri-traumatic dissociation and a reduction in hyperarousal as found within previous investigations (Griffin et al., 1997; Lanius et al., 2010; Ginzberg et al., 2006). As the measure of dissociation used within the current study was an experimenter-designed questionnaire, which tapped a number of items which may have been more related to VR related engagement rather than PTSD related dissociation, it is possible that hypothesis 4 may have been supported were a standardised questionnaire used to measure dissociation. Hypothesis 4 merits re-investigation using a dissociation questionnaire that has shown established reliability and validity, such as the clinical administered dissociative states scale (Bremner et al., 1998) or the peritraumatic dissociative experiences questionnaire (Marmar, Weiss & Metzler, 1997).

Overall the results of this study illustrate that arousal related peri-traumatic responses explain the largest amount of variance in electrophysiological and peripheral startle responding, supporting cognitive (Brewin, 1996,2001, 2010; Ehlers & Clark, 2000) and emotional processing (Foa et al., 1989, 1993, 1998; Lanius, 2010) models of PTSD development which hold peri- and post-trauma processing as of greatest importance in the prediction of PTSD symptomology. However a number of biological (gender and genetics) and ecological (stressful life events and anxiety sensitivity) also illustrated predictive relationships with startle responses, suggesting that the proposition encompassed by diathesis stress conceptualisations of PTSD (McKeever & Huff, 2003; Elwood et al., 2009), that both biological and ecological factors (diatheses) are integral to the explanation of pathology, would be useful to incorporation into existing PTSD models. Findings, in regard to the main thesis hypothesis (see section 2.9) will be discussed further within the general discussion chapter 9.

5.5.1 Limitations and future directions

As discussed previously the homogeneity of sample, in terms of age and educational status, reduces conclusions that can be drawn for the current results and may be responsible for the finding of male gender as a risk factor of increased SC responses and habituation. Furthermore one cannot rule out the possibility that the neutral foreground and sound may have had non neutral connotations for some participants. Although individuals with PTSD diagnosis were excluded, some individuals within the sample may have been involved in or witnessed car accidents which could have influenced their interpretation of the neutral car horn sound as traumatic and/or negative, whilst others may have negative associations with the neutral foreground picture as it was of a real world place that was familiar to the participants (the local town centre). If a comparable neutral VR film had been presented and used to make up the neutral foreground, this would have allowed for control over participants association with both foregrounds.

To allow for increased immersion within the contexts, the emotional modulation of startle responding was investigated in two separate 15 minute blocks counterbalanced across participants. However it is possible that habituation of startle responding occurred during block one and resulted in a dramatic reduction in startle responding on block two, independently of the emotional content/context of block two. The counterbalanced study design, and potential for habituation prior to the second differently valenced block, means that trauma and neutral distinctions would only therefore be visible via between subjects differences in responding to block one (depending on whether individuals who were presented with the trauma first showed greater responses than those presented with the neutral block first). This could have accounted for the apparent lack of emotional modulation of startle responses. The known heterogeneity in individuals startle responses means that emotional modulation is less likely to be visible in a between subjects comparison, which will be more influenced by individual differences in baseline startle. Future studies should alternate randomly between trauma and neutral trials within blocks, in a within subjects design, to allow for clearer elucidation of the emotional modulation of the startle response within individuals without current issues of habituation.

Within this study electroencephalographic startle responses were only analysed from the mid brain scalp topographies due to their known associations with startle ERP responses. However this theory driven focus did not allow for the investigation of whether the regional differences which were found to be in line with Heller's model of neural substrates of emotional functions

also supported the hemispheric aspects of Heller's model; of right sided dominance for unpleasant valences. Future studies should explore such hemispheric specificities in regional ERP startle responses and follow up the current findings, of regional modulation of emotional and arousal related startle processing, to explore pathological associations in clinical populations and change in response to therapy. Future avenues for investigation also include the replication of the emotion-modulated startle ERP onset and P2 amplitude findings.

As current findings indicate that PTSD-related pre and peri-trauma risk factors are predictive of startle related hyperarousal responses post-trauma, this leads to the question of whether such predictive risk associations are set in stone or can be modified by post-trauma emotion regulation strategies to result in adaptive changes. Future studies should explore whether manipulation of emotional regulation strategies can modulate reflex and electrophysiological startle responding.

5.5.2 Conclusion

Results illustrate that both pre and peri-trauma factors are important in the prediction of reflex and electrophysiological startle responses, with peri-traumatic HR responses showing high predictive associations with both reflex and autonomic startle responses. Interestingly, without accounting for peri-traumatic responses the importance of more subtle pre-trauma factors, such as influences of genetics, may not become apparent. Although no consistent profile of genetic risk factors was found between startle response measures, NPS a allele was found to be predictive of reflex eyeblink magnitudes and habituation and in neutral contexts ARRA2B s allele was predictive of increased HR responding. These findings illustrate the genetic component of startle responding and highlight the need for further work to elucidate pathological associations and epigenetic mechanisms. Findings suggest that trait predictors of PTSD such as anxiety sensitivity may differ in their risk or protective effects via contrasting alterations in autonomic responding (i.e. startle HR and SC responses respectively). The association between psychosocial factors (i.e. life events) and electrophysiological responses highlights the importance of a multidisciplinary all encompassing model for the development of PTSD, and supports the application of diathesis stress models to PTSD. Across all post-trauma psychophysiological startle response measures investigated within the current study, the most consistent pattern of findings was that a heightened cardiovascular response during the VR-trauma exposure is predictive of post-trauma exaggerated startle responses towards ecologically valid startle sounds. Whilst other findings within this chapter are of importance as a source of preliminary data, they require further investigation and replication to avoid over-

interpretation and to rule out the possibility that they are simply the result of chance findings resulting from multiple comparisons. Peri-traumatic HR was however consistently found to be an important risk factor in the development of post-trauma hyperarousal responses; supporting previous analogue research which has illustrated the importance of peri-traumatic HR responses in predicting post-trauma phenotypic symptom expression (Holmes et al., 2004).

6 PRE- AND PERI-TRAUMATIC RISK AND RESILIENCE FACTORS IN THE DEVELOPMENT OF PTSD-LIKE STRESSOR RELATED MEMORY DISTORTIONS IN AN ANALOGUE SAMPLE EXPOSED TO A VIRTUAL REALITY TRAUMA

6.1 ABSTRACT

Previous research points towards the importance of peri-traumatic responding in the development of PTSD, however clinical investigations are unable to adequately measure or account for such factors; even in prospective studies where peri-traumatic reactions are still inherently assessed retrospectively. This study employs an analogue trauma design to explore the relative role of pre-trauma vulnerabilities and peri-traumatic reactions in determining PTSD phenotypic trauma memory distortions, in the acute post-trauma phase. A virtual reality scenario (Iraq World) was used to investigate the predictive capacity of peri-traumatic physiological reactions (HR, SCL) and mood responses in determining fragmented or disjointed trauma recall and distressing intrusive trauma memories, relative to the predictive contribution of previously documented PTSD related pre-trauma genetic, trait and psychosocial factors. Peri-traumatic responses were found to predict cued recall and intrusive trauma memories, and mediate the influences of previously reported pre-trauma vulnerabilities on cued recall accuracy and intrusion distress. Free recall accuracy and sequencing errors were predicted by female gender, psychosocial and genetic factors, whist cardiovascular intrusion responses were predicted by genetic factors alone. The present findings extend previous research by indicating that the respective risk imparted by pre and peri trauma factors differs depending on the way in which post-trauma symptoms are assessed. Whilst peri-traumatic arousal responses are important in predicting involuntary and cued retrieval, pre-trauma characteristics and genetic factors are key to the prediction of free recall distortions and physiological intrusion responses.

6.2 INTRODUCTION

Post-traumatic stress disorder is associated with a contrasting profile of memory distortions, with significant impairments in coherence and accuracy of voluntary memories on the one hand and increases in involuntary memory intrusions on the other (DSM-V, 2013). The frequency of trauma related intrusive memories and trauma recall fragmentation in the immediate post-trauma phase, has been associated with current (Laposa & Alden, 2003) and subsequent (Murray et al., 2002; Laposa & Alden, 2003; Schooler et al., 1999; Amir, Stafford, Freshman & Foa, 1998) PTSD severity; although the predictive capacity in relation to PTSD

diagnosis at 6 months has only been found to be between 8-9% for intrusions(Ehlers & Clark,2005; Michael et al., 2005) and 13% for memory disorganisation (Murray et al., 2002). However, the characteristics of intrusive memories, such as the associated distress, nowness and lack of context, have been shown to offer stronger predictions of PTSD development; explaining 43-51% of the variance in PTSD diagnosis at 6 months (Ehlers & Clark,2005; Michael et al., 2005). Intrusion distress has also been shown to be predictive of increased intrusion frequency at 9 and 12 months (Schooler et al., 1999). These findings highlight recall and intrusion related memory distortions and characteristics as important PTSD symptom measures, especially within analogue paradigms hoping to elucidate factors implicated in risk of PTSD development.

Patient studies have implicated a plethora of pre-trauma variables with PTSD pathology and symptom development; including emotional, psychological, environmental and biological vulnerability factors. A number of anxiety related traits have been associated with PTSD, including anxiety sensitivity (ASI) (Leen-Feldner et al.,2008; Feldner et al.,2006; Feldner et al.,2008), harm avoidance (Richman & Frueh, 1997; Gill, 2005) and trait anxiety (Gregrek et al., 1996). Previous exposure to traumatic (Brewin, 2000; Ozer et al., 2003) and stressful life events (Solomon et al.,1988; Scott & Stradling, 1994; Joseph et al., 2000) has been associated with PTSD pathology, with some studies illustrating that stressful life events prove more predictive of symptomology (Mol et al., 2005). Patient and animal research has implicated a number of anxiety related genetic polymorphisms, including BDNF Met allele (Frielingsdorf et al., 2008; Chen et al, 2006; Hashimoto, 2007; Yu et al., 2012), 5HTTLPR s allele (Hariri et al, 2002; Wurtman, 2005; Munafo et al.,2008; Lesch et al, 1996), NPS T allele in panic disorder (Domschke et al., 2010) and D2Taq1 T (Lawford et al., 2006); however mixed results exist across the literature with regards to the relative importance of BDNF, 5HTTLPR and D2Taq1 as endophenotypes of PTSD (i.e Broekman, Olff & Boer, 2007; Grabe et al., 2009; Rady et al., 2011) and research into NPS is in its infancy. Interestingly the ADRA2B polymorphism has been shown to relate directly to memory distortions post-trauma, with the short allele (deletion variant) associated with increases in intrusive recollections (de Quervain, et al.,2007).

The importance of peri-traumatic responses in the prediction of PTSD related memory distortions is highlighted by models of PTSD development (Ehlers and Clark, 2000; Brewin, 1996, 2001, 2010), which hold that differences in traumatic memory processing are key to the development of PTSD symptoms and pathology. Moreover, meta-analytic analysis has shown peri-trauma factors to have stronger effects on the PTSD development than pre-trauma factors in both adult (Brewin et al., 2000) and child (Trickey et al., 2012) samples. Negative peri-

traumatic emotional reactions have been related to heightened pathology (Ozer et al, 2002), peri-traumatic cognitive processing has been associated with disorganized memories and PTSD development (Halligan, Michael, Clark & Ehlers, 2003) and peri-traumatic dissociation has been related to heightened PTSD symptomology (Holeva & Tarrier, 2001; Engelhard et al., 2003). Gender may influence the relationship between vulnerability factors and PTSD development, with females being shown to have a stronger positive association between ASI scores and PTSD (Feldner et al., 2008)and peri-traumatic arousal being found to only predict PTSD development in males (Christiansen & Elklit, 2012). However, the investigation of the contribution of peri-traumatic responses to symptom development and pathology is retrospectively assessed within patient samples and may therefore be affected by developing symptoms, such as error prone subjective evaluations and inaccurate memories. Memory distortions are symptomatic of PTSD, and as such, controlled prospective investigation of the contribution of peri-traumatic arousal to such memory distortions is called for.

Controlled trauma exposure and measurement of peri-trauma responses is best achieved within analogue designs; which allow for the objective measurement of subsequent recall accuracy and coherence, without such factors confounding peri-traumatic data (as is the case in retrospective designs). A wide body of analogue research has illustrated that peri-traumatic processing can be effectively experimentally manipulated, with such manipulations resulting in alterations in phenotypic memory distortions. Data driven peri-traumatic processing has been shown to be associated with both increase in trauma-film related memory intrusions over 1 week of diary recording (Halligan et al., 2002; Laposa &Rector, 2012), and trauma-film memory inaccuracy and disorganisation tested at a one week follow up (Halligan et al., 2002). Furthermore, research has shown both emotional and physiological peri-traumatic responses to be associated with intrusion development. Intrusion frequency has been shown to be associated with peri-traumatic increases in anxiety (Laposa & Alden, 2008), negative mood (Davis & Clark, 1998), dissociation (Holmes & Bourne, 2008; Laposa & Rector, 2012) and reductions in HR responses; especially around intruding sequences (Folkins et al., 1968; Holmes et al., 2004). Reductions in HR towards visual stimuli have been associated with an orienting response, whilst increases have been associated with a defence response (Sokolov, 1963; Hare, 1973). The findings of Folkins et al. (1968) and Holmes et al (2004) suggest intrusion development is associated with a peri-traumatic orienting response, however further work is needed to clarify these initial findings. Moreover, research has yet to explore the impact of peri-trauma responses on recall distortions or intrusion severity and intrusion related autonomic reactivity. Orr et al., (1993) have shown that physiological arousal (HR and

SC) during trauma imagery is highly associated with PTSD diagnosis; these findings suggest that increased physiological responsiveness during intrusive trauma imagery may also be associated with pathological PTSD development. Investigation of the pre- and peri-trauma individual difference factors which can predict such physiological intrusion arousal responses would aid in elaborating the mechanisms by which physiological reactivity towards intrusions occurs.

Although the body of work by Holmes et al has made full use of the ability of analogue designs to allow for the manipulation of peri-traumatic processing and measurement of subsequent change in post-trauma memories, little research has employed non-manipulative approach. Simply examining the effect of pre-trauma individual differences and peri-trauma responses on the prediction of PTSD phenotypic memory distortions can also allow for elucidation of key predictive associations. Laposa and Alden (2008) investigated the relationship between pre- and peri-trauma vulnerability factors in the development of intrusive memories post-trauma and found that peri-traumatic anxiety mediated the relationship between pre-trauma traits (trait anxiety, depression, dissociation) and intrusion frequency. Patient studies have highlighted a wide range of potential pre-trauma PTSD risk factors, with evidence that in addition to the trait measures investigated by Laposa and Alden (2008), biological mechanisms (such as genes) and life events play an important role in PTSD vulnerability. To date no patient or analogue designs have incorporated such risk factors together into one design, allowing for investigation of the relative importance and contribution of individual factors to the prediction of PTSD symptomology and the potential for peri-trauma responses to mediate these effects. Furthermore, although the majority of analogue investigations have assessed the automatic experiences of memory intrusions in the days following the trauma-film, patient studies have shown that deliberate thought suppression is associated with PTSD diagnosis (Cameron, Palm & Follette, 2010) and symptom severity (Vaquez, Hervas & Perez-Sales, 2008). Thought suppression is known to produce a contradictory rebound effect in which related thoughts are increased (Wegner & Zankos, 1994), an effect which has been confirmed in trauma survivors instructed to suppress thoughts of the trauma (Shipherd & Beck, 2005). These findings suggesting that thought suppression related intrusions may be a useful avenue for further investigation.

This exploratory study will employ an analogue trauma design, measuring key pre-trauma biological (genetics, gender), environmental (life events, trait anxiety, anxiety sensitivity and harm avoidance) factors and peri-traumatic emotional and physiological (heart rate, skin conductance) responses. VR-trauma exposure will allow for the controlled investigation of the

subsequent intrusive thoughts during a thought suppression task and the accuracy and coherence of trauma recall (cued and free recall). As current PTSD would impact upon the interpretation of results, individuals with PTSD will be screened out; whilst presence of depression (BDI scores) and other mental health problems will be controlled for in the analysis.

The aim of this exploratory investigation is to determine which set of pre- and peri-trauma variables best predicts phenotypic memory distortions. It is expected that a higher presence of anxiety related traits (ASI, STAI_T, HA), recent stressful life events, genetic risk allele expression (BDNF Met, 5HTTLPR s (and l/l AG), ADRA2B s, NPS T, D2Taq1 T,) and peri-traumatic increases in arousal, anxiety and low mood, will be predictive of free recall trauma memory distortions and increased incidence and severity of intrusive trauma memories. Previous research illustrates that peri-traumatic HR reductions are associated with the development of spontaneous intrusions (Holmes et al., 2004), however, although analogue research has explored the thought suppression related intrusion frequency (Davies & Clark, 1998), no research has looked at the relationship between biological and ecological pre-trauma risk factors and peri-traumatic reactions in the development of intrusions during a deliberate thought suppression task. A further aim of the current study is therefore to extend intrusion literature by exploring the effects of pre- and peri-traumatic factors on physiological arousal at the time of the intrusive memory (HR and SC responses). It is hypothesised, in line with the findings of Holmes et al (2004), that HR reduction during the traumatic sequence of the VR scenario will be associated with increased number and severity of trauma related intrusions; however, due to the lack of previous research pertaining to peri-traumatic responding and its effect on trauma recall and physiological responses to traumatic intrusions, this aspect of the research is exploratory, and as such no formal hypotheses have been derived.

In line with the findings of Laposa and Alden (2008) it is hypothesised that peri-traumatic self-reported anxiety will mediate the relationship between pre-trauma personality vulnerabilities and intrusion development (i.e. the associations between pre-trauma factors and analogue intrusions will be better accounted for by the influence of pre-trauma factors on peri-trauma anxiety and the respective influence of peri-trauma anxiety on intrusions). A further aim of the research is to also extend the findings of Laposa and Alden (2008) by exploring the mediating effects of physiological peri-traumatic trauma responses on recall related memory disturbances and address whether peri-traumatic responses also mediate the relationship between pre-trauma environmental (prior life events) and biological (genetic) vulnerabilities.

6.2.1 Research questions and Hypothesis

Q1. What are the predictive effects of pre-trauma individual differences on post-VR memory distortions, intrusive trauma memories and physiological responding at the time of the intrusive memories?

H1: Anxiety related traits, stressful life events and risk allele expression (BDNF Met, 5HTTLPR s (and l/l AG), ADRA2B s, NPS T, D2Taq1 T,) will be predictive of free recall trauma memory distortions and increased incidence and severity of intrusive trauma memories.

Q2. What are the predictive effects of peri-traumatic responses on post-VR memory distortions, intrusive trauma memories and physiological responding at the time of the intrusive memories?

H2a: Peri-traumatic anxiety, arousal and negative mood responses will be predictive of free recall trauma memory distortions and increased incidence and severity of intrusive trauma memories

H2b: HR reduction during the traumatic sequence of the VR scenario will be associated with increased number and severity of trauma related intrusions.

H2c: Peri-traumatic anxiety will mediate the relationship between pre-trauma personality vulnerabilities and intrusion development.

6.3 METHOD

6.3.1 Participants

See Chapter 4 Study 1 participants section 4.2.1.1.

6.3.2 Measures

See the following sections within Chapter 4 Measures section (4.1.1):

Screening questionnaires section 4.1.1.1: EEG and VR screening questionnaire, MINI, BDI-II.

Trait questionnaires section 4.1.1.2: ASI, STAI, HA

Life events questionnaires section 4.1.1.3: SRRS, traumatic life events checklist

State questionnaires section 4.1.1.4: SAM mood manikin, VAS mood scale and peri-trauma dissociation measure.

Memory questionnaires section 4.1.1.5: Free recall and thought suppression questionnaire.

Genotyping section 4.1.2.

Psychophysiological responses section 4.1.3: SC and ECG (i.e. HR).

Computer tasks sections 4.1.4: VR Iraq world, Thought suppression task.

6.3.3 Procedure

See Methods Chapter 4 Procedure section 4.2.1.2 for an overview of the full study design from which the data within this chapter were collected. The same set of pre- and peri-trauma factors will be analysed across this and the preceding Chapter 5; however the outcome measures covered within this chapter relate only to memory distortion analogue symptomology (Free recall, cued recall and thought suppression induced intrusions).

As a brief re-cap, the data within this chapter explored the influence of pre- and peri-trauma individual differences on the prediction of VR-trauma related memory distortions. Following exposure to a virtual reality trauma (Iraq world), after a 10 minute gap, memory distortions were first assessed by a VR-free recall task in which participants were asked to write down in as much detail and in a chronological order all that they could remember of the VR-trauma scenario. Secondly participants were given a multiple choice questionnaire to assess cued recall of the VR-scenario. Lastly participants completed a 3 minute thought suppression task in which they were instructed to try to not think about any aspect of the VR-trauma scenario for 3 minutes and asked to press a key to indicate every time they had a memory come to mind. At the end of the thought suppression task participants filled out the thought suppression strategies questionnaire. SC and HR responses were recorded during VR-trauma exposure and the thought suppression task. The VR-trauma memory distortion outcome variables and individual difference predictor variables are depicted in table 6.1.

Table 6.1: Variables included in Chapter 6 analysis of memory distortion. Summary of the risk and resilience factors pre- peri and post-trauma and analogue symptom measures.

Pre-trauma	Peri-trauma	Phenotypic symptom Measure: Memory distortions
PERSONALITY: ▪ STAI-T ▪ ASI ▪ HA **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events **GENE POLYMORPHISMS:** ▪ 5HTTLPR ▪ BDNF ▪ D2 Taq1 ▪ NPS ▪ ADORA 2B **GENDER** *COVARIATES:* ▪ *Mini neuropsychiatric assessment (MINI)* ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)* ▪ *Drug use* ▪ *Computer gaming* ▪ *Beck depression inventory (BDI)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ SAM arousal difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**FREE RECALL:** ▪ Content inaccuracy ▪ Sequence ratio disorganisation **CUED RECALL:** ▪ Inaccuracy score (15 items) **INTRUSIONS (thought suppression):** ▪ Form ▪ Distress ▪ Frequency ▪ HR response ▪ SC response

6.3.3 Data Pre-processing

See the following sections within Methods Chapter 4 pre-processing section (*4..2.1.3*):

Genetics section 4.2.1.3.1.

Physiological measures section 4.2.1.3.3: Intrusion response scores, VR scenario responses

Free recall coding section 4.2.1.3.4: Content accuracy, Sequence recall

Checks for normal distribution section 4.2.1.3.5.

6.3.4 Statistical analysis

Zero order correlations were carried out as a form of exploratory analysis to determine which predictor variables were significantly associated with outcome measures. Where no prior hypotheses were present, only significantly correlated predictors were entered into the regression model for each outcome variable. Predictors were entered using forced entry method in a hierarchical fashion as illustrated in figure 5.2, to allow for the impact of successively more important variables to be assessed with each additional block; covariates were added as the last block to check that they had no effect on the final model. A sample size of 80 allows for three predictors to be entered into the model at any one time (Field, 2005, pp.173). Addition of >3 regressors within any one model can result in instability of the model, however testing different combinations of three predictors within separate models and observing the overall change in model fit and significance of individual predictors is an acceptable statistical method for exploratory analysis, such as this, as each model will remain stable (Field, 2005, pp.173). As such, when >3 predictor variables showed significant correlations with an outcome measure, different models were assessed until the best fitting model for that outcome was produced. Where multivariate outlying cases changed the regression model qualitatively, the model with these cases replaced with a value one unit larger or smaller than the next score in the distribution (Tabachnick & Fidell, 2001) is reported. Due to highly uneven group sizes on the cigarette variable, with regression analysis indicating multivariate outliers on all six cases, this predictor was not included in regression models; although it was retained for exploratory zero order correlational analysis.

6.4 RESULTS

6.4.1 Utility of VR-trauma induction: Manipulation check

See chapter 5 Section 5.4.1 for results relating to the effectiveness of the VR-trauma induction.

6.4.2 VR-trauma recall

6.4.2.1 Cued recall

6.4.2.1.1 Correlations

Cued recall inaccuracy was associated with female gender ($r(73)=-.286$, $p=.013$) and a deceleration in HR responses during the VR-trauma sequence compared to the rest of the VR scenario ($r(70)=-.323$, $p=.006$).

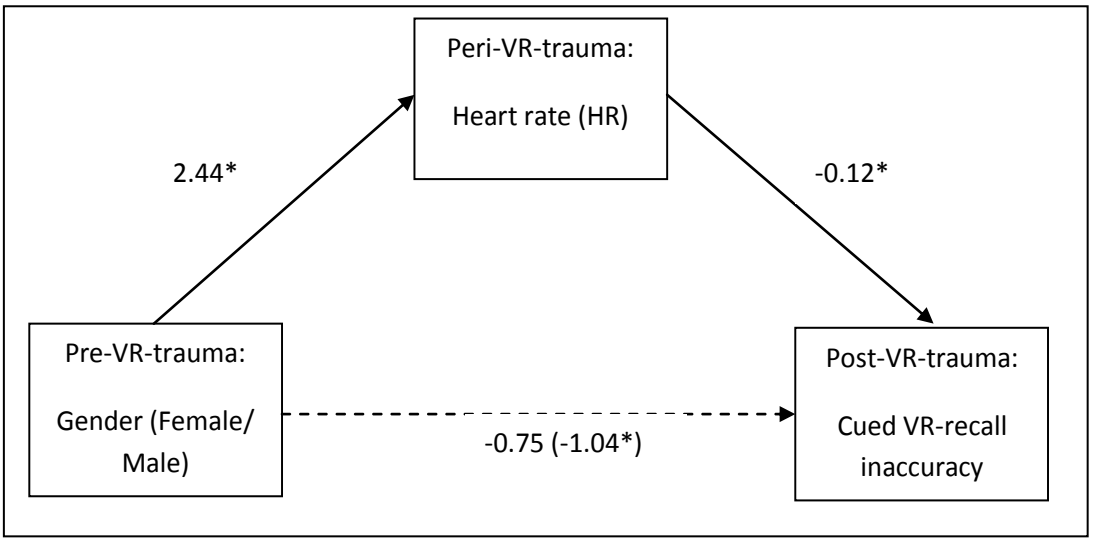
6.4.2.1.2 Regression

When entered into the model alone female gender significantly predicted a poorer cued recall, however gender no longer made a significant contribution to the prediction of cued recall accuracy when peri-traumatic HR response (in the trauma sequence compared to the rest of the VR) was accounted for. The final model accounted for 13.9% of the variance in cued recall inaccuracy; with peri-traumatic HR responding showing significant predictions of cued recall inaccuracy scores. A comparative decrease in HR towards the traumatic scene within the VR scenario, predicted an impairment of cued recall memory post-trauma. Interestingly, peri-traumatic HR response appeared to mediate the relationship between female gender and impaired cued recall (table 6.2), with the Baron and Kenny (1986) conditions for mediation met with a significant zero order correlation between gender and peri-traumatic HR throughout the duration of the VR scenario ($r(79)=.283$, $p=.01$) . This mediation was confirmed via bootstrapping analysis following 5000 re-samples. Whilst the total effect of HA on intrusion distress was significant (TE=2.34, SE=0.44, $p=.022$), the direct effect was not (DE=1.67, SE=0.45, $p=.100$). Peri-traumatic HR response across the whole VR-exposure mediated the relationship between female gender and cued recall inaccuracies (IE lower 95% CI=0.026, upper 95% CI=0.794), females were more likely to experience decreased peri-traumatic HR responses, and through decreased peri-traumatic HR responses, more likely to experience a reduced recall for the traumatic event on a cued recall test (figure 6.1). These findings illustrate female gender exerts its maladaptive effects on traumatic cued recall via its influence on peri-traumatic physiological responses.

Table 6.2 Hierarchical regression analysis for biological pre-trauma factors and peri-trauma reactions predicting cued recall inaccuracy

	B	*SE B*	β
Step 1			
Constant	9	0.27	
gender	-1.04	0.44	-.27*
Step 2			
Constant	9.34	0.3	
gender	-0.75	0.45	-.19
HR Trauma-VR	-0.12	0.05	-.27*

Note R^2= .072 for Step1 (p=0.22); ΔR^2 =.077 for Step 2 (p=.023). Final model R^2 =.139 p=.006 *p<.05. **p<.01. ***p<.001. gender = females coded '0' and males coded '1'



*Note: * p<0.05, the coefficient in parenthesis is the direct effect of gender on cued recall inaccuracy when the mediator has not been accounted for.*

Figure 6.1: Mediation model of cued recall inaccuracy. The mediation of the association between female gender and recall innacuracy by peri-traumatic HR deceleration.

6.4.2.2 Free recall sequence disorganisation

6.4.2.2.1 Correlations

Free recall memory disorganisation was associated with a number of pre- and peri-traumatic factors. Female gender (r(81)=-.277, p=.011), fewer stressful life events in the past year (r(74)=-.345, p=.002) and carrying the Val/Val BDNF polymorphism (r(80)=-.250, p=.023) represented pre-trauma associations with memory sequencing distortions.

6.4.2.2.2 Regression

The best fitting model accounted for 28.5% of the variance in sequence ratio scores and included the predictors BDNF, SRRS and gender (table 6.3). Carrying the homozygote Val polymorphism, experiencing fewer stressful life events in the last year and being female predicted greater disorganisation of free recall for the VR trauma. Compared to a model containing female gender as a single predictor, a significant improvement in the model fit was obtained by the addition of stressful life events in the second block and the addition of BDNF in the final block. Other exploratory models, that included peri-traumatic HR responding, indicated that HR trauma response did not make a significant contribution to the prediction of free recall disorganisation, over and above the pre-trauma variables in the model and the total models accounted for a lower percentage of variance. Interestingly these findings show that unlike the prediction of cued recall, free recall disorganisation is best predicted by pre-trauma vulnerability factors including female gender, carrying the Val/Val polymorphism of BDNF and experiencing a smaller number of stressful life events in the last year, rather than peri-traumatic responses.

Table 6.3: Hierarchical regression analysis for biological and ecological pre-trauma factors predicting free recall sequencing distortions

	B	*SE B*	β
Step 1			
Constant	1.91	0.01	
gender	-0.02	0.01	-.25*
Step 2			
Constant	1.89	0.01	
gender	-0.02	0.01	-.25*
SRRS	-0.00	0.00	-.35**
Step 3			
Constant	1.861	0.02	
gender	-0.02	0.01	-.24*
SRRS	-0.00	0.00	-.39***
BDNF	-0.03	0.01	-.32**

Note R^2= .06 for Step1 (p=.031); ΔR^2 = .124 for Step 2 (p=.001); ΔR^2 = .099 for Step 3 (p=.002). Final model R^2 =.285 p<.001 *p<.05. **p<.01. ***p<.001. gender = females coded '0' and males coded '1'

6.4.2.3 Free recall content inaccuracy

6.4.2.3.1 Correlations

Free recall VR-trauma memory omissions were associated only with biological pre-trauma risk factors, with female gender ($r(81)=-.219$, $p=.047$), NPS A allele ($r(81)=-.276$, $p=.012$) and 5HTTLPR L_A allele ($r(80)=-.247$, $p=.025$) associated with VR-trauma recall inaccuracies.

6.4.2.3.2 Regression

Content inaccuracy was significantly predicted by gender (table 6.4), however the model fit significantly increased with the addition of genetic SNPs NPS and 5HTTLPR, with the final model accounting for 17.3% of the variance in memory inaccuracies. A higher number of free recall trauma memory omissions was predicted by female gender, NPS A allele and 5HTTLPR L_A allele. Female gender is a previously documented risk factors for PTSD development; these findings add support to the literature by illustrating that, within a controlled analogue design, they play a crucial role in predicting poorer free recall of a traumatic memory.

Table 6.4: Hierarchical regression analysis for biological pre-trauma factors predicting free recall VR-trauma memory omissions

	B	*SE B*	β
Step 1			
Constant	0.15	0.01	
gender	-0.02	0.01	-.22*
Step 2			
Constant	0.07	0.03	
gender	-0.02	0.01	-.21*
NPS	-0.02	0.01	-.24*
5HTTLPR	-0.03	0.01	-.25*

Note R^2= .05 for Step1 (p=.048); ΔR^2 = .125 for Step 2 (p=.004). Final model R^2 =.141 p=.002 *p<.05. **p<.01. ***p<.001. gender = females coded '0' and males coded '1'

6.4.3 VR-trauma intrusions

During the thought suppression task the mean number of intrusions experienced across all participants was 7.36, which ranged from 0-25 intrusions. The average percentage of distress experienced in relation to theses intrusions was 22.6%. The form in which these intrusions were experienced is presented in table 6.5.

Table 6.5: The frequencies of different forms of intrusive memories during the thought suppression task

	Verbal	Visual	Mixture of visual and verbal
Form of intrusion reported	8 (9.9%)	30 (37%)	43 (53.1%)
Form of intrusion reported most often experienced	18 (24%)	57 (76%)	

6.4.3.1 Number of intrusions

6.4.3.1.1 Correlations

The frequency of intrusive VR-trauma memories within a thought suppression task was positively correlated with peri-traumatic increases in state anxiety ($r(78)=.288$, $p=.010$), no other pre- or peri-trauma factors predicted intrusion frequency.

6.4.3.1.2 Regression

A greater number of intrusive thoughts was predicted by a greater peri-traumatically induced increase in anxiety as measured by difference in STAI state scores pre and post (table 6.5), and accounted for 8.3% of the variation in the number of intrusions experienced during the thought suppression task. As no pre-trauma vulnerability factors were found to predict the number of intrusive trauma memories this indicates that peri-trauma anxiety is more influential on the subsequent ability to suppress traumatic intrusions post-trauma, during a thought suppression task; although it only has a small predictive effect.

Table 6.6: Regression analysis predicting VR-intrusion frequency during a thought suppression task

	B	*SE B*	β
Constant	0.68	0.06	
STAI_S change	0.01	0.004	.29**

Note R^2= .083 (*p*=.01). *p<.05. **p<.01. ***p<.001

6.4.3.2 Intrusion form (verbal/visual)

6.4.3.2.1 Correlations

A predominance of visual, as opposed to verbal, intrusions, was associated only with increases in peri-traumatic SC responding during the VR-trauma sequence compared to the preceding VR sequences (*r*(72)=.229, *p*=.050).

6.4.3.2.2 Regression

An increased SC response during the traumatic sequence of the VR compared to the preceding VR content accounted for a small (7.1%) amount of the variance in experience of intrusive memories as verbal or visual in their form (table 6.6). Although the overall model was significant, SC during trauma only showed a trend towards the prediction of visual intrusive memories (p=.055).

Table 6.7: Regression analysis predicting VR-intrusion form (verbal/visual) during a thought suppression task

	B(SE)	*lower*	*exp b*	*upper*
Constant	.86	.924	37.21	1498.7
SC Trauma-VR	3.617			

Note R^2= .077 (Hosmer & Lemeshow), .055 (Cox & Snell), .082 (Nagelkerke). Model (1)=4.173, *p*=.041 *p<.05. **p<.01. ***p<.001

6.4.3.3 Intrusion distress

6.4.3.3.1 Correlations

The severity of thought suppression related VR-intrusions was associated with a number of pre- and peri-trauma risk factors. Intrusion distress was correlated with reduced trait harm avoidance ($r(78)=-.314$, $p=.005$), BDNF Val/Val polymorphism ($r(77)=.259$, $p=.021$) and peri-traumatic state anxiety ($r(76)=.363$, $p=.001$), visual analogue anxiety ($r(78)=.227$, $p=.043$), arousal ($r(76)=.305$, $p=.007$), low mood ($r(78)=.316$, $p=.004$), HR ($r(76)=.295$, $p=.009$) and reduced dissociation ($r(76)=-.223$, $p=.048$).

6.4.3.3.2 Regression

The best fitting model accounted for 22% of the variation in intrusion distress and included HA, BDNF and STAI_S difference scores (table 6.7). BDNF did not significantly predict intrusion distress; the addition of BDNF to the model did not improve the model fit over HA alone. The addition of STAI_S to the model significantly increased the model fit and showed the potential to mediate the relationship between HA and intrusion distress.

Table 6.8: Hierarchical regression analysis for ecological and biological risk factors and peri-trauma responses predicting VR-intrusion severity during a thought suppression task

	B	*SE B*	β
Step 1			
Constant	9.74	2.01	
HA	-0.32	0.11	-.31**
Step 2			
Constant	8.61	2.08	
HA	-0.27	0.11	-.27*
BDNF	1.19	0.67	.20**
Step 3			
Constant	6.61	2.11	
HA	-0.21	0.11	-.21
BDNF	1.07	0.64	.18
STAI_S	0.09	0.03	.30**

Note R^2= .098 for Step1 ($p=.006$); ΔR^2 = for Step 2 ($p=.08$); ΔR^2 =.086 for Step 3 ($p=.006$). Final model R^2 =.220 $p<.001$ *$p<.05$. **$p<.01$. ***$p<.001$

Mediation was explored further in a separate model including HA and STAI_S only, which was found to explain 19% of the variance in intrusion distress. The conditions for partial mediation

were met in this preliminary analysis (Baron & Kenny, 1986), with a reduction in the significant simple effect of HA on intrusion distress occurring when the significant effects of peri-anxiety were controlled for in step 2 (table 6.8), with the relationship between HA and peri-anxiety illustrating a significant zero-order correlation ($r(80)=-.227$, $p=.040$). However results based on 5000 bootstrapped samples showed that the relationship between HA and peri-anxiety was not significant within this model (t=-1.89, SE=0.39, p=.063), therefore no longer meeting the Baron and Kenny (1986) conditions for mediation. Moreover, because zero was within the 95% confidence interval (IE lower 95% CI= -.192, upper 95% CI= .005), the indirect effect was shown to not be significantly different from zero and therefore non-significant ($p>.05$). High levels of peri-traumatic anxiety did not mediate the relationship between low levels of trait harm avoidance and experiencing intrusive VR-trauma memories as distressing.

Table 6.9: Hierarchical regression analysis testing conditions for mediation for HA and peri-trauma anxiety predicting intrusion severity

	B	*SE B*	β
Step 1			
Constant	9.74	2.00	
HA	-0.32	0.11	-.31**
Step 2			
Constant	7.57	2.04	
HA	-.25	0.11	-.25*
STAI_S	.09	0.03	.31**

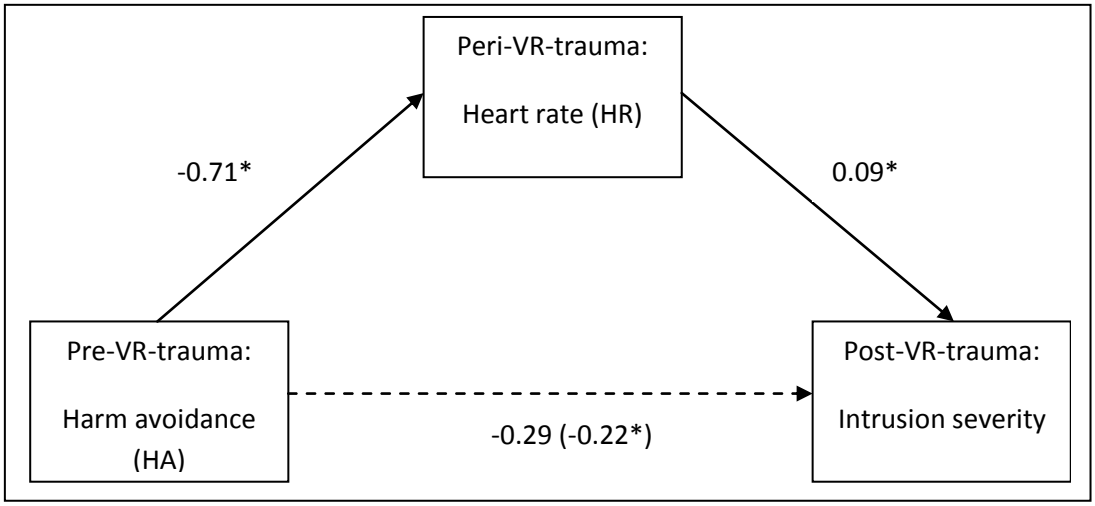
Note R^2= .098 for Step1 (p=005); ΔR^2 =.092 for Step 2 (p=.005). Final model R^2 =.19, $p<.001$ *$p<.05$. **$p<.01$. ***$p<.001$

The initial conditions for mediation of the relationship between HA and intrusion distress also appeared to be met for peri-traumatic arousal, dissociation and HR response towards the trauma; with zero order correlations showing respective simple effects with intrusion distress as described in section 6.4.1.1, and illustrating significant correlations of HA with peri-traumatic arousal($r(80)=-.245$, $p=.027$), dissociation ($r(81)=.237$, $p=.031$) and HR response($r(79)=-.237$, $p=.013$). As such the potential for these other peri-trauma response measures to act as mediators was followed up within bootstrapped regression analysis.

In the analysis of the mediating effects of peri-traumatic arousal and dissociation results based on 5000 bootstrapped samples showed that the relationship between HA and peri-trauma

arousal (t=-1.7, SE=0.067, p=.094) and peri-trauma dissociation (t=-1.96, SE=0.303, p=.054) were not significant within respective models, therefore no longer meeting the Baron and Kenny (1986) conditions for mediation. Moreover, because zero was within the 95% confidence interval for arousal (IE lower 95% CI= -.167, upper 95% CI= .007) and dissociation (IE lower 95% CI= -.136, upper 95% CI= .006) analysis, the indirect effect was shown to not be significantly different from zero and therefore non-significant (*p*>.05). Neither high levels of peri-traumatic arousal or dissociation mediate the relationship between low levels of trait harm avoidance and experiencing intrusive VR-trauma memories as distressing.

In the analysis of the mediating effects of peri-trauma HR responses, results based on 5000 bootstrapped samples indicated that both the association between peri-trauma HA and HR (TE=-2.6, SE=0.274, *p*=.011) and the association between peri-trauma HR and intrusion distress (TE=-2.07, SE=0.046, *p*=.042) were significant. Moreover, whilst the total effect of HA on intrusion distress was significant (TE=-2.6, SE=0.112, *p*=.011), the direct effect was not (DE=-1.95, SE=0.114, *p*=.055)Peri-traumatic state anxiety fully mediated the relationship between HA and intrusion distress (IE lower 95% CI= -.176, upper 95% CI= -.007), participants who indicated low levels of trait harm avoidance were more likely to report experiencing peri-traumatic anxiety, and through high levels of peri-traumatic anxiety, more likely to experience intrusive VR-trauma memories as distressing (figure 6.2). Because zero is not in the 95% confidence interval, the indirect effect is significantly different from zero at $p < .05$ (two tailed).



*Note: * p<0.05, the coefficient in parenthesis is the direct effect of HA on Intrusion severity when the mediator has not been accounted for.*

Figure 6.2: Mediation model of intrusion severity. Mediation of the association between reduced trait HA and intrusion severity by peri-traumatic HR acceleration.

As significant mediation was apparent for peri-traumatic HR responding, a regression model was ran to determine the amount of variance explained. 13.1% of the variance in intrusion distress was accounted for by HA and HR during the trauma sequence of the VR. Moreover in support of the bootstrapping analysis HR response during the traumatic sequence (compared to BL) can be seen to mediated the relationship between HA and intrusion distress, with its addition in block 2 (table 6.9).

Table 6.10: Hierarchical regression analysis for HA and peri-trauma HR predicting intrusion severity

	B	*SE B*	β
Step 1			
Constant	9.23	2.03	
HA	-0.29	0.11	-.29*
Step 2			
Constant	8.06	2.07	
HA	-0.22	0.11	-.22
Peri-HR	0.09	0.05	.23*

Note R^2= .081 for Step1 (p=011); ΔR^2 =.05 for Step 2 (p=.042). Final model R^2 =.131, p=.005 *p<.05. **p<.01. ***p<.001

6.4.3.4 HR response towards intrusive memories

6.4.3.4.1 Correlations

HR amplitudes towards VR-related intrusive memories during a thought suppression task were associated with NPS T allele (r(75)=-.233, p=.041) and 5HTTLPR s allele (r(74)=-.271, p=.018).

6.4.3.4.2 Regression

HR deceleration in response to intrusive memory occurrence was predicted by presence of the serotonin s allele and the NPS T allele, accounting for 11.6% of the variance (Table 6.10). Both NPS and 5HTTLPR gene SNP's significantly predicted HR in response to intrusive memories, with the 5HTTLPR s allele and NPS T allele predicting HR decelarations. Findings of a significant predictive relationship between the s allele of 5HTTLPR a well studied risk factor for PTSD, and HR deceleration in response to intrusive trauma memories, is in line with the findings of

(Holmes et al, 2004), that HR deceleration during the intruding trauma film sequence is associated with an increased number of intrusive memories.

Interestingly, the contrasting role of NPS in suppressing anxiety, whilst inducing wakefulness and hyperarousal, was additionally supported by findings of a negative association of the T allele with trait anxiety (χ^2 (80)= -.287, *p*=.009) and state anxiety induced by the VR scenario (χ^2 (81)= -.292, *p*=.007).

Table 6.11: Regression analysis predicting HR responding towards intrusive VR-memories during a thought suppression task

	B	*SE B*	β
Constant	9.37	1.09	
NPS	-1.76	0.87	-.22*
5HTTLPR	-2.37	1.08	-.24*

Note R^2= .116 (*p*=.01). *p<.05. **p<.01. ***p<.001

6.5 DISCUSSION

The aim of this study was to explore influence of pre- and peri-trauma risk factors on the development of PTSD like memory recall distortions and intrusive trauma memories. Moreover the relative importance of peri-traumatic individual differences over potentially less predictive pre-trauma factors and the potential for peri-traumatic factors to mediate the effects of pre-trauma factors were of particular interest in light of previous research.

Findings illustrated that following exposure to a VR-trauma a number of pre-trauma individual differences (including gender, life events, trait HA scores and genetics) and peri-trauma responses (including HR, anxiety and arousal) predicted the development of problems with free and cue recall for the VR-trauma and increased traumatic intrusion frequency, distress and HR response during a thought suppression task. Not all pre-trauma individual difference associations were in the direction predicted by hypothesis 1 and in contrast to hypothesis 2b an increased peri-traumatic HR response was in fact associated with intrusion related distress. However, the hypothesised (2a) influences of increased peri-traumatic self-reported anxiety on intrusion frequency and severity were supported, and peri-traumatic HR responses were

found to mediate the influence of pre-trauma traits on intrusion related distress (in line with hypothesis 2c) and cued recall accuracy.

6.5.1 Cued recall

Interestingly the influence of female gender on cued trauma recall inaccuracy was mediated by its association with reductions in peri-traumatically induced HR responses. This finding supports previous findings that female gender is associated with increased PTSD development following trauma exposure (Breslau & Davis, 1992; Van Loey, Maas, Faber & Taal, 2003; Darves-Bornoz et al., 2008; Stein, Walker, & Forde, 2000; Tolin & Foa, 2006), but illustrates that the previously documented PTSD risk associated with being female may in fact be a consequence of its influences on physiological peri-traumatic responding - which cannot be measured in patient studies. In light of known association between HR reductions towards emotionally evocative visual stimuli and a stimuli orienting response (Sokolov, 1963; Hare, 1973), the current findings illustrate female gender predicts impaired cued recall for traumatic events through its influences on eliciting an orienting response towards the VR-trauma experience. These results indicate that, in contrast to the findings of Christiansen and Elklit (2012), peri-traumatic responses can mediate the risk of PTSD symptom development (i.e. trauma memory distortions) within females whilst conferring resilience in male; whilst supporting the findings of Holmes et al (2004), that peri-traumatic HR deceleration illustrates a state of fear bradycardia and is predictive of trauma-film related memory distortions. Within the current study it also appears that a more sustained state of fear bradycardia occurred during the orienting response towards the arousing and adversive startle sounds in females; this sustained bradycardia has been found for highly adversive stimuli (Lang et al., 1997) and been compared to the 'freeze' response in animals. Furthermore Holmes et al (2004) posited that this bradycardia response may be implicated in enhanced SAM memory formations and reduced VAM memory formations; a theory which is supported by the current association with reduced cued recall accuracy, suggesting mechanism by which female gender may be associated with increased risk of PTSD development.

6.5.2 Free recall

Free recall organization and accuracy was predicted by gender, with females showing more recall inaccuracies and sequencing errors. This finding is consistent with previous reports that female gender is a risk factor in the development of PTSD symptoms (Perkonigg et al., 2000) and illustrates a parallel risk factor across cued and free recall assessments of trauma

memories. Whilst peri-trauma responses were not found to predict trauma related free recall profiles a number of other pre-trauma individual differences imparted an influence.

The finding that lower self-reported number of stressful life events leads to greater trauma memory disorganisation was unexpected, but may suggest that experiencing stressful life events can infer a level of resilience towards subsequent stressful or traumatic events.

Sequencing errors in the order of VR recall were predicted by female gender, fewer recent stressful life events and BDNF Val/Val gene expression, with the combination of these factors predicting 28.5% of the variance in disjointed trauma recall. Whilst the association with female gender was in line with literature implicating female gender as a risk factor for PTSD the direction of the effects found for stressful life events and BDNF were not in line with previous findings. The finding that the homozygote Val allele predicted sequencing errors is perhaps surprising in light of previous literature which has found that Met allele carriers show poorer episodic memory accuracy (Egan et al., 2003) and reduced hippocampal activation during memory tasks (Hariri et al., 2003); however previous literature has only explored memory accuracy and not sequencing errors. Furthermore, it is possible that memory for traumatic episodic events carries different predictive allelic associates than memory for normal episodic events. Interestingly the BDNF homozygote Val polymorphism has been implicated in trait anxiety (Lang et al., 2005) but shown inconstant associations with PTSD (Valente et al., 2011; Broekman et al., 2007). It has been posited that inconsistencies in the literature may be the product of epigenetic effects (Terracciano et al., 2010), which have been shown to play a role in BDNF functional expression (Gatt et al., 2009); however the lack of an interaction effect between the number of stressful life events and BDNF allelic risk within the current study does not support this explanation. The current findings therefore imply that the Val allele impacts risk of trauma memory disorganisation while the Met allele produces increased recall organisation. The finding that an increase in stressful life events was associated with more cohesive VR-memory recall is suggestive of stress inoculation effects as found for startle related ERP processing in chapter 5. Low dose treatment with glucocorticoids (a stress hormone) has indeed been shown to supplement traditional exposure based PTSD treatments and result in improvements in memory based symptoms (Aerni et al., 2004; Schelling et al., 2006; de Quervain & Margraf, 2008). The current findings support the proposition that low levels of stress inoculate against trauma related memory problems, implicating memory disorganisation as the mechanism by which glucocorticoids improve PTSD treatment outcomes.

Recall inaccuracies were predicted by female gender, NPS A allele expression and 5HTTLPR L allele expression. The finding of increased memory accuracies in NPS T allele carriers is in line with animal and human studies showing that the NPS receptor expression and NPS efficiency improves memory consolidation (Han, 2013; Lukas &Neumann, 2012; Fendt et al., 2010; Lennertz et al, 2012); suggesting that the NPS A allele may impart risk for PTSD symptomatic memory distortions. Although the 5HTTLPR s allele has been previously associated with PTSD development (Lee et al., 2005), meta-analysis across studies has shown inconsistent effects (Munafo et al, 2005; Middeldorp et al., 2007). Moreover, within the current study only the A/G combination with L/L expression was grouped with the S allele to form an additional risk variant[12] , however patient studies have shown that the A addition can impart risk of increased amygdala activity (Lau et al., 2005).. Interestingly, triallelically classified 5HTTLPR studies have found the low expression variant to only be associated with PTSD under high stress conditions (Kilpatrick et al., 2007; Koenen et al., 2009) and to have protective effects under low risk conditions (Koenen et al., 2009) and the high expression variant to be associated with lifetime risk of PTSD development (Grabe et al., 2009). The current results are therefore consistent with triallelically defined 5HTTLPR literature and suggest that L_A expression is associated with a reduced accuracy of free recall trauma memories.

6.5.3 Intrusive memories

Prior research has not investigated the predictors of cardiovascular responses towards intrusive trauma memories and although previous studies have investigated the associates of the frequency and severity of spontaneous intrusions, the current paradigm explored intrusive VR-memories elicited during a deliberate thought suppression task. Results show that both 5HTTLPR s allele and NPS T allele expression predicted decreased HR responses during thought suppression related intrusive memories. It has been previously shown that T allele carriers illustrate HR elevations during a behavioural avoidance task (Domschke et al., 2010); this is in contrast to the current findings during a thought suppression task. The 5HTTLPR s allele has been associated with increased neutral reactivity towards emotional stimuli (Hagen et al., 2011); the traumatic nature of the intrusive thoughts within the current study illustrates s allele dependent physiological increases towards emotional stimuli. In light of prior research implicating s allele expression in PTSD diagnosis (Lee et al., 2005) and NPS T allele in female panic disorder (Domschke et al., 2010), the current findings add support to the role of fear learning in the development of arousal related conditions such as PTSD (Foa & Riggs, 1993; Foa

[12] in line with findings that the A/G combination behaves like the s allele (Nakamura et al., 2000)

& Rothbaum, 1998) and panic disorder (Bouton, Mineka & Barlow, 2001); however cardiac orienting responses and fear bradycardia (decreased HR), rather than traditionally posited increased physiological states, may become associated with unwanted thoughts and feelings, causing decelerated cardiac states to become a conditioned cue triggering such thoughts or feelings. Results suggest that genetic factors may facilitate cardiac orienting responses and fear bradycardia responses during thought suppression tasks and as such increase the propensity for conditioning to occur between intruding memories and physiological responses. These findings extend previous research by showing that HR deceleration at the time of the thought suppression related intrusive VR-memories may also be in important factor for further investigation in clinical samples, and support animal and human studies which have highlighted the importance of the NPS T allele in PTSD and panic disorder.

Across the prediction of intrusion frequency and characteristics peri-traumatic responses were shown to be important predictors. Intrusion frequency was predicted by peri-traumatic state anxiety alone, supporting the findings of Davis and Clark (1998), that negative peri-traumatic emotional reactions are associated with trauma-film intrusion frequency, and illustrating the previously documented importance of peri-traumatic effects in the prediction of PTSD symptomology (Brewin et al., 2000; Trickey et al., 2012). However the predicted association (hypothesis 2b) between peri-traumatic HR decelerations and increases in the number of intrusive trauma memories was not found, failing to replicate the findings of Holmes et al. (2004) within a thought suppression paradigm. The predominance of visual intrusions over verbal intrusions was related to peri-traumatic SC responding, although its predictive effects only illustrated a trend. This finding is in line with the Ehlers & Clark (2000) model of PTSD development, illustrating that increased physiological arousal may prevent the formation of more adaptive verbal memory traces with trauma sequences being processed and stored in a visual form which is susceptible to automatic retrieval. However, as such an association only reached a trend in predictive regression analysis, findings should be interpreted tentatively and further replication is needed to support and elaborate on factors which may influence this association.

Heightened distress in relation to intrusive thoughts has been associated with PTSD diagnosis in patient samples (Cameron, Palm & Follette, 2010). Within the current analogue design, contrary to expectations, lower harm avoidance (HA) scores were found to be associated with increased distress in response to intrusive memories. However, the effect of HA on intrusion related distress was found to be mediated by peri-traumatic HR, illustrating that participants who indicated low levels of trait harm avoidance were more likely to report experiencing peri-

traumatic anxiety, and through high levels of peri-traumatic anxiety, more likely to experience intrusive VR-trauma memories as distressing. HR increases are associated with a defence response (Sokolov, 1963; Hare, 1973). The current findings therefore illustrate that individuals who do not avoid harmful situations (i.e. low harm avoidance scores) express a defence response towards the VR-trauma scenario – perhaps this defence response is a learnt mechanism to detach oneself from a situation and as such not think or worry about the possible harm associated within a given context – and it is this defence response to the trauma which causes subsequent increases in the severity of intrusive trauma memories. Further research is needed to replicate this finding and explore the mechanisms by which harm avoidance may impart peri-traumatic HR accelerations.

The results of the current study support the utility of VR-trauma for use in analogue PTSD research. Furthermore, whilst the predictive importance of peri-trauma factors is highlighted in the development of cued recall and thought suppression related intrusive memories, thus supporting cognitive (Brewin, 1996,2001, 2010; Ehlers & Clark, 2000) and emotional processing (Foa et al., 1989, 1993, 1998; Lanius, 2010) models of PTSD development in their predominant emphasis on peri-traumatic processes. The results also suggest that the application of a diathesis stress conceptualisation of PTSD (McKeever & Huff, 2003; Elwood et al., 2009) would aid in explaining the importance of biological and ecological pre-trauma factors in predicting free recall and intrusion related HR responses within this study. Moreover, the dynamic interplay between pre- and peri-trauma factors illustrated in the mediations for cued recall and intrusion distress support the supposition of the diathesis stress model (McKeever & Huff, 2003; Elwood et al., 2009) that peri-trauma responses activate the risk associations between pre-trauma factors and post-trauma symptom development. Findings, in regard to the main thesis hypotheses (see section 2.9) will be discussed further within the general discussion chapter 9.

6.5.4 Limitations

Within the current paradigm intrusive memories were induced within a laboratory based thought suppression task; although this allowed for ease of concurrent measurement of HR and SC responses, it meant that the natural development of intrusive memories was not assessed. Previous studies assessing the prediction of intrusive memories have used an intrusion diary recorded over the course of the following days; it is possible that the prediction of intrusions resulting from the deliberate suppression of thoughts may differ from automatic intrusions which occur in daily life. As such the current finding of an association between

increased peri-traumatic HR and intrusion severity, as opposed to the finding of Holmes et al. (2004) that intrusion frequency is predicted by reductions in peri-traumatic HR responses, may be the result of paradigm differences in the inducement and measurement of intrusive trauma memories. Future studies should assess whether thought suppression related intrusion development and the experience of automatic intrusions are predicted by the same or different individual difference profiles, to elucidate whether direct comparisons between such literatures are warranted.

Interestingly, research has suggested that thought suppression related intrusions may not be a PTSD specific mechanism, with PTSD and trauma-exposed controls showing comparable frequency and severity of intrusive trauma memories during a thought suppression task (Beck, Gudmundsdottir, Palyo, Miller & Grant, 2006); implying that intrusion diary paradigms may in fact be a better analogue for the elicitation of PTSD specific mechanisms. However other research has found that although individuals with PTSD, compared to a trauma exposed control group, show comparable thought suppression related intrusions on neutral tasks, the PTSD group showed a rebound effect on trauma related thought suppression (Shipherd & Beck, 2005). The inconsistencies across the literature indicate more research is needed to clarify the PTSD specific nature of thought suppression induced trauma intrusions. However, research has indicated that suppression based coping is associated with intrusion frequency in a patient population (Vazquez et al., 2008), providing support for the measurement of intrusions within a thought suppression paradigm. On this note, it would also have been of interest to investigate the effects of pre-trauma trait suppression in predicting intrusions and memory distortions within the current study, and future work should further explore the effects of trait emotion regulation on the development of PTSD symptoms whilst accounting for the influences of peri-traumatic responding.

The homogeneity of the current sample restricts the conclusions that can be drawn, as the mean age of participants was only 20.5 years old and they all came from a university population. Moreover, due to the sample size there was insufficient power to investigate epistasis effects across genes or to look at epigenetic influences (apart from where the results indicated such effects would be worth further investigation). Epistasis and epigenetic influences on the functional expression of genes are now well evidenced and commonly accepted (for review see Marian, 2012), as such in small studies such as this, where these effects cannot be analysed or controlled for, the influence of other factors on current results cannot be ruled out.

6.5.5 Conclusions

Following exposure to a VR-trauma (Iraq world), female gender was shown to be associated with poorer recall for traumatic experience; however this effect was mediated by associated reductions in peri-traumatic HR response in the prediction of cued recall inaccuracies, and genetic factors (BDNF, 5HTTLPR and NPS) were found to have independent and larger predictive power in the explanation of disorganised and inaccurate free recall memories. HR responses during thought suppression related intrusive trauma memories were also predicted by genetic factors, with carriers of the s allele of the 5HTTLPR polymorphism and t allele of the NPS polymorphism showing increased HR responses towards intrusions, in line with findings that such allelic profiles are more frequent in individuals with PTSD and panic disorder respectively. In the prediction of intrusion frequency and severity (i.e. self-reported distress) increases in peri-traumatic anxiety, arousal and HR responses were key. Moreover, peri-traumatic HR responses mediated the relationship between pre-trauma traits and intrusion severity; illustrating that HR increases, rather than reductions, may be more predictive of the severity of intrusive memories.

7 RELATIVE INFLUENCES OF EMOTION REGULATION STRATEGIES AND INDIVIDUAL DIFFERENECES ON THE ALTERATION OF THE ACOUSTIC STARTLE RESPONSE FOLLOWING VIRTUAL REALITY TRAUMA EXPOSURE

7.1 ABSTRACT

Post traumatic stress disorder develops in certain individuals following exposure to a traumatic life event and is defined by symptoms of hyperarousal, which commonly manifest themselves in exaggerated startle responsivity. Previous studies have found emotion regulation manipulations successful in inducing change in automatic fear responses, such as the acoustic startle response. Whilst reappraisal has illustrated reductions in affective, reflex eye-blink and electroencephalographic ERP startle responses, suppression, although successful in reducing reflex responding, has demonstrated a lack of affective changes and increases in sympathetic activation. However, few studies have manipulated both regulation strategies within the same paradigm and the influence of acceptance based reappraisal (which is a better analogue of effective reappraisal based treatment strategies in PTSD) has not been explored. The current study set out to explore whether, following exposure to a virtual reality trauma (virtual Iraq) and neutral scenario (suburban environment), experimentally instructed emotion regulation strategies (acceptance and coping based reappraisal, behavioural suppression compared to a control group) can alter affective, peripheral and electrophysiological emotion modulated (trauma-gunshot/neutral-car horn) startle responses, and investigate the effects of trait emotion regulation (reappraisal and suppression) styles on this association. Furthermore, as pre- and peri-trauma individual differences are known to be important in predicting post-trauma symptomology, an additional important point of investigation was whether startle response profiles are better predicted by pre- and peri-trauma factors. Interestingly the predicted trauma augmented emotional-modulation of startle responses was not found, with facilitation of sympathetic startle responses in fact occurring towards neutral stimuli; suggesting perhaps that the perceptual properties of the natural sounds were more important in such modulations. Whilst the adaptive effects of reappraisal on reduced startle responding were not replicated using acceptance based reappraisal, behavioural suppression was shown to reduce affective and reflex eye-blink responses, whilst lengthening the habituation of sympathetic arousal. Pre- and peri-trauma individual differences explained additional variance in startle responses over and above the influences of concurrently employed emotion regulation strategies. These data suggest that while post-trauma behavioural suppression can

modulate startle responding, pre- and peri-trauma factors add additional and supplementary predictive influences.

7.2 INTRODUCTION

Reappraisal and acceptance are key aspects of cognitive restructuring, which constitutes an important part of evidenced based CBT treatments for PTSD (NICE, 2005). In accordance with their role in treatments for PTSD, emotion regulation difficulties including a lack of emotional acceptance or limited ability to reappraise have been associated with increased PTSD symptom expression (Tull, Barrett, McMillan & Roemer, 2007). Therapeutic techniques such as reappraisal appear to be adaptive because they occur early in the emotion generation processes and alter the cognitive evaluations of emotional experiences prior to response initiation. However, other emotional regulation techniques, such as suppression act later upon overt response modification processes and are believed to have maladaptive long term effects in maintaining PTSD symptomology (Ehlers & Clark, 2000). The Gross model of emotion regulation (Gross, 1998a, 1998b, 2001) holds that reappraisal, as an antecedent focused emotion regulation strategy, can reduce emotional, physiological and behavioural emotional responses, by altering the meaning attached to emotional experiences. This model highlights the adaptive role of cognitive restructuring PTSD therapy, in altering pathological trauma related emotions and responses, which may in turn alter maladaptive cognitions, attributions and beliefs. Suppression on the other hand forms a response focused emotion regulation strategy, occurring post-emotional experience and recruiting effortful processes in the alteration of emotionally-expressive behaviours, such as retaining a straight face in a game of poker irrespective of the positive or negative nature of the cards in your hand. The effortful response inhibition processes involved in behavioural suppression have been shown to result in increased physiological responses, as the body battles to inhibit responses towards previously initiated emotional interpretations (Gross, 2002). This interpretation is supported by findings illustrating that alterations in physiological responding are specific to emotional contexts, with behavioural suppression producing no significant changes in physiology during neutral films (Gross & Levenson, 1997); showing that physiological alterations are the consequence of emotionally specific behavioural inhibition. Interestingly avoiding thinking about a traumatic event has been posited to be associated with PTSD symptom development and maintenance cycles, by inhibiting the adaptive processing of trauma memories to allow for the integration of such memory traces both temporally and contextually within the

autobiographical memory base (Ehlers & Clark, 2000). In support of the maladaptive effects of behavioural suppression specifically, a reduction in facial fear expression has been shown to be highly correlated with reductions in PTSD treatment efficacy (Foa et al., 1995).

Research supports the assumption that suppression reduces expressive behaviour whilst increasing physiological responding (Gross, 2002). However whilst reappraisal has consistently produced significant reductions in negative emotional affect (Ray, McRae, Ochsner & Gross, 2010), alterations in physiological arousal are not evident. Gross (1998a) investigated the effects of both suppression and reappraisal within the same paradigm. It was found that during a short disgust eliciting film, participants instructed to suppress their responses showed reduced facial disgust reactions together with increased physiological arousal, whilst those instructed to reappraise showed decreases in self-reported emotional disgust but no alterations in HR or SC. These findings, together with a review of emotion regulation studies showing a lack of physiological effects for reappraisal manipulations (Gross, 2002), suggest that whilst suppression had detrimental effects on increased physiological arousal states, reappraisal only influences emotionally based responses (i.e. affect and reflex eye-blink startle responses- as reviewed below). Although suppression induced increases in physiological arousal have been found in response to a number of negative emotional experiences (Gross & Levenson, 1997), decreases in heart rate (HR) have also been reported (Gross & Levenson, 1993). In order to address some of the inconsistencies in the literature in regards to the physiological effects of reappraisal and suppression it seems important to investigate the emotional and physiological aspects of reappraisal and suppression with a single experimental paradigm.

Hyperarousal is a core symptom in the diagnosis of PTSD and within this symptom cluster a commonly experienced problem is the development of an exaggerated startle response (DSM-IV, 1994, 2000). Exaggerated startle SC responses, emotional fear responses and slower startle SC habituation rates have also been shown to be predictive of more severe PTSD symptoms at a four month (Shalev et al., 2000) and one year follow up (Pole et al, 2009). Research has shown that emotion regulation strategies, including reappraisal and suppression, can effectively alter behavioural and physiological startle responses. A reduced startle reflex, an automatic physiological emotional reaction to loud sounds measured using electromyography (EMG), has been found in individuals instructed to reappraise their emotions towards negative pictures, compared to enhancement or maintenance instructions (Jackson et al., 2000). As startle responding is an automatic behavioural measure of fear, this finding also supports the ecological validity of reappraisal induced self-reported emotional changes shown in previous

literature illustrating they are not the mere consequence of demand characteristics. The manipulations of behavioural suppression in response to acoustic startle stimuli has shown that although, compared to controls, no changes occur in negative emotional expression, reductions in behavioural emotional expression occur (such as sudden bodily movements and cries), together with increased sympathetic cardiovascular activation (Hagemann, Levenson & Gross, 2006).These studies illustrate the malleability of the startle reflex response, with reappraisal and suppression of startle responses both appearing to produce reductions in reflex responding. However further research is necessary to confirm such effects, especially in regards to suppression where EMG eye-blink was not recorded in the aforementioned study.

Emotional reappraisal manipulations have not only been successful in illustrating alterations in emotional experiences, but have demonstrated observable changes in brain responses. Down-regulation of adversive emotional experiences (i.e. reappraisal), whilst viewing emotional pictures, has been associated with simultaneous and lasting (for 10-15 minutes post-task) down-regulation of amygdala activation (Walter et al., 2009; Erk et al., 2010), in addition to increased activation of lateral and medial prefrontal regions (Ochsner, Bunge, Gross & Gabrieli, 2002). Differences in ERPs towards negative pictures have been found when individuals are instructed to either positively reappraise the image or simply attend to it (Gootjes, Fanken, & Van Strien, 2011). Reappraisal was associated with reduced amplitudes of the P300 and late positive potential (at 450-650ms) over the central-parietal area, compared to attending. Furthermore, the effect of reappraisal on ERP processing responses was found to persist for longer in a sub group of practitioners of a yogic-based meditative technique (which is a form of acceptance based reappraisal), with reduced amplitude of the late positive potential at both 450-650ms and 800-1000ms for reappraisal compared to attend conditions. Differences in amplitudes and latencies of event-related potentials (ERPs) in individuals using reappraisal based emotion regulation techniques, illustrate the neural effects of emotion regulation on emotional processing. However, despite the importance of such preliminary findings they do not allow for causal inferences to be drawn due to the study design. Although it may be the case that the long term practice of meditation results in an increased ability to regulate ones emotions, another alternative is that individuals who are intrinsically better at regulating their emotions may be more likely to practice meditative techniques. If the latter was the case, the results discussed above could indicate inherent electroencephalographic differences are associated with trait emotion regulation factors, rather than illustrating the malleability of ERP responses in response to learnt reappraisal strategies as the authors conclude. Controlled

investigation of the modulation of electrophysiological processes by reappraisal is warranted and research into the effect of suppression on ERP responses is lacking.

Indeed research has illustrated that there are individual differences in preferences towards the use of different emotion regulation strategies; such trait differences have the potential to affect the success of experimental manipulations and could have influenced the findings of Gootjes et al. (2011) as discussed above. Investigation of the consequences of individual differences in emotional regulation style on emotional, behavioural and physiological responses towards emotional stimuli has shown comparable response profiles to those seen in experimentally manipulated paradigms. Trait reappraisal, as measured by the ERQ (Gross & John, 2003), is associated with increased positive emotional experience and expression, and reduced negative emotional experience and expression, whilst trait suppression correlates with reduced positive emotional experience and expression, reduced negative emotional expression and produces no effect on, or increases in, negative emotional experience (Gross & John, 2003). In addition, tendencies towards trait emotional reappraisal have been found to confer pathological resilience and are associated with fewer clinical symptoms of depression and anxiety and the use of positive coping strategies during stressful events, whilst trait suppression appears to infer pathological risk with a higher incidence of depression and anxiety symptoms among individuals high on trait suppression and a reduced awareness and expression of their emotions during stressful events (Gross & John, 2003; John & Gross, 2004; Aldao, Nolen-Hoeksema & Schweizer, 2010). A reduced propensity to make use of adaptive emotion regulation strategies, such as reappraisal and acceptance, has been associated with increases in PTSD symptoms which are indicative of PTSD diagnosis (Tull, Barrett, McMillan, Roemer, 2007). However, whilst small to medium effect sizes for reappraisal illustrate the presence of an association with anxiety disorders, larger predictive associations for suppression illustrate that the presence of maladaptive processing styles infer greater pathological risk than a lack of adaptive styles (Aldao et al, 2010). Research carried out to date has not partialled out the effects of trait emotion regulation techniques on the association between manipulated emotion regulation and consequent affective, physiological and electrophysiological responses towards emotional contexts. Such analysis has the potential to increase our understanding of the mechanisms by which individual differences in trait emotion regulation strategies may produce differential treatment responses towards cognitive restructuring, which could be explored further in future studies.

It is known there are a number of individual differences in anxiety related pre-trauma traits, previous life events and peri-trauma emotional and physiological reactions which predict susceptibility to the development of PTSD. Previous investigation of individual differences in startle responding have specifically highlighted female gender as risk factor, but illustrated a lack of an association with age or anxiety traits (Quevedo, Smith, Donzella, Schunk & Gunnar, 2009); whilst the results of previous startle investigations within this thesis (Chapter 5) have highlighted peri-traumatic responses as particularly important in explaining variance in subsequent startle responses . Whilst a diathesis stress conceptualisation of PTSD would posit that pre- and peri-trauma factors are of greatest importance in the development of PTSD (McKeever & Huff, 2003; Elwood et al., 2009), cognitive and emotional processing models place increased emphasis on peri- and post-traumatic mechanisms and explicitly state the importance of post-traumatic (Brewin, 1996, 2001, 2010; Foa & Riggs, 1993; Foa & Rothbaum, 1998,; Ehlers & Clark, 2000) and peri-traumatic (Lanius, 2010) emotion regulation in the development of PTSD symptomology. In light of the importance of pre- and peri- individual differences posited by diathesis stress models this leads to the question whether the inherent influences of pre- and peri-trauma individual difference vulnerabilities can predict alterations in affective, physiological and electrophysiological startle responses, over and above the explicit post-trauma manipulation of emotion regulation techniques .

This study will address a number of outstanding research questions in relation to the role of emotion regulation in alleviation or facilitation of PTSD related emotional and electrophysiological startle responses, and the influence of individual differences in such relationships. An immersive Iraq virtual reality scenario will act as a trauma analogue and a contextually matched neutral suburban virtual reality scenario will act as a neutral control comparison, to assess whether such associations are emotionally specific or become generalised to previously neutral stimuli. In addition the use of a VR-trauma analogue will allow for further investigation of the utility of VR scenarios in analogue PTSD paradigms. The current study will explore the affective, peripheral and electrophysiological mechanisms by which experimentally instructed emotion regulation strategies (acceptance reappraisal, behavioural suppression, non-instructed control) alter responses to trauma and neutral valenced acoustic startle sounds and congruent foreground VR stills, and whether these findings change when the effect of trait emotion regulation styles are controlled for. As both acceptance and positive reappraisal are found to be adaptive emotion regulation strategies (Tull et al., 2007; Aldao et al., 2010), this investigation will explore the consequences of acceptance based reappraisal in which individuals are instructed to focus on personal strength

and coping abilities rather than trying to positively reappraise negative experiences; which is a more ecologically valid manipulation in line with cognitive restructuring in PTSD treatment (NICE, 2005). An additional aim of the investigation is to explore whether pre- and peri-trauma factors significantly add to the explanation of variance in startle responses, over and above the effects of post-trauma emotion regulation manipulations. Participants will alternate randomly between regulation and non-regulation on trauma trials, but never be required to regulate on neutral trials. Instead the neutral trials, as with the trauma non-regulation trials, will be used to assess generalisation of alterations in startle responding. The findings of this investigation will elaborate our understanding of how acceptance based reappraisal (treatment analogue) and behavioural suppression (pathological analogue) of acoustic startle stimuli are associated with alterations in affective states, attentional processes (ERP responses) and physiological reactions (EMG, SC, HR); and individual differences affecting outcomes. It is hoped that the findings will highlight potential biological mechanisms by which cognitive restructuring therapy (reappraisal) produces adaptive change in hyperarousal symptoms and by which pathological processes (suppression) may dispose towards hyperarousal.

7.2.1 Research questions and hypothesis

Q1: Are affective and electrophysiological startle mechanisms sensitive to trauma versus neutral valence effects following exposure to a virtual reality trauma? And is there ER manipulation dependent differences in responses, when individuals are required to regulate their emotions to trauma stimuli (TR), receive uninstructed exposure to trauma stimuli (TV) and receive uninstructed exposure to neutral stimuli (N).

> *H1: Affective and physiological startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli. ER manipulation effects will be greatest on TR trials.*

Q2: Do explicitly instructed emotion regulation strategies influence affective, physiological (eye-blink, HR and SC) and brain processing (ERP) startle responses?

> *H2a: Decreased negative affect and increased positive affect during the startle paradigm will apparent for the reappraisal group compared to control group. However, no affect modification will be apparent for the suppression group compared to the control group.*

> *H2b: Both suppression and reappraisal will attenuate participants reflex startle eye-blink responses and habituation of these responses. The control (view) condition is expected to show heightened reflex responses compared to the two emotion regulation groups.*

H2c: Suppression will be associated with increases in startle HR amplitudes and SC magnitudes and habituation, compared to the non-instructed control group. However, no modification of sympathetic activation will be apparent for the reappraisal group.

H2d: Reappraisal will be associated with increased and delayed brain processing of acoustic startle (ERP) compared to the non-instructed control group. It is unknown whether suppression will alter ERP processes, as such mechanisms remain unstudied.

Q 3: Are experimental manipulations of reappraisal and suppression associated with differential startle responding when the effects of trait emotion regulation styles (reappraisal and suppression) are controlled for?

Q4: Are pre- and peri-trauma individual differences profiles predictive of altered startle responding, over and above the effects of manipulated emotion regulation strategies?

7.3 METHOD

7.3.1 Participants

See Methods Chapter 4 section 4.2.2.1, and appendix 16 for a flow chart of participant attrition and group allocation.

7.3.2 Measures

See the following sections within Methods Chapter 4:

Screening questionnaires section 4.1.1.1: EEG and VR screening questionnaire, PHQ9 and PC-PTSD.

Trait questionnaires section 4.1.1.2: ASI, STAI, HA, ERQ

Life events questionnaires section 4.1.1.3: SRRS, Traumatic life events checklist from the CAPS

State questionnaires section 4.1.1.4: VAS mood scale and peri-trauma dissociation measure.

Psychophysiological responses section 4.1.3: EEG, SC, ECG (i.e. HR) and EMG.

Computerised tasks section 4.1.4: VR Iraq world, Neutral VR suburban city scenario, Startle paradigm with randomised design.

7.3.3 Procedure

See Methods Chapter 4 Procedure section 4.2.2.3 for an overview of the full study design from which the data within this chapter were collected. The same set of pre-, peri and post--trauma factors will be analysed across this and the proceeding Chapter 8; however the outcome measures covered within this chapter relate only to the startle response analogue symptom measurement.

As a brief re-cap, the data within this chapter explored the influence of emotion regulation strategies (suppression, reappraisal, and non-instructed control group) on post-trauma startle responses (EMG, HR, SCR) and startle processing (ERPs), following exposure to a virtual reality trauma (Iraq world) and a virtual reality neutral scenario (suburban town). See appendix 13 for the reappraisal, suppression and control group startle task instructions. The startle task consisted of 4 blocks of 24 randomised trials; with the caveat that trials of the same type (stimulus valence and instruction combination) could not appear more than three times sequentially. Participants were exposed to 95 dB startle stimuli with either trauma (gunshot) or neutral (car horn) contents; a valence congruent foreground was also presented, which was made up of a series of different stills from the Iraq-VR and neutral-VR respectively. Startle trials were divided into trauma regulate emotions (TR) trials in which participants were instructed to use their ER strategy (25% of total trials), trauma non-instruction viewing trials (TV; 25% of total trials) and neutral (N) non-instruction viewing trials in which they viewed the stills and listened to the startle stimuli without modification of their responses (50% of the total trials). SC and HR responses were recorded during VR-trauma exposure and EEG, eye-blink EMG, SC and HR responses were recorded during the thought suppression task. The predictor and outcome variables are depicted in table 7.1.

Table 7.1: Variables included in Chapter 7 analysis of startle responses following ER manipulation. Summary of the pre- peri- and post-trauma risk and resilience factors, and analogue symptom measures.

Pre-trauma	Peri-trauma	Post-trauma	Phenotypic symptom measure of Stress sensitization
PERSONALITY: ▪ ASI ▪ STAI-T ▪ HA ▪ ERQ **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events checklist **GENDER** *COVARIATES:* ▪ Computer gaming ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**EMOTION REGULATION MANIPULATION:** ▪ Suppression vs. Reappraisal vs. Control (No manipulation)	**STARTLE (N/TV/TR trial types):** ❖ VAS Mood (positive and negative) ❖ ERP ▪ PCA (P2 & P3 amplitude) ▪ Startle ERP onset latency ❖ EMG (make into t-scores) ▪ Response magnitude ▪ Habituation ❖ HR ▪ Response amplitude ❖ SCR (range correct) ▪ Response magnitude ▪ Habituation

7.3.4 Data Pre-processing

See the following sections within Methods Chapter 4 pre-processing section (*4.2.2.3)*:

EEG section 4.2.2.3.1: Temporal PCA, Startle ERP onset latency

Physiological measures section 4.2.2.3.2: Startle response scores, VR scenario responses

Checks for normal distribution section 4.2.2.3.3.

7.3.5 Statistical analysis

To explore the effects of emotion regulation on startle responses, ANOVA was carried out to test the effects of the group emotion regulation manipulation on each startle response outcome measure and significant interactions were followed up with tests of simple effects. ANCOVA analysis was subsequently carried out to investigate the effects of the group manipulation when individual differences in trait emotion regulation (ERQ reappraisal and suppression sub scales) were controlled for. Covariate effects within ANCOVA analysis are not discussed, as the covariates are used to explain a portion of the variance in existing ER manipulation effects and illustrate unique (covariate independent) relationships with the response outcome variables. All assumptions of ANCOVA were tested prior to running the analysis. Independence of the dependent variable (group manipulation) and the covariates ERQ reappraisal ($F(1,19)=0.74$, $p=.76$) and suppression ($F(1,19)=0.9$, $p=.6$) was found and homogeneity of regression slopes was present on all startle response measures. Where the assumption of sphericity was not met in ANOVA/ANCOVA analysis, results were tested and reported using the Huynh-Feldt corrected F statistic. This initial analysis was carried out to allow for investigation of emotion regulation effects across all three manipulation conditions[13] and across neutral and trauma trial types on all physiological measures, and additionally across components and regions in EEG analysis and time in mood analysis. Furthermore this trial dependent ANOVA analysis allowed for elicitation of trial effects prior to creating averaged (i.e. trial independent measures) core outcome measures, to assess predictive effects of individual differences, when trial responses were comparable to such an extent that the separate regression of individual differences on each would not make theoretic sense; as described further in 7.4.3.1. Due to the nature of the study design, with trauma-regulate (TR) and trauma-view (TV) trials both measuring non-instructed trauma startle responses in the control group, analysis was carried out in such a way that the artificial trauma trial type distinction for the control participants was never analysed. As such neutral (N) and TR trials were analysed separately from N and TV trials, across all groups to allow for investigation of regulation facilitated effects and the presence of carry over effects on TV trials, whilst the TR and TV trial type distinction was analysed only for individuals in the two emotion regulation (suppress and reappraise) groups.

Following initial ANOVA and ANCOVA analysis, all subsequent analysis investigated effects on core outcome measures for each electrophysiological and peripheral parameter. Zero-order

[13] Where running such analysis in regression to compare all three group manipulations would have required

correlations were carried out to test the relationships between all individual difference predictor variables (pre- and peri-trauma vulnerabilities) and each outcome measure, and to control for predictor variable multicollinearity in later regression models. The only predictor variables which showed inter-correlations of >.7 was a positive relationship between playing computer games and an increased peri-traumatic HR during the first Iraq virtual reality exposure ($r(117)=.76$, $p=.002$); however both variables were never correlated with the same outcome in the correlation table and hence were never entered into a regression model together. A number of the outcome measures showed high correlations (>.7) within a single measurement parameter (e.g. SC response) across different trial types and time points (e.g. SC response on trauma view and neutral trials). Correlated outcomes were examined further using Cronbach's alpha to assess their internal consistency, on items with Cronbach's alpha >.7 a composite measure was created independent of trial type. Correlations were subsequently carried out to determine pre- and peri-trauma individual difference factors that were correlated with the core outcome measures. Correlated individual differences factors were entered into a regression model on each outcome measure to assess predictive effects and the size of the variance explained by these factors. To control for the influence of manipulated emotion regulation in the investigation of the influence of individual difference variables over and above manipulated effects, individual difference regression models all contained the group manipulation as a dummy variable in block one. To explore the influence of emotion regulation strategies and PTSD related pre and peri-trauma factors, subsequent blocks within each model were comprised of predictor variables which showed significant zero order correlations with the respective outcome measure. Where outlying cases changed the regression model qualitatively the model with these cases replaced with a value one unit larger or smaller than the next score in the distribution (Tabachnick & Fidell, 2001) is reported.

7.4 RESULTS

7.4.1 Utility of VR-trauma induction: Manipulation check

Across all mood reports, negative mood was found to significantly increase, whilst positive mood was found to significantly reduce. Furthermore whilst anxiety significantly increased post-VR, calmness reduced; illustrating that the VR-trauma induced negative mood change and arousal induction (See table 7.2).

Correlations between physiological and self-report (change scores) peri-traumatic measures showed that increased HR response during the traumatic sequence of the VR film, compared to the preceding portion of the VR scenario, was associated with an increased self-report of STAI (r(111)=.25, p=.008), dissociation (r(110)=-.285, p=.002) and trauma SC response, corrected against preceding film section (r(113)=.404, p<.001) and corrected against resting baseline response (r(113)=.334, p<.001). HR response in the trauma sequence compared to BL response was also associated with STAI (r(111)=.218, p=.02) and trauma SC response, corrected against preceding film section (r(113)=.235, p=.011) and corrected against resting baseline response (r(113)=.760, p<.001). SC responding during the traumatic sequence of the VR film, compared to baseline responding, was negatively associated with dissociation (r(112)=-.293, p=.002). These findings provide support for the validity of the self-report measures used within this VR paradigm.

Table 7.2: Change in mood ratings from pre-VR to post-VR exposure

Mood variable	Pre-VR	Post-VR	*t*	*df*
Sad	.99 (1.26)	3.24 (2.30)	10.98***	119
Happy	6.33 (1.74)	4.22 (2.08)	11.87***	119
Anxious	1.85 (1.98)	4.85 (2.63)	-8.59***	119
Depressed	.76 (1.19)	2.15 (2.07)	-7.97 ***	119
Calm	6.96 (1.66)	3.91 (2.19)	14.36***	119
Hopeless	.66 (1.01)	2.23 (2.15)	-8.35***	119
Angry	.52 (0.68)	2.32 (2.32)	-8.7***	119
STAI-S	32.21 (7.43)	46.55 (11.43)	-14.74***	119

Note. ***= p<.001. Standard deviations appear in parenthesis below means

The neutral nature of the suburban VR scenario was also confirmed by the lack of significant changes in happiness from pre (M=6.26) to post (M=6.08) (t(119)=1.81, p=.074), calmness from pre (M= 6.76) to post (M=6.68) (t(117)=.48, p=.633), hopelessness from pre (M=.85) to post (M=0.80) (t(117)=.65, p=.517) and STAI state pre (M=32.65) to post (M=32.43) (t(116)=.48, p=.631). There was a significant reduction in sadness from pre (M=1.46) to post (M=1.13) (t(117)=3.26, p=.001), anxiety pre (M=3.03) to post (M=2.33) (t(117)=3.75, p<.001), depression pre (M=1.01) to post (M=0.84) (t(117)=2.62, p=.01); however unexpectedly there was a significant increase in anger pre(M=0.53) to post (M=0.63) (t(117)=-2.01, p=.046). Although the suburban VR did not act as a positive mood induction, it did result in a general reduction in negative affect, possibly due to a heightened level of anticipatory worry prior to the VR viewing.

Further support for successful anxiety and arousal induction as a result of the traumatic Iraq scenario was illustrated by significant increases in negative and anxious mood and SC responses from neutral VR to trauma VR viewings (table 7.3). HR was slightly higher during the trauma (M=-1.80) compared to the neutral (M=-1.37) VR scenario, however this difference failed to reach significance (t(116)=.86, p=.392).

Table 7.3: Change in mood from post-neutral to post-trauma VR scenarios

Mood variable	Mean neutral VR	Mean trauma VR	*t*	*df*
SC	.09 (0.18)	.19 (0.26)	-5.74***	121
STAI	-.21 (4.85)	14.48 (10.77)	-12.4***	115
Low mood	-.37 (2.01)	7.33 (6.85)	-11.92***	119
Anxiety	-.70 (2.03)	3.00 (3.82)	-9.62***	119

Note. ***= *p*<.001. Standard deviations appear in parenthesis below means

7.4.2 Subjective evaluations of startle sounds

Although evaluations of the trauma and neutral sounds did not differ across group manipulation conditions (Table 7.4), in general participants found the gun shot sound significantly more distressing and upsetting and the car horn sound more loud and unpleasant(Table 7.4), potentially due to the higher frequency composition of the car horn sound.

Table 7.4: Differences in subjective sound valence and quality evaluations across group manipulations and averaged over all participants

Subjective evaluation		Reap Count	Sup Count	Control Count	Total Count	Group effect χ^2	Total effect χ^2
Distressing	**Gun-shot**	18	21	22	61	2.19	47.82***
	Car horn	7	7	10	24		
	Same	9	7	5	21		
Upsetting	**Gun-shot**	26	26	22	74	3.49	10.65**
	Car horn	2	4	6	12		
	Same	6	5	9	20		
Loud	**Gun-shot**	2	2	3	7	1.61	27.94***
	Car horn	23	22	20	65		
	Same	9	11	14	34		
Unpleasant	**Gun-shot**	8	14	11	33	2.43	58.12***
	Car horn	18	15	17	50		
	Same	8	6	9	23		

Note: **= p<0.01, ***= p<0.001; Reap = reappraisal manipulation, Sup= suppression manipulation, Control = no-manipulation.

7.4.3 Role of manipulated emotion regulation (ER) in startle responses

The proceeding section will answer the following research questions, within respectively indicated analysis:

ANOVA:

Q1: Are affective and electrophysiological startle mechanisms sensitive to trauma versus neutral valence effects following exposure to a virtual reality trauma? Are there ER manipulation dependent differences in responses, when individuals are required to regulate their emotions to trauma stimuli (TR), receive uninstructed exposure to trauma stimuli (TV) and receive uninstructed exposure to neutral stimuli (N)?

Q2: Do explicitly instructed emotion regulation strategies influence affective, physiological (eye-blink, HR and SC) and brain processing (ERP) startle responses?

ANCOVA

Q 3: Are experimental manipulations of reappraisal and suppression associated with differential startle responding when the effects of trait emotion regulation styles (reappraisal and suppression) are controlled for?

Where analyses are testing predictions based on prior research findings, rather than exploring new research avenues, specific hypotheses are listed in regards to each emotional and physiological startle response parameter.

7.4.3.1 Negative and Positive Mood

The following analysis will investigate the influences of emotion regulation manipulations on self-reported negative and positive mood measured at four intervals across course of the acoustic startle paradigm (and baseline corrected against mood measured immediately prior to the startle paradigm), addressing hypothesis 2a:

> *H2a: Decreased negative affect and increased positive affect during the startle paradigm will apparent for the reappraisal group compared to control group. However, no affect modification will be apparent for the suppression group compared to the control group.*

In support of the hypothesised direction of mood change in relation to startle stimuli, main effect of mood was present (F(1, 112)=148.83, p<.001) showing that in general the startle paradigm induced higher negative mood (M=0.52) than positive mood (M=-3.01); with a linear (F(1,112)=61.34, p<.001) time by mood interaction (F(2.87, 320.83)=28.17, p<.001) illustrating significantly higher negative mood ratings at time one (M=0.75) with a linear decrease across the startle task (F(1,288.6)=29.07, p<.001; Bonferroni corrected) and lower positive mood ratings at time one (M=-3.75) with a linear increase (F(3,322.28)=47.13, p<.001; Bonferroni corrected) (figure 7.1). Although the main effect of mood remained when controlling for TRAIT ER STYLE scores the interaction across time was no longer significant (F(3,320.25)=0.14, p=.935) , suggesting it was driven in part by individual differences in ER styles.

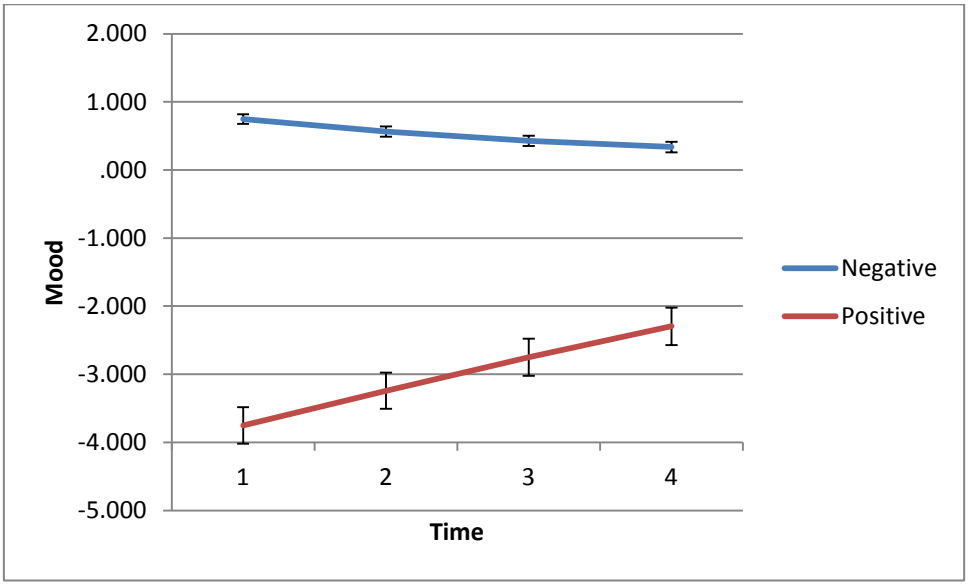


Figure 7.1: Time by mood interaction for VR affect. Habituation of positive and negative mood across the startle task (baseline corrected against mood prior to the startle paradigm).

The main effect of regulation group only approached significance in ANOVA analysis (F(2,112)=2.99, p=.051) and when controlling for trait ER STYLE scores (F(2, 110)=2.82, p=.064); illustrating a trend towards increased overall mood, induced by the startle task, in the suppress group compared to the control group (MD=0.58, SE=.25, p=.065). However, a significant mood by regulation group interaction was present (F(2, 322.11)=4.43, p=.014), which remained when controlling for trait ER STYLE scores (F(2, 112)=4.43, p=.014). Follow up simple effects analysis and post hoc tests showed that ER manipulation group responses differed across positive mood (F(2,112)=3.98, p=.062; Bonferroni corrected) but not negative mood (F(2,112)=3.59, p=.42; Bonferroni corrected) affects; with the regulation group main effect and the mood by ER interaction effect driven specifically by a lower positive mood

during the startle task in the control group compared to the suppress group (MD=1.52, SE=.587, p=.032; Bonferroni corrected). This finding is in contrast to hypothesis 2a in relation to the presence of suppression related effects on startle induced mood responses and respective lack of reappraisal related mood alterations (figure 7.2).

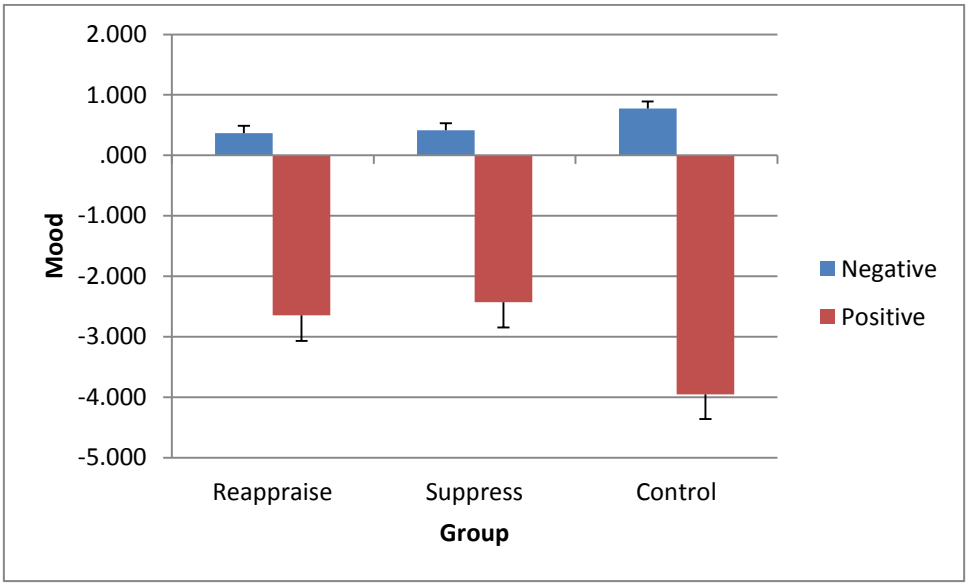


Figure 7.2: Group by mood interaction for VR affective. Mean differences in startle paradigm induced positive and negative mood (baseline corrected against mood prior to the startle paradigm), across ER manipulation and control groups.

The time by regulation group interaction approached significance in both ANOVA analysis (F(5.75, 322.11)=2.05, p=.061) and when controlling for trait ER STYLE scores (F(6,322.59)=2.14, p=.050). The covariate time by group interaction effect (figure 7.3), was on the border of significance and was driven by increased mood reporting in the suppress group at time 4, compared to time 1 (MD=0.49, SE=0.16, p=.024; Bonferroni corrected) and 2 (MD=0.47, SE=0.15, p=.022; Bonferroni corrected) and the control group at time 3 compared to time 1 (MD=0.7, SE=0.2, p=.007; Bonferroni corrected) and time 4 compared to time 1 (MD=0.75, SE=0.18, p=.001; Bonferroni corrected) and time 2(MD=0.53, SE=0.18, p=.039; Bonferroni corrected); with no mood change across time in the reappraise group, again disconfirming the hypothesised reappraisal effects. This interaction was not driven differentially by changes in either negative or positive mood reporting, with a lack of a significant three way interaction between time, mood and regulation group in ANOVA analysis (F(5.73, 320.84)=1.41, p=.215) or ANCOVA analysis controlling for trait ER STYLE (F(5.73,

320.25)=1.36, *p*=.232), suggesting that the aforementioned interaction illustrates a general increase in mood reporting, of both valences, across time.

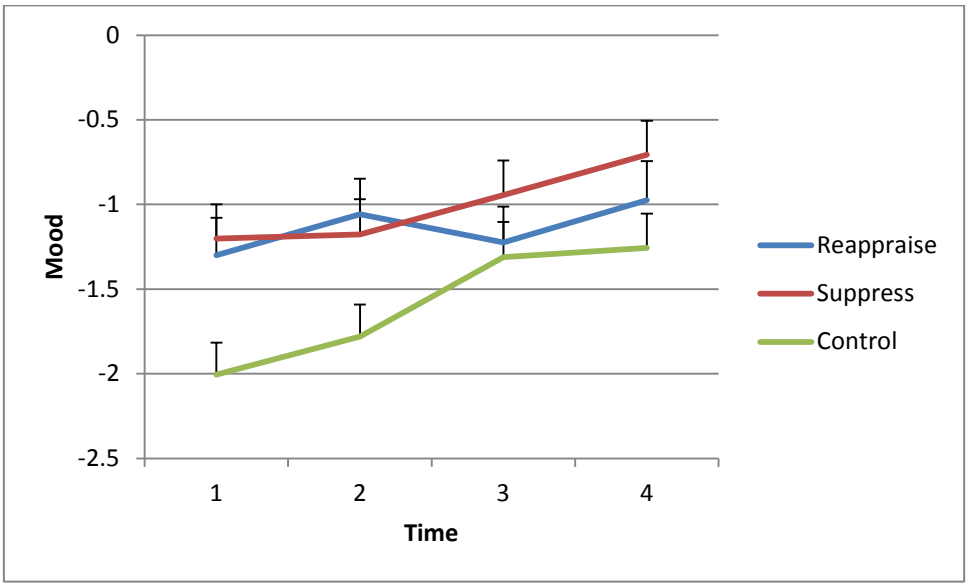


Figure 7.3: Time by group interaction for VR affective (approaches significance). Mood reporting across the startle task (baseline corrected against mood prior to the startle paradigm), across ER manipulation and control groups.

7.4.3.2 EMG

The following analysis will investigate the influences of emotion regulation manipulations on the magnitude of automatic eye-blink responses in relation to TR, TV and N acoustic startle trials, addressing hypothesis 1 and 2b:

H1: Affective and physiological startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli. ER manipulation effects will be greatest on TR trials.

H2b: Both suppression and reappraisal will attenuate participants reflex startle eye-blink responses and habituation of these responses. The control (view) condition is expected to show heightened reflex responses compared to the two emotion regulation groups.

7.4.3.2.1 EMG magnitude

No main effect of regulation group was found across any of the comparisons (TR/TV: $F(1,75)=0.81$, $p=.37$; N/TR: $F(1,115)=0.54$, $p=.584$; N/TV: $F(1,115)=0.84$, $p=.443$) and no effect of trial type was found for startle eye blink responses across the TR and TV comparison ($F(1,75)=0.09$, $p=.766$) or N and TV comparison ($F(1,115)=2.22$, $p=.139$); with N and TR

comparison only producing a trend towards a trial main effect ($F(1,115)=3.44$, $p=.066$), which was no longer present when controlling for trait ER styles ($F(1, 113)=0.66$, $p=.419$) .

However in partial support of hypothesis 1 and 2b EMG facial eye blink responses across trauma regulate (TR) and trauma non-regulate (TV) trials illustrated a significant interaction of trial type and regulation group ($F(1,75)=6.65$, $p=.012$), which remained when controlling for trait ER styles ($F(1,73)=5.61$, $p=.021$). Follow up simple effects analysis illustrated that this interaction was driven by significantly reduced eye-blink startle responses on TR trials compared to TV trials in individuals instructed to suppress their behavioural responses ($F(1, 37)=5.83$, $p=.042$; Bonferroni adjusted), whilst reappraisal had no significant effects on eye blink startle across TR and TV trials ($F(1,38)=2.04$, $p=.324$; Bonferroni adjusted) (Figure 7.4). The interaction between trial type and regulation group also approached significance in the comparison of N and TR trials in ANOVA ($F(2,115)=3.04$, $p=.052$) and covariate analysis ($F(2, 113)=2.53$, $p=.084$), but did not reach significance for the comparison of N and TV trials ($F(2,115)=0.18$, $p=.84$). The trend for a trial by regulation group interaction, in comparison of N and TR trials, was again driven by the reduction in startle eye-blink on TR trials compared to N trials for the suppression group($F(1,38)=0.54$, $p=.026$; Bonferroni adjusted), with no trial effect present for the control ($F(1,37)=6.86$, $p=.94$; Bonferroni adjusted) or reappraisal ($F(1,40)=1.84$, $p=.37$; Bonferroni adjusted) groups (Figure 7.5).

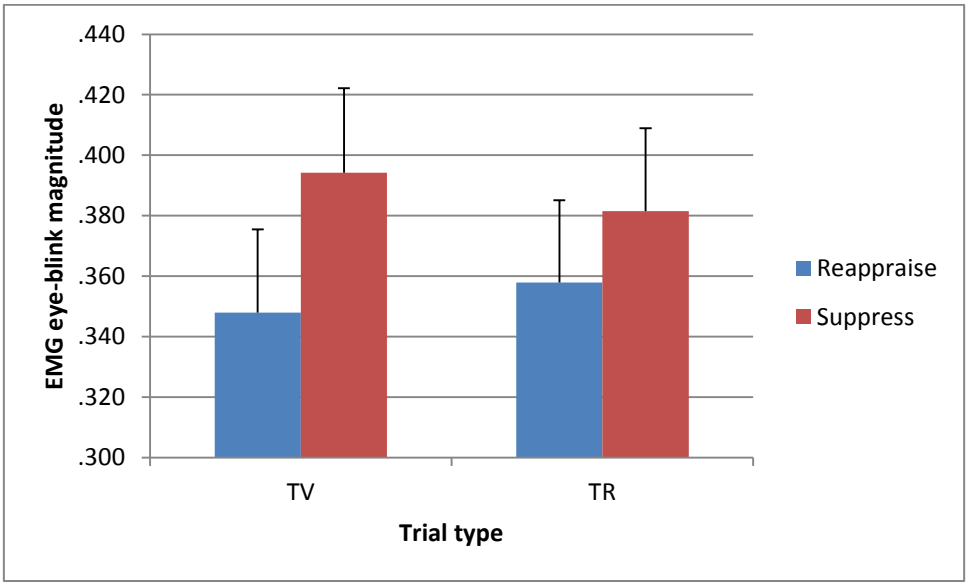


Figure 7.4: The magnitude of startle eye-blink responses on trauma non-instruction trials (TV) and trauma regulate (TR) trials across the two regulation groups.

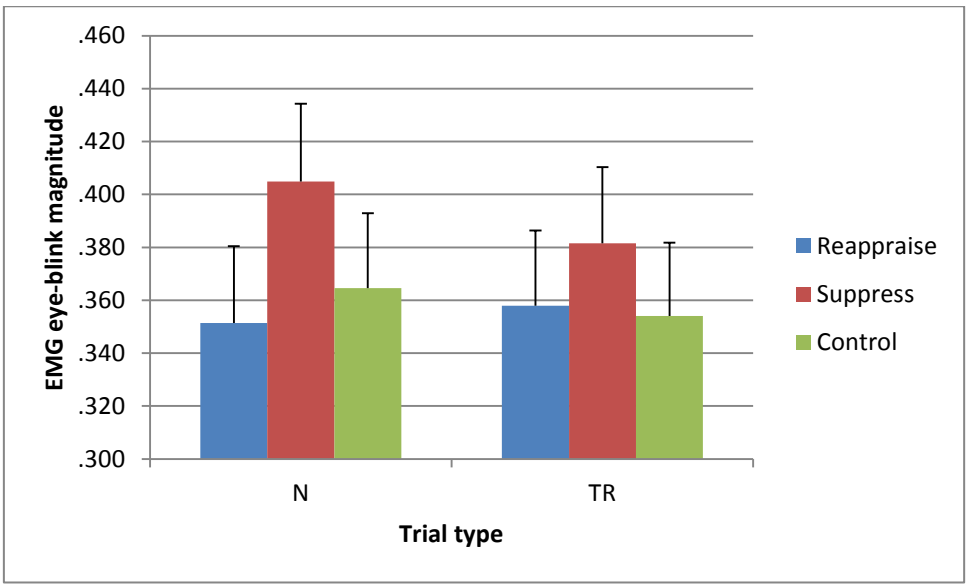


Figure 7.5: The magnitude of startle eye-blink responses for neutral and trauma regulate trials across regulation manipulation and control groups, controlling for the effects of trait reappraisal and suppression styles; comparison of neutral and trauma-regulate (TR) trials.

7.4.3.2.2 EMG habituation

The data does not support hypothesis 1 or 2b in relation to the habituation of startle eye-blink responses. For the number of trials to reach EMG non-response habituation criterion, there were no significant interactions or main effects, for any of the analysis of trial type or ER manipulation condition.

7.4.3.3 Skin conductance (SC)

The following analysis will investigate the influences of emotion regulation manipulations on the magnitude of SC responses in relation to TR, TV and N acoustic startle trials, addressing hypothesis 1 and 2c:

H1: Affective and physiological startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli. ER manipulation effects will be greatest on TR trials.

H2c: Suppression will be associated with increases in startle HR amplitudes and SC magnitudes and habituation, compared to the non-instructed control group. However, no modification of sympathetic activation will be apparent for the reappraisal group.

7.4.3.3.1 SC magnitude

Findings for startle related SC magnitudes did not support hypothesis 1. Although SC responses differed between neutral and trauma trial types (N/TV (F(1,115)=9.77, p=.001; N/TR (F(1,115)=10.96, p=.001), surprisingly this was driven by higher SC responses on neutral trials (M=0.16) compared to TV (M=0.15) and TR (M=0.15) trials; the effect of trial type was no longer apparent when controlling for trait differences in ER styles across N and TR trials (F(1,113)=0.032, p=.859 and reduced to a trend in comparison of N and TV trials (F(1,113)=3.28, p=.073). No differences in SC response magnitudes were apparent across trauma regulate (TR) and non-regulate (TV) trials and (F(1,75)=0.02, p=.884) no significant ER manipulation main effects (N/TV: F(2,115)=1.03, p=.362; N/TR: F(2,115)=1.15, p=.319; TR/TV: F(1,75)=1.32, p=.254) or trial type interactions (N/TV: F(1,115)=0.21, p=.813; N/TR: F(1,115)=0.32, p=.73; TR/TV: F(1,75)=0.02, p=.90) were apparent in ANOVA, or when controlling for trait ER styles.

7.4.3.3.2 SC habituation

Hypothesis 1 was not supported for startle SC habituation, with the number of trials to reach SC habituation not differing between trials in general (N/TV: F(1,115)=1.66, p=.201; N/TR: F(1,115)=0.8, p=374. ;TR/TV: F(1,115)=, p=.272) or between trials over ER manipulation group (N/TV: F(2,115)=0.4, p=.674; N/TR: F(2,115)=0.55, p=.578 ;TR/TV: F(1,75)=0.11, p=.741) in ANOVA analysis, or when controlling for trait ER styles.

Evidence was found to support hypothesis 2c in relation to SC habituation trajectories. No main effects of regulation group were present for comparisons of trauma TR and TV trials in ANOVA (F(1,75)=2.19, p=.143) , or when controlling for trait ER styles (F(1,73)=1.53, p=.22). However, there was a trend towards a main effect of regulation group in analysis of N and TV trials (F(1,115)=0.55, p=.084), which remained when controlling for trait ER styles (F(2,113)=2.5, p=.087); this trend was driven by increased trials to SC habituation in the suppress (M=10.96) relative to the control (M=7.02) group (MD=3.94, SE=1.78, p=.087), with the reappraise group (M=8.27) showing no differences in SC habituation profiles compared to the suppress (MD=-2.69, SE=1.80, p=.414) or control group (MD=1.24, SE=1.77, p=.1.00). Furthermore, there was a significant main effect of ER manipulation group for the analysis of N and TR trials (F(2,115)=3.7, p=.028) (figure 7.6), which remained when the effects of trait ER style were controlled for (F(2,113)=3.7, p=.027). Post hoc contrasts illustrated that the SC responses in the suppression group (M=11.24) took longer to habituate compared to the control (M=6.45) group (MD=4.79, SE=1.76, p=.023), with no differences in SC habituation

profiles between the cope group (*M*=8.78) compared to the suppress (MD=-2.45, SE=1.78, p=.513) and control groups (MD=2.33, SE=1.75, p=.555).

No trial type by ER manipulation interactions were present in ANOVA (N/TV: *F*(2,115)=0.4, *p*=.674; N/TR: *F*(2,115)=9.82, *p*=.551; TR/TV: *F*(1,75)=0.11, *p*=..741) or ANCOVA (N/TV: *F*(2,113)=3.7, *p*=.689; N/TR: *F*(2,113)=0.56, *p*=.575; TR/TV: *F*(1,73)=0.12, *p*=.734) analysis.

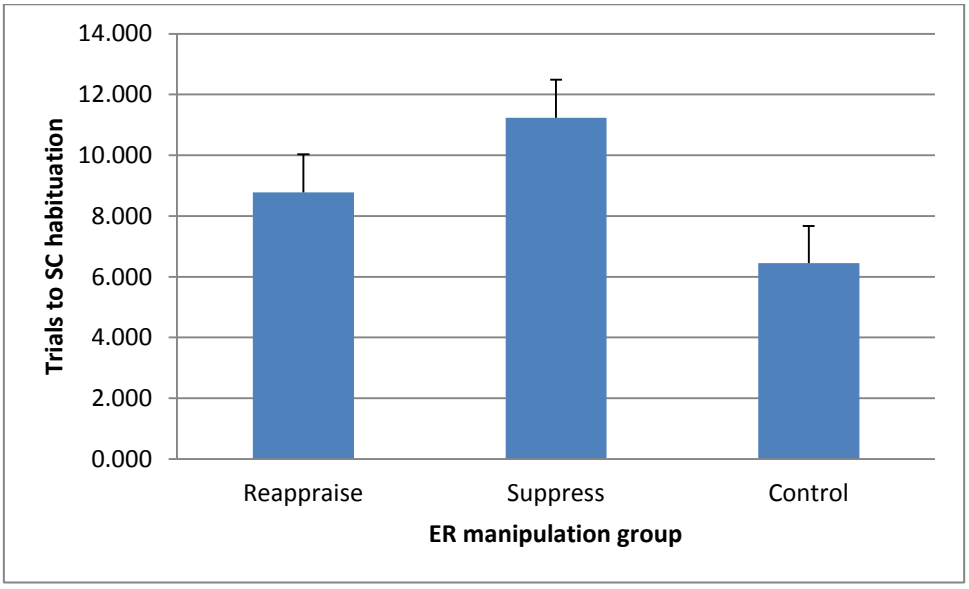


Figure 7.6: Number of trials to reach SC habituation (i.e. criterion of non-response on two successive trials) across each of the ER manipulations and control group; comparison of N and TR trials.

7.4.3.4 Heart rate (HR) amplitude

The following analysis will investigate the influences of emotion regulation manipulations on the amplitude of HR responses in relation to TR, TV and N acoustic startle trials, addressing hypothesis 1 and 2c:

> *H1: Affective and physiological startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli. ER manipulation effects will be greatest on TR trials.*
>
> *H2c: Suppression will be associated with decreases in startle HR amplitudes and SC magnitudes and habituation, compared to the non-instructed control group.*

In contrast to hypothesis 1, HR responses differed between neutral (N) trials and trauma TV trials (*F*(1,109)=5.2, *p*=.024) and TR trials (*F*(1,109)=5.28, *p*=.024) trials with increased HR amplitudes on N trials (*M*=2.83) compared to TV (*M*=2.76) and TR (*M*=2.76) trials; however

when controlling for trait ER scores the trial type differences were no longer apparent (N/TV: $F(1,107)=0.00$, $p=.996$; N/TR: $F(1,107)=0.22$, $p=.638$). Furthermore, HR responses showed no differentiation between trauma regulate (TR) and non-regulate (TV) trials in ANOVA analysis ($F(1,70)=0.00$, $p=.995$) or when controlling for ERQ scores ($F(1,68)=0.34$, $p=.56$).

There was no difference in HR responses across the regulation manipulation groups in ANOVA (N/TV: $F(2, 109)=0.33$, $p=.717$; N/TR: $F(2,109)=0.44$, $p=.65$; TR/TV: $F(1,70)=0.04$, $p=.847$) or when controlling for the influence of trait ER styles (N/TV: $F(2, 107)=0.18$, $p=.839$; N/TR: $F(2,107)=0.2$, $p=.82$; TR/TV: $F(1,68)=0.09$, $p=.767$), and no interaction between trial type HR and regulation group for comparisons of N and TR trials ($F(1,109)=1.59$, $p=.208$) or TR and TV trials ($F(1,70)=0.36$, $p=.551$); showing a general lack of support for hypothesis 2c in relation to HR amplitude change. However, the interaction between trial type and regulation group approached significance comparison of N and TV trials ($F(2,109)=2.67$, $p=.074$) and remained when controlling for trait ER styles ($F(1,107)=2.42$, $p=.093$). Follow up simple effects analysis illustrates the trend is driven by increased HR responses on neutral trials compared to trauma trials in the control group ($F(1,39)=5.794$, $p=.042$, Bonferroni adjusted), with no trial type differences in HR responses for the suppress ($F(1,35)=3.58$, $p=.134$, Bonferroni adjusted) or reappraise ($F(1,35)=0.49$, $p=.976$, Bonferroni adjusted) groups.

7.4.3.5 EEG

7.4.3.5.1 PCA components

The following analysis will investigate the influences of emotion regulation manipulations on the amplitude and latency of principal components underlying startle ERPs, in relation to TR, TV and N acoustic startle stimuli, addressing hypothesis 1 and 2d:

H1: Affective and physiological startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli. ER manipulation effects will be greatest on TR trials.

H2d: Reappraisal will be associated with increased and delayed brain processing of acoustic startle (ERP) compared to the non-instructed control group. It is unknown whether suppression will alter ERP processes, as such mechanisms remain unstudied.

In addition to analysis of hypothesised effects, analysis was carried out to explore the nature of differences between the P2 and P3 PCA startle components and the scalp topography of these electroencephalographic brain responses. A significant main effect of startle ERP

components was present across all PCA analysis (N/TR: $F(1,114)=6.93$, $p=.01$; N/TV: $F(1,114)=7.59$, $p=.007$; TR/TV: $F(1,75)=7.51$, $p=.008$), with generally increased component scores on P2 ERP component (N/TR: $M=1.06$; N/TV: $M=1.07$; TR/TV: $M=1.15$) compared to P3 (N/TR: $M=0.68$; N/TV: $M=0.67$; TR/TV: $M=0.64$) ERP component; however the differences in amplitudes across components was related to trait ER styles, with the main effect no longer present in ANCOVA($F(1,73)=3.01$, $p=.087$) . A significant effect of region (N/TR: $F(1,114)=59.03$, $p<.001$; N/TV: $F(1,114)=49.66$, $p<.001$; TR/TV: $F(1,75)=43.21$, $p<.001$) and a component by region interaction (N/TR: $F(1,114)=106.4$, $p<.001$; N/TV: $F(1,114)=105.36$, $p<.001$; TR/TV: $F(1,75)=87.03$, $p<.001$)was also apparent for PCA component analysis, with Bonferroni corrected simple effects analysis illustrating that the P2 startle component was greater in the frontal region than the parietal region (N/TR: $F(1,114)=138.47$, $p<.001$; N/TV: $F(1,114)=135.7$, $p<.001$; TR/TV: $F(1,75)=3.36$, $p<.001$) and the P3 was greater in the parietal than frontal region (N/TR: $F(1,114)=32.17$, $p<.001$; N/TV: $F(1,114)=35.88$, $p<.001$; TR/TV:$F(1,75)=119.55$, $p<.001$); see figure 7.7 for an illustration of the interaction effect. Greater amplitudes were found in the frontal posterior mid region (N/TR: $M=1.49$; N/TV: $M=1.5$; TR/TV: $M=1.6$) compared to the parietal mid region (N/TR: $M=0.63$; N/TV: $M=0.65$; TR/TV: $M=0.69$) for the earlier component, and greater amplitudes were found in the parietal mid region (N/TR: $M=0.85$; N/TV: $M=0.87$; TR/TV: $M=0.86$) compared to the frontal posterior mid region (N/TR: $M=0.5$; N/TV: $M=0.48$; TR/TV: $M=0.42$) for the later component. However, again, when controlling for the effects of trait ER styles on the outcome both the region main effect and component interaction were no longer apparent.

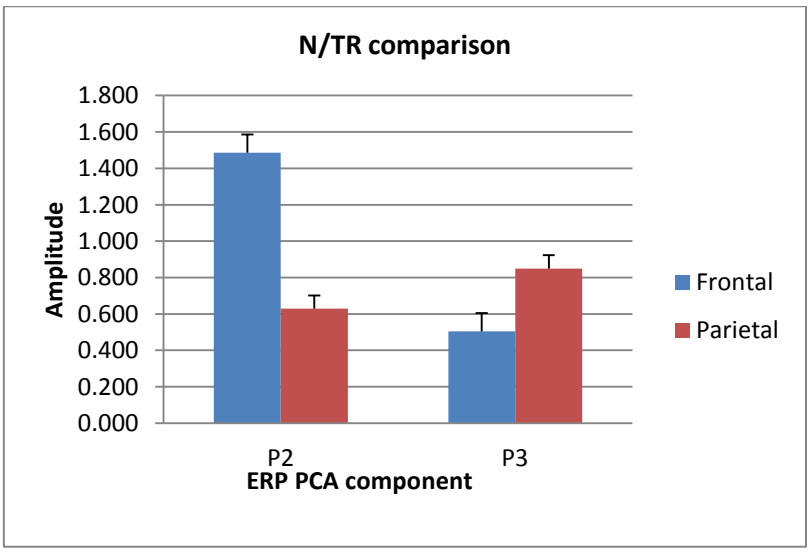


Figure 7.7: P2 and P3 startle ERP component amplitudes across the mid brain within the frontal-posterior brain region and the parietal brain region (without controlling for the influence of trait ER styles), an illustration of the effect within N and TR comparisons.

A significant effect of trial type was apparent across all trial comparisons (N/TR: $F(1,114)=49.626$, $p<.001$; N/TV: $F(1,114)=93.34$, $p<.001$; TR/TV: $F(1,75)=15.6$, $p<.001$) , with greater component scores towards neutral trials (N/TR: $M=0.8$; N/TV: $M=.8$) in comparison with trauma TR and TV trials,(N/TR: $M=0.94$; N/TV: $M=0.96$) and towards TV trials (M=0.93) compared to TR trials (M=0.86) ; however the differences in amplitudes across components was related to trait ER styles, with the main effect no longer present in ANCOVA analysis. Illustrating that hypothesis 1 related trial effects are dependent upon individual differences in trait ER styles. Comparisons of N and TR trials ($F(1,114)=32.53$, $p<.001$) and N and TV ($F(1,114)=43.58$, $p=<.001$) showed a significant interaction between component and trial type (i.e. sound valence). Follow up simple effects analysis illustrated this interaction was due to a lack of trial type differences for the P3 startle component amplitudes (N/TR: $F(1,114)=1.65$, $p=.402$, Bonferroni adjusted; N/TV: $F(1,114)=0.73$, $p=.788$, Bonferroni adjusted; TR/TV: $F(1,75)=2.56$, $p=.228$, Bonferroni adjusted) (TR/N analysis TR: $M=0.65$ N: $M=0.71$; TV/N analysis TV: $M=0.66$, N: $M=0.69$), and increased P2 startle ERP responses on both trauma trials compared to neutral trials, see figure 7.8 for an example (N/TR: $F(1,114)= 103.95$, $p<.001$; N/TV: $F(1,114)=152.131$, $p<.001$) (TR: $M=1.23$, N:$M=0.89$, TV: $M=1.27$ $N{:}M=0.88$), with comparisons of trauma types illustrating a significant increase in P2 startle amplitudes on TV trials compared to TR trials ($F(1,75)=5.28$, $p=.048$, Bonferroni adjusted). However the addition of the trait ER covariates reduced the interaction to a trend for the N and TR comparison ($F(1,112)=3.32$, $p=.071$) and non-significance for N and TV comparison $F(1,112)=1.9$, $p=.171$).

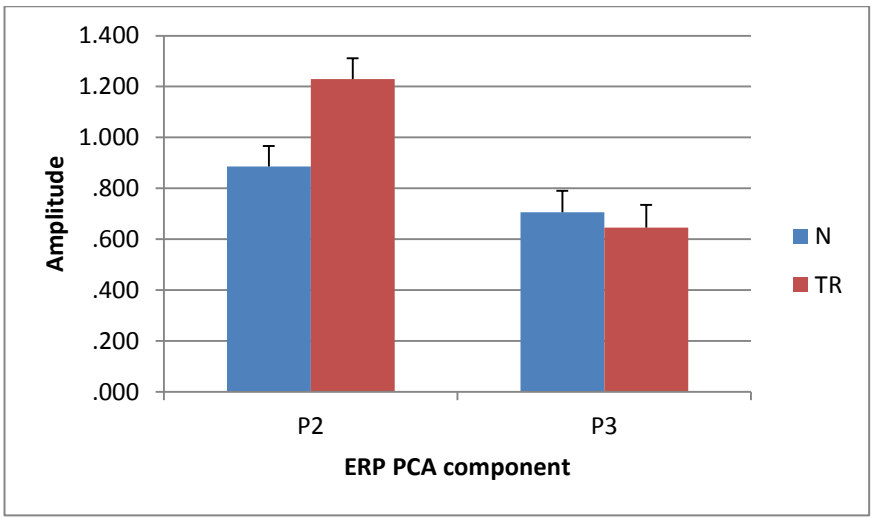


Figure 7.8: P2 and P3 startle ERP component amplitudes across the startle trial types (without controlling for the influence of trait ER styles), an illustration of the effect within N and TR comparisons.

There was no effect of regulation group on overall amplitudes of ERP P2 and P3 startle components, or any interactions with regulation manipulation group. Providing no support for hypothesis 2d in relation to PCA derived P2 and P3 startle ERP components.

7.4.3.5.2 ERP onset latency

The following analysis will investigate the influences of emotion regulation manipulations on the amplitude and onset latency of startle ERPs, in relation to TR, TV and N acoustic startle stimuli, addressing hypothesis 1 and 2d:

H1: Affective and physiological startle responses will be increased towards trauma related stimuli compared to neutrally related stimuli. ER manipulation effects will be greatest on TR trials.

H2d: Reappraisal will be associated with increased and delayed brain processing of acoustic startle (ERP) compared to the non-instructed control group.

In addition to analysis of hypothesised effects, analysis was carried out to explore the time at which electroencephalographic startle responses occurred within different brain regions. A significant main effect of region was apparent across all analysis, (N/TR: $F(1,114)=70.01$, $p<.001$; N/TV: $F(1,114)=73.31$, $p<.001$; TR/TV: $F(1,75)=47.1$, $p<.001$) with earlier times of startle ERP responding occurring in the frontal posterior mid region (N/TR: $M=209.26$; N/TV: $M=208.73$; TR/TV: $M=203.97$), compared to the parietal region (N/TR: $M=236.95$; N/TV: $M=236.22$; TR/TV: $M=231.1$)n; however brain regional differences in the time of the startle

ERP were in fact related to trait differences in ER styles, with the effect of region lost in N and TV, and TR and TV ANCOVA analysis, and reduced to a trend in the N and TR ANCOVA analysis (F(1,73)=2.78, p=.098).

No differences were apparent in ERP onset latencies across trauma TR and TV trials (F(1, 75)=0.86, p=.358). However ERP startle responses did vary across N and TR comparisons (F(1,114)=17.52, p<.001) and N and TV (F(1,114)=22.71, p<.001) trial comparisons, with earlier ERP onset latencies occurring on TR (M=217.09) and TV (M=215.82) trials compared to N (M=229.12) trials; however trial dependent differences in the time of the startle ERP were in fact related to trait differences in ER styles, with the trials effect no longer present with the addition of ERQ scores as covariates. Illustrating that hypothesis 1 related trial effects are dependent upon individual differences in trait ER styles. Additionally, when accounting for the influence of the trait ER styles on analysis of trauma TR compared to TV trials an interaction between trial type and region was apparent (F(1,73)=9.96, p=.002). Follow up simple effects analysis illustrated that this interaction was due to a faster ERP onset latency on startle TV trials compared to TR trials in the frontal region (F(1,73)= 4.4, p=.078, Bonferroni correction) and no significant differences in onset latency for trauma trial types in the parietal region (F(1,73)= 3.75, p=.114, Bonferroni correction) with a marginally larger difference between onset latencies of ERP responses across the two regions on TR trials (FrPm: M=204.79, Pm: M=232.19) compared to TV trials (FrPm: M=203.17, Pm: M=230).); however correction for multiple comparisons reduced the frontal effect to only a trend, and plots (figure 7.9) and means illustrate that trial type differences are very minimal within both regions. Disconfirming hypothesis 2d in relation to the onset latency of startle ERP responses, no effects or interactions with regulation group were found across any analysis.

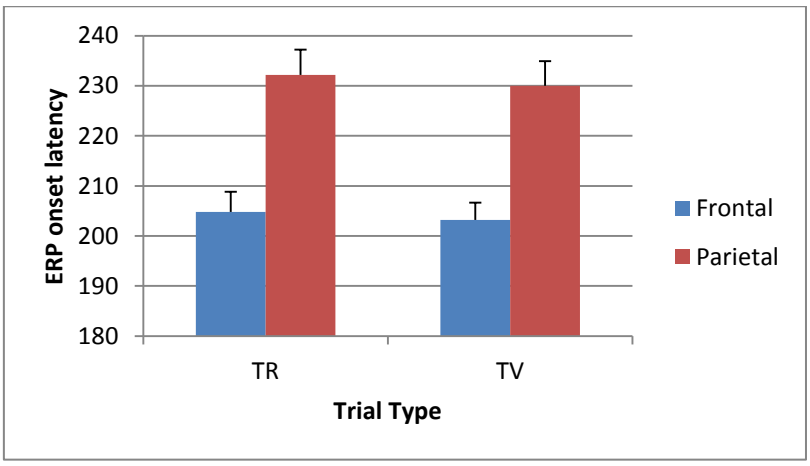


Figure 7.9: ERP onset latency on trauma TR and TV trials across the mid brain within the frontal-posterior brain region and the parietal brain region; controlling for the influence of trait ER styles.

7.4.4 Role of pre- and peri-VR-trauma individual differences in startle responses, over and above ER manipulations

The proceeding section will answer the following exploratory research question:

Q5: Are pre- and peri-trauma individual differences profiles predictive of altered startle responding, over and above the effects of manipulated emotion regulation strategies?

7.4.4.1 Creation of summed outcome measures of emotional and physiological startle responses

Due to the lack of consistent trial (TR/TV/N) by regulation group manipulation effects across ANOVA and ANCOVA analysis, and the high correlations and Cronbach's alphas of >.7 across trial type responses for each startle outcome measure (Table 7.10); physiological responses were summed across trial type to create a generalised startle response measure. The same was true of across task negative and positive mood responses, with the 4 mood measurement time points showing high correlations and cronbach's alpha's within each mood (Table 7.10). As such, these time dependent scores also were summed to create a single outcome variable representing startle related positive affect and negative affect respectively. The only exception to these high correlations was for the comparison of neutral and trauma trials for ERP onset latency scores across both the frontal and parietal brain region (Table 7.5). Therefore, although TR and TV trials were averaged to create a trauma independent ERP variable, the distinction

between neutral and trauma trials was retained so as neutral and trauma represented two separate outcome measures for each brain region. Furthermore due to the high negative correlations and Cronbach's alpha values >.7 across early and late component scores across ERP PCA scores, difference scores were calculated by taking away the late component from the early component, so as greater difference scores represented increased early startle processing responses and decreased late startle processing responses (as also created for PCA components within Chapter 5). All averaged outcome measures were then used within subsequent regression analysis exploring the influence of individual differences.

Table 7.5: Trial type inter-correlations and Cronbach's alphas. The minimum correlation coefficients and Cronbach's alpha values across trial type correlations for each measure.

Response measure	r	α
EMG magnitude	.954	.977
EMG habituation	.85	.919
SC magnitude	.752	.857
SC habituation	.76	.861
HR amplitude	.757	.861
Difference score: PCA FrPm	.903	.949
Difference score: PCA Pm	.839	.912
Onset latency FrPm N/T	.458	[a.]
Onset latency Pm N/T	.613	[a.]
Onset latency FrPm TR/TV	.722	.833
Onset latency Pm TR/TV	.857	.923
Positive mood	.680 [b.]	.920
Negative mood	.706	.945

Note: N/T= neutral and trauma (TR and TV) comparisons.

[a.] Cronbach's alpha was not run due to the coefficient value failing to approach the critical value of .7.

[b.] Cronbach's alpha was run as the coefficient approached the critical value of .7.

7.4.4.2 Mood

7.4.4.2.1 Individual difference correlations

Negative mood during the startle task was correlated with peri-traumatic VAS anxiety (r(110)=.245, p=.009) and STAI state anxiety scores (r(111)=.235,p=.012), whilst positive mood was negatively correlated with drinking in the last 24 hours (r(112)=-.201, p=.032), ASI scores (r(113)=-.265, p=.004) and peri-traumatic VAS anxiety (r(110)=-.235, p=.013), STAI state anxiety (r(111)=-.392, p<.001) and low mood(r(110)=-.301, p=.001).

7.4.4.2.2 Regression

Experiencing a negative mood during the startle task was significantly predicted by group manipulation and peri traumatic anxiety responses, which together explained 13% of the variance in negative affect (table 7.6). The suppression and reappraise manipulation variables were negatively related to negative mood, illustrating that individuals in the control condition experienced increased negative affect during the startle task, compared to the two emotion regulation conditions. The addition of the two peri-traumatic anxiety response variables significantly improved the model fit; although these peri-trauma predictors did not significantly predict negative affect in themselves. Furthermore the addition of peri-trauma predictors in block two reduced the predictive association of the suppression versus control manipulation variable to a trend.

33.1% of the variance in differences in positive affect induced during the startle task was explained by the group manipulation, ASI scores, peri-trauma anxiety and low mood, and consuming alcohol in the last 24 hours (table 7.7). All predictors, except for peri trauma low mood and VAS anxiety significantly predicted differences in startle induced positive affect at all stages of the model. A reduction in positive mood over that startle task was associated with higher ASI scores and being within the no manipulation (view) control group, experiencing higher peri-trauma state anxiety and drinking alcohol within the last 24 hours.

Table 7.6: Hierarchical regression analysis for post trauma ER and peri-trauma factors predicting negative affect during the startle paradigm

	B	*SE B*	β
Step 1			
Constant	0.77	0.12	
reappraisal	-0.41	0.18	-.25*
suppression	-0.39	0.17	-.24*
Step 2			
Constant	0.14	0.53	
reappraise	-0.44	0.17	-.27*
suppress	-0.34	0.17	-.21
VAS anxiety_VR	0.05	0.04	.18
STAI state anxiety_VR	0.09	0.1	.11

*Note R^2= .062 for Step1 (p=0.33); ΔR^2 =.068 for Step 2 (p=.02). Final model R^2 =.13 p=.005 *p<.05. **p<.01. ***p<.001. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control.*

Table 7.7: Hierarchical regression analysis for post-trauma ER, ecological pre-trauma and peri-trauma factors predicting positive affect during the startle paradigm

	B	*SE B*	β
Step 1			
Constant	-3.86	0.42	
reappraisal	1.34	0.61	.235*
suppression	1.42	0.61	.249*
Step 2			
Constant	9.58	3.61	
reappraise	1.38	0.57	.242*
suppress	1.39	0.57	.245*
ASI	-8.97	2.40	-.332***
Step 3			
Constant	13.05	3.71	
reappraise	1.45	0.54	.256**
suppress	1.03	0.55	.180
ASI	-7.43	2.33	-.275**
VAS anxiety_VR	-1.00	0.39	-.347*
Low mood_VR	-0.09	0.40	-.024
STAI state anxiety_VR	0.03	0.12	.030
Step 4			
Constant	12.32	3.61	
reappraise	1.57	0.53	.276**
suppress	1.30	0.54	.228*
ASI	-6.83	2.27	-.253**
VAS anxiety_VR	-1.09	0.38	-.379**
Low mood_VR	0.04	0.39	.010
STAI state anxiety_VR	0.03	0.11	.032
Drank in last 24hrs	-1.50	0.55	-.230**

Note R^2*= .062 for Step1 (p=0.33);* ΔR^2 *=.11 for Step 2 (p<.001) ;* ΔR^2 *=.109 for Step 3 (p=.002) ;* ΔR^2 *=.05 for Step 4 (p=.007). Final model* R^2 *=.33.3 *p<.05. **p<.01. ***p<.001. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control.*

7.4.4.3 EMG

7.4.4.3.1 EMG magnitude

7.4.4.3.1.1 Correlation

No individual difference variables measured pre- or peri-traumatically correlated significantly with EMG response magnitudes and as such no regression models were ran on individual differences.

7.4.4.3.1.2 Regression

Regression analysis, regressing the group manipulation variable alone did not account for a significant amount of variance in EMG startle magnitudes (F(2,117)=.611, p=.545).

7.4.4.3.2 EMG habituation

7.4.4.3.2.1 Correlation

No individual difference variables measured pre- or peri-traumatically correlated significantly with EMG response habituation and as such no regression models were ran on individual differences.

7.4.4.3.2.2 Regression

Regression analysis, regressing the group manipulation variable alone did not account for a significant amount of variance in EMG startle habituation rates (F(2,117)=.564, p=.57).

7.4.4.4 SC

7.4.4.4.1 SC magnitude

7.4.4.4.1.1 Correlation

SC magnitude was positively with peri-traumatic SC responses during the traumatic explosion scene (*r*(116)=.345, *p*<.001).

7.4.4.4.1.2 Regression

15% of the variance in SC responses towards startling sounds was explained by group manipulation and SC responding during the traumatic explosion sequence of the Iraq VR. Although group manipulation did not reach significance in block one, the introduction of peri-traumatic SC responses in block two produced a significant effect of the suppression versus control variable (table 7.8), illustrating that when accounting for variance in peri-trauma SC responses individuals in the suppress group showed higher SC responses towards startling sounds, compared to those in the control condition.

Table 7.8: Hierarchical regression analysis for post-trauma ER and peri-trauma factors predicting SC magnitudes during the startle paradigm

	B	*SE B*	β
Step 1			
Constant	0.14	0.01	
reappraisal	0.01	0.01	.048
suppression	0.19	0.01	.163
Step 2			
Constant	0.12	0.01	
reappraise	0.01	0.01	.073
suppress	0.02	0.01	.205*
SC explosion_VR	0.08	0.02	.363***

Note R^2= .021 for Step1 (p=.289); ΔR^2 =.13 for Step 2 (p<.001). Final model R^2 =.151, p<.001. *p<.05. **p<.01. ***p<.001. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control.

7.4.4.4.2 SC habituation

7.4.4.4.2.1 Correlation

SC habituation was negatively associated with gender (r(116)=-.230, p=.012) (illustrating that males have a slower SC habituation towards startling sounds) and peri-traumatic low mood (r(113)=-.194, p=.038), and positively with peri-traumatic SC responses during the traumatic explosion scene (r(116)=.311, p=.001).

7.4.4.4.2.2 Regression

24% of the variance in SC trials to habituation criterion was explained by group manipulation, gender and peri-traumatic low mood and SC responses (table 7.9). Although the initial group manipulation block was significant, significant increase in the model fit were also produced by the addition of gender at block two and peri-traumatic responding at block three; with all variables, except for reappraisal manipulation and peri-traumatic low mood, conferring a significant prediction in the final block.

Table 7.9: Hierarchical regression analysis for post-trauma ER, biological pre-trauma and peri-trauma factors predicting SC habituation during the startle paradigm

	B	*SE B*	β
Step 1			
Constant	6.62	1.19	
reappraisal	1.91	1.73	.115
suppression	4.45	1.73	.268*
Step 2			
Constant	9.16	1.48	
reappraise	1.96	1.68	.118
suppress	4.50	1.68	.272**
gender	-4.01	1.44	-.248**
Step 3			
Constant	12.44	3.71	
reappraise	2.07	1.58	.125
suppress	4.81	1.59	.290**
gender	-3.19	1.42	-.197*
SC explosion_VR	10.14	2.48	.344***
Low mood_VR	-1.39	0.86	-.143

Note R^2= .056 for Step1 (p=.04); ΔR^2 =.061 for Step 2 (p=.006) ; ΔR^2 =.125 for Step 3. Final model R^2 =.243, p<.001. *p<.05. **p<.01. ***p<.001. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control; gender = males coded '0' and females coded '1'

7.4.4.5 HR amplitude

7.4.4.5.1 Correlation

HR amplitudes during the startle task was negatively associated with gender (r(110)=-.197, p=.037), Illustrating that males have a larger startle HR response.

7.4.4.5.2 Regression

Although gender significantly predicted HR amplitudes (t(111)=-2.1, p=.038), the overall model including group manipulation failed to reach significance (F(3,111)=1.64, p=.186).

7.4.4.6 EEG

7.4.4.6.1 PCA components

7.4.4.6.1.1 Correlation

Zero order correlations illustrated positive associations between peri-traumatic SC responding during the traumatic explosion scene and PCA difference scores in the parietal (r(115)=.187, p=.044) and frontal posterior (r(115)=.191, p=.039) brain regions. As the PCA values here represent a difference score (early component minus late component), these correlations illustrates that increased peri-traumatic SC responses are associated with a greater earlier brain processing of the startling sounds in both parietal and frontal-temporal regions, and vice versa.

7.4.4.6.1.2 Regression

Peri-traumatic SC responding and group manipulation failed to predict PCA component (P2 & P3) difference scores, with individual predictors and overall models non-significant for both parietal brain responses (F(3,117)=1.23, p=.303) and frontal posterior brain responses towards startling sounds (F(3,117)=1.23, p=.303).

7.4.4.6.2 Onset latency

7.4.4.6.2.1 Correlation

No significant zero order correlations were found between pre- or peri-trauma predictor variables and ERP onset latency in the Parietal region or on neutral trials in the frontal parietal region, and as such no regressions were ran to explore individual differences. Responses in the frontal posterior region on trauma trials were however negatively correlated with gender (r(115)=-.241, p=.009), indicating that males have a generally later ERP response towards startling stimuli, and positively with current computer gaming (r(115)=.287, p=.002).

7.4.4.6.2.2 Regression

10% of the variance in ERP onset latencies on trauma trials in the frontal posterior region was predicted by a model containing group manipulation, gender and current computer gaming (table 7.10). Although gender produced a significant increase in model fit, the predictive effect of gender was lost with the addition of computer gaming in the final block.

Regression models containing the grouping manipulation variable alone failed to reach significance for parietal brain responses towards trauma sounds (F(2,116)=0.2, p=.823) and neutral sounds (F(2,116)=0.94, p=.394), and frontal posterior responses towards neutral sounds (F(2,116)=0.1, p=.908).

Table 7.10: Hierarchical regression analysis for post-trauma ER and biological and ecological pre-trauma factors predicting the ERP onset latency during the startle paradigm: FrPm region on trauma trials

	B	*SE B*	β
Step 1			
Constant	202.1	5.11	
reappraisal	-1.07	7.27	-.016
suppression	4.82	7.32	.071
Step 2			
Constant	212.65	6.36	
reappraise	-1.22	7.08	-.018
suppress	4.95	7.13	.072
gender	-16.23	6.10	-.242**
Step 3			
Constant	201.36	8.08	
reappraise	-0.48	6.97	-.007
suppress	6.67	7.06	.098
gender	-8.06	7.05	-.120
current gaming	15.93	7.22	.233*

Note R^2= .006 for Step1 (p=.696); ΔR^2 =.059 for Step 2 (p=.009) ; ΔR^2 =.039 for Step 3 (p=.029). Final model R^2 =.243, p=.015. *p<.05. **p<.01. ***p<.001. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control; gender = males coded '0' and females coded '1'

7.5 DISCUSSION

This investigation aimed to replicate previous findings of valence dependent startle responding, for traumatic and neutral naturalistic sounds, and elucidate the effects of emotion regulation (ER) strategies on trauma related startle processing, following exposure to a VR-trauma scenario (Iraq World). ER strategies (acceptance based reappraisal and behavioural suppression) were manipulated post-trauma exposure, compared to a non-instructed control group, to clarify their respective effects on post-trauma PTSD like hyperarousal symptoms (exaggerated startle affect, physiology and processing responses). An additional avenue of interest was whether individual differences associated with risk for PTSD development would add to the predictive explanation of altered startle responses, over and above those predicted by manipulated ER strategies. Importantly, the VR-trauma scenario 'Iraq world' was shown to induce significant negative mood change and anxiety, supporting the utility of VR as a useful tool for investigating the development of PTSD symptomology within an analogue paradigm.

7.5.1 Valence dependent startle responses

The finding that startle responding is potentiated by fear is a robust effect across the literature (Grillon & Baas, 2003), it was therefore hypothesised that affective and physiological startle responses would be increased towards the trauma related gunshot startle stimulus with VR-trauma foreground pictures, compared to the neutral car horn stimulus and neutral-VR foreground pictures. The lack of a fear potentiated startle response across all physiological measures indicates that while the VR-trauma did induce a negative mood state and increased anxiety it may have not induced substantial and long lasting fear, potentially due to rapid habituation within an analogue design.

In addition to fear potentiation, startle responses have been shown to vary across dimensions of valence (Grillon & Bass, 2003); with suggestion that startle eye-blink potentiation is facilitated specifically by affective differences as opposed to emotional arousal (Nitschke et al., 2002) and higher startle blink potentiation shown towards unpleasant contexts (Bradley et al., 1993) and sounds (Bradley & Lang, 2000). Interestingly, contrary to previous findings, the current results show a lack of valence dependent startle blink potentiation; with no overall differences in startle response habituation or eye-blink magnitudes across neutral and trauma trials. Furthermore, the findings obtained from other physiological measures suggest that differences in the perceived properties of the startle stimuli, rather than affective differences in valence, may be more important in predicting alterations in autonomic startle responses. Increased SC and HR responses were found on neutral trials which were perceived as more loud and unpleasant[14], compared to trauma trials which were perceived as more distressing and upsetting. Importantly previous studies have often used white noise startle and manipulated valence only by changing foreground pictures (Nitschke et al., 2002; Bradley et al., 1993); it seems that when affective startle sounds are additionally used, the subjectively perceived properties of these startle sounds rather than the valence attached to the sound content itself may be more important in altering physiological startle responses. The increased frequency bands and more abrupt rise and fall times of the neutral sound are believed to have influenced participants' evaluations of the loudness and unpleasantness of the sounds, and subsequent physiological responses. Although instantaneous rise and fall times are a feature of sounds typically used to induce a reflex startle blink response, neither of the sounds used

[14] Although the gunshot and car horn startle sounds were matched for overall decibel level (95dB), they inherently differed in sound frequency composition and rise and fall times. The neutral sound had a higher frequency composition, remained in the high frequency band for a longer duration during the sound and had faster rise and fall times.

within the current experiment had this property as they were ecologically valid 'real world' sounds rather than white noise as used to obtain instantaneous rise and fall times. However, although previous research has shown emotional augmentation of visual startle probe reflex responding towards unpleasant ecologically valid sounds (Bradley & Lang, 2000), within the current study the sounds were used as the startle elicitor themselves and illustrated no differences in their startle eye-blink potentiation. Previous literature has illustrated that increasing the decibel level of a sound facilitates increases blink startle potentiation, especially in PTSD patients (Morgan et al., 1996), and contributes to increased arousal ratings without affecting emotional ratings of naturally occurring sounds (Bradley & Lang, 2000). However the findings suggest that high frequency sounds, compared to low frequency sounds, may also facilitate increased physiological startle responses to a greater extent than valence dependent facilitations; although the role of faster rise and fall times in such effects cannot be completely ruled out. Interestingly although such research has not been previously carried out in humans, low frequency sounds have been shown to elicit only fleeting behavioural startle responses, compared to high-frequency sounds, in blueback herring (Nestler, Ploskey, Pickens, Menezes & Schilt, 1992). The current findings and the results of animal research into frequency effects on startle responding call for further investigation of the effects of sound property on reflex and physiological startle responding.

In addition to augmentation of peripheral startle responses on neutral trials, valence dependent alterations in brain processing were also apparent. Neutral stimuli resulted in generally larger amplitudes of ERP startle P2 and P3 components (within PCA analysis), and a later overall startle ERP response (within ERP onset latency analysis), compared to trauma stimuli. ERP findings suggest that although individuals may have attended and processed trauma stimuli faster, neutral stimuli required increased attention and processing resources. Such findings could again be a result of the higher frequency composition of the neutral sounds. Interestingly, although previous studies have shown that P2 responses are increased towards pleasant pictures (Amrhein, Muhlberger, Pauli & Wiedermann, 2004), the current findings do not support this interpretation for startle ERP responses; with increased amplitude in the frontal P2 startle component found on trauma trials compared to neutral trials. As the trauma stimuli were rated as more distressing and arousing compared to the neutral stimuli, it appears that P2 amplitudes towards startling stimuli are not augmented by positive valence.

7.5.2 Emotion regulation (ER) dependent startle responses

In the analysis of the effects of ER manipulation on startle responses it was posited (research question 3 and 4) that individual differences in trait styles of reappraisal and suppression, which show comparative influences on affective responding to manipulated ER strategies (Gross & John, 2003) and have been associated with pathology and PTSD symptoms (Aldao et al., 2010; Tull et al., 2007), could influence group outcomes. In fact controlling for the effects of trait ERQ styles did not produce any qualitative alterations in the regulation group effects, suggesting that controlling for trait differences in ER does not improve the ability to see the effects of ER manipulations. However, a number of trial type effects (on SC and HR) and all ERP trial and region main effects were found to be no longer apparent when trait differences in ER styles were accounted for, illustrating the influence of individual difference variables in the prediction of startle responses as discussed in section 7.5.3.

Although the startle paradigm was found to increase negative mood and reduced positive mood, which habituated over the course of the startle task, the hypothesised effects of the ER manipulations were not supported (hypothesis 2a). Findings illustrated a lack of reappraisal affect modification and, in contrast with the hypothesised lack of suppression affect modulation, a lower reduction in positive mood was found in the suppress group compared to the control group. Results indicate that behavioural suppression can have adaptive effects on increasing positive affect experiences during negative situations. Interestingly the influence of behavioural suppression on positive emotional experience has been previously reported for paradigms involving positive emotional films (Gross & Levenson, 1997), where behavioural suppression has effectively reduced positive emotional experiences. Moreover, when both positive and negative mood has been assessed in response to startle (Hagemann et al., 2006), behavioural suppression towards a single startle probe has been shown to reduce positive affect in a non-suppression-unanticipated-startle group compared to a non-suppression-anticipated-startle group and a behavioural suppression group (comparable to the current findings). However, investigations which have illustrated a lack of behavioural suppression induced affective alterations towards negative stimuli interestingly only measured changes in negative mood states and not increases in positive mood states (Gross & Levenson, 1993; Gross,1998); negative mood states were also not found to be affected by suppression within this study and the study carried out by Hagemann et al (2006). These findings indicate that the influence of suppression on changes in affective states may only be measureable through respective increases or decreases in positive emotional experiences. However, the finding of a lack of reappraisal based affect modifications within the current study is surprising in light of

previous findings that down-regulated reappraisal reduces affective emotional experiences during negative film viewings (Gross, 2002) and during startle paradigms (Ray et al., 2010). As the current studies aimed to tap more ecologically valid reappraisal techniques as they may be applied in cognitive restructuring treatment for PTSD, acceptance based reappraisal was instructed. Within the traditional emotion regulation literature in general, and within the studies of Gross (2002) and Ray et al. (2010), reappraisal instructions explicitly specify changing the way one thinks to decrease the negative emotional response which is elicited. It is possible that the explicit instruction to initiate cognitive strategies that decrease negative emotions may allow for more individualised selection of reappraisal techniques which produces more effective reductions in affect, alternatively this explicit instruction may produce demand characteristics which result in reductions in self-reported negative mood states. Interestingly, as no alterations were found in reflex EMG eye-blink within the current study or that of Ray et al (2010), this adds further supports the interpretation of previous illustrated affect alterations as a demand characteristic of the reappraisal instructions.

Although the magnitude of startle eye-blink responses did not show the hypothesised emotional facilitation, instead showing increased magnitudes towards neutral stimuli, ER manipulations were shown to modulate responses on trauma trials. Reflex startle eye-blink responses were found to be inhibited on trauma regulate trials compared to trauma non-regulate trials in individuals instructed to suppress the overt emotional behavioural responses, whilst individuals in the reappraisal and control groups showed no modulations in reflex startle responding. The finding of suppression based inhibition of startle responding is in line with hypothesised effects, models of ER (Gross, 1998a, 1998b, 2001), and previous reports that suppression reduced emotionally expressive behaviours during negative scenarios (Gross, 1998) and in response to a single startle stimulus (Hagemann et al., 2006). This is the first evidence illustrating that suppression can also successfully inhibit reflex startle responses as measured using objective physiological measurements. Although reappraisal of adversive film and picture content has been consistently associated with adaptive changes in expressive behaviour (Gross, 2000) and reappraisal based reflex startle inhibition has been reported (Jackson et al., 2000), the current finding is in line with more recent startle studies which have shown a lack of such reflex modifications (Eippert et al, 2007; Ray et al., 2010). These findings suggest that reflex anxiety responses such as the eye-blink startle response may be better controlled by behavioural suppression techniques than cognitive based reappraisal strategies.

In line with the hypothesised lack of the reappraisal induced sympathetic alterations, the reappraisal group was not found to differ in comparison to the control group or suppression

group in startle related SC magnitudes and habituation or HR amplitudes. Whilst no conclusive suppression based alterations in heart rate (HR) amplitudes were apparent, SC habituation rates (though not magnitudes) were found to vary by ER group manipulations in accordance with hypothesised effects; illustrating that suppression may only affect sympathetic activation which is measured by SC responding, as opposed to HR which is a measure of both sympathetic and parasympathetic activation. The finding of only sympathetically dependent emotion regulation effects is interesting in light of previous studies illustrating that SC startle responses can predict later PTSD symptom development in the acute post trauma phase (Guthrie & Bryant, 2005), while HR and eye-blink EMG startle responses may develop in line with diagnosis rather than representing a vulnerability factor (Shalev et al., 2000; Orr et al, 2003; Griffin, 2008). Across the course of the startle task individuals in the suppression group showed a slower reduction (i.e. increased trials to habituation) in SC responding towards startle stimuli, compared to control group. These finding are consistent with previous experimental data across adversive film and startle paradigms showing that suppression increases (Gross 1998; Hagemann et al., 2006) and reappraisal has no influence on sympathetic activation in emotional contexts (Gross, 1998; Eippert et al., 2007; Ray, 2010). Replicating the finding of Gross and Levenson (1997) that suppression effects on sympathetic activation were independent of the emotional context of the task, increased suppressive SC habituation were found to be independent of startle trial type. Supporting suggestions that suppression facilitates physiological arousal as a result of the behavioural effort associated with such an ER strategy (Gross, 2000).

ERP startle components were found to be unaltered, in amplitude or latency, by manipulations in reappraisal or behavioural suppression. Gootjes et al (2011) have previously shown that ERP amplitudes towards negative pictures can be down-regulated (i.e. reduced in magnitude) with cognitive reappraisal and fMRI investigations have shown reappraisal dependent alterations in activation within emotionally related brain regions in response to adversive visual scenes (Ochsner, Bunge, Gross & Gabrieli, 2002;Walter et al., 2009; Erk et al., 2010). However, the current findings suggest that the reflex nature of startle responses perhaps inhibits instructed emotion regulation strategies from effectively altering rapid brain processing responses.

In analysis of ER manipulation effects, acceptance based reappraisal was not found to influence affective or electrophysiological startle responding, compared to behavioural suppression ER manipulations or control group responses. The lack of hypothesised reappraisal alterations in startle related negative affect and reflex eye-blink is not only in contrast to ER literature exploring influences on responses towards negative visual scenes (Gross, 2000) but is

also surprising in light of the focus of cognitive-behavioural (CBT) PTSD treatments on reappraisal based cognitive change strategies, which have proved effective in PTSD symptom reduction. It is unclear why such effects were not replicated within this study, but it is possible that the length of reappraisal training and practice carried out was insufficient to act as an effective manipulation. Alternatively, as reappraisal is a cognitively effortful emotion regulation technique involving continuous cognitive engagement to facilitate antecedent-focused emotional change (Gross, 1998), fatigue effects as a result of the 45 minute startle ER task may have impacted effective reappraisal. Whilst suppression is also an effortful process the behavioural nature of this strategy may have been less affected by cognitive fatigue effects. Interestingly, findings for the suppression manipulation indicate that whilst suppression has maladaptive effects on SC response habituation (i.e. increased arousal), it may in fact have protective effects on affect modulation (i.e. mood) and reflex startle blink responses (i.e. automatic defence responses), at least in the short term during active suppression; although rebound effects of suppression were not tested within this study so the long term consequences cannot be assessed. The association between suppression of behavioural expression (behaviours) and reductions in associated emotional experiences (feelings) is in fact in line with the CBT model of linked processes between thoughts, behaviours and feelings; where changing behaviours, it is posited that this will have comparative effects on feelings and thoughts. This model is supported by the current findings in relation to behavioural suppression on emotional feelings, however opposing changes were present for physiological emotional responses and furthermore changing thoughts (i.e. reappraisal) was found to have no influence on emotions or behaviours. The results suggest that emotional and reflexive defence responses are dissociated from physiological arousal responses when behavioural suppression is taking place, further research is needed to elucidate the mechanisms which result in such a juxtaposing profile of responses and determine whether increases in positive affect can be seen in contexts other than the startle paradigm.

7.5.3 Role of PTSD individual difference risk factors, over taught emotion regulation strategies, in the prediction of startle responses

Emotion regulation manipulations were found to be predictive of startle response profiles in regards to startle induced mood changes and sympathetic responses (SC response magnitudes and habituation); however individual difference factors added explained variance to the

overall model. No pre or peri-trauma vulnerability factors were found to be correlated with reflex eyeblink, heart rate or P2 versus P3 ERP component startle responses. However, both pre-trauma individual differences in gender, trait anxiety and peri-traumatic responding were found to be important predictors of affective responding, sympathetic activation and brain processing speeds.

While peri-traumatic responses did add to the explained variance in negative mood responses, the only significant effect illustrated that the suppression manipulation was associated with a reduction in negative mood during the startle task, compared to controls. Increases in positive mood were significantly predicted by both reappraisal and suppression manipulations, compared to the control condition, together with negative associations with trait anxiety sensitivity, peri-traumatic anxiety and alcohol use. A large amount of variance (33.1%) in positive mood responses to startle stimuli was explained by a combination of ER strategies, anxiety sensitivity and peri-traumatic responses, supporting previous reports of trait anxiety modulated startle responses (Quevedo et al., 2010). These findings illustrate that whilst ER manipulations (especially suppression) are predictive of alterations in affective states, individual differences are also important in the prediction of changes in positive mood states specifically.

In predicting SC startle responses, peri-traumatic SC illustrated the largest predictive effects explaining 12.6% of the variance in SC habituation profiles and 13% of the variance in SC magnitudes; illustrating that peri-traumatic arousal is strongly associated with subsequent startle response arousal. Interestingly only after adjusting for these strong effects of peri-traumatic SC responses, was it possible to see the smaller influences of the suppression manipulation on startle SC habituation. Supporting earlier ANOVA findings, the suppression ER manipulation (compared to the control group) also found to be important predictors in startle SC habituation; however gender[15] and peri-trauma SC respectively explained increased variance in SC habituation rates, over the ER manipulation alone. These findings illustrate that, as would be expected, increased sympathetic activation during a trauma is predictive of increased post-trauma startle related SC responses; however more importantly, behavioural suppression and gender also play a part in predicatively modifying sympathetic activation towards startling sounds.

The prediction of the ERP onset latencies illustrated an effect of gender, with males showing slower ERP response latencies, which was better explained by individual differences in

[15] Male gender was associated with increased SC habituation rates, compared to females

computer gaming[16]. It is unclear why gaming was predictive of alterations in ERP startle processing times, though it is possible that individuals who are used to computer gaming may process virtual reality related scenes (foreground VR images) differently due to increased emotional habituation towards such environments, which may have impacted upon the processing of overlaid startle responses. Alternatively, perhaps repeated exposure to loud sounds experienced during computer games meant that the direction of attention resources towards such startling stimuli was slowed when they are encountered in comparable virtual contexts. A further possibility is that certain personality traits or cognitive variables which have not been assessed within this study are predictive of who partakes in gaming as an adult, and it may in fact be these characteristics rather than the experience of gaming itself which predicts ERP processing speed alterations, or that the ERP effect itself predicts involvement in gaming.

Although it is perhaps unsurprising that increases in peri-traumatic anxiety responses are predictive of similar anxiety responses towards equally unpleasant startling sounds, these results of this investigation do however add support to the assumption that peri-traumatic responses are more predictive than pre-trauma factors (Brewin et al., 2000; Ozer et al., 2003; Trickey et al., 2012). Interestingly however, contrary to the previous findings within the same meta-analysis, that factors measured post-trauma are also highly associated with PTSD-like symptomology, within the current study post-trauma manipulation of ER strategies were found in general to be less predictive of post-trauma startle than both pre- and peri-trauma factors. These results support the robust nature of the startle response by illustrating associations with stable individual differences (Fendt & Koch, 2013), but suggest that whilst peri-trauma factors can influence startle related hyperarousal, post-trauma emotion regulation had no effects.

7.5.4 Limitations

The generalisability of the present results may be limited by homogeneity of the population sampled, all of whom were university students. This sample may have had different motivation to participate (i.e. monetary compensation and university course credits) compared to a general population sample who may be more engaged in the experimental paradigm. It is possible that a lack of engagement and conformity with reappraisal instructions within this sample was responsible for the null findings in regards to reappraisal based emotional modulation of startle responses. The short duration of reappraisal teaching time prior to the ER startle task (10 minutes) may have also been insufficient to alter regulation styles, although

[16] Current gaming was associated with a delayed startle ERRs, compared to non-gamers

participants self-reports of peri-startle processing styles were generally consistent with respectively manipulated strategies. Furthermore, previous studies which have explored ER dependent startle modulations have used shorter duration paradigms, with one only using a single startle stimulus. The 45 minute duration of this startle task, following an hour of prior recording set up, questionnaires and VR exposure may have induced significant fatigue effects which influenced engagement and maintenance of ER strategies; potentially effecting cognitively based reappraisal based strategies more than behaviourally based suppression strategies. Replication of these findings within a general population sample and the separation of physiological and electroencephalographic recordings into two separate investigations, limiting the pre-startle task set up time and allowing longer time for the teaching and practice of reappraisal prior to the startle task, is warranted.

7.5.5 Conclusions

In sum no evidence was found for trauma related augmentation of startle responses, with increased physiological and electroencephalographic responses occurring in fact on neutral trials. It is believed that the perceptual properties of the sounds, such as high or low frequency compositions, may in fact have a greater influence on responding when natural sounds are used to induce startle. Expressive suppression appeared to impart adaptive reductions in affective and reflex startle responses, at least in the short term during active participation in suppression; however it also resulted in slower SC habituation trajectories, illustrating a mechanism by which suppression may lead to sustained arousal which may have maladaptive effects in the long term. Further research is needed to explore whether the adaptive effects of suppression on increases in positive mood state and defence reflex responding continue post-suppression, or whether rebound effects such as those reported for the suppression of thoughts (Wegner, Schneider, Cater & White, 1987) may induce a reduction in positive affect and increases in negative affect and reflex defence responding following removal of the requirement to actively suppress emotional behaviours. Individual differences in trait ER styles did not influence the effects of ER manipulations on startle responding when accounted for as a covariate; suggesting that trait emotion regulation styles do not alter the effectiveness of taught emotion regulation strategies. In support of the influence of pre-trauma individual difference factors on startle responding, pre-trauma variables including gender and anxiety sensitivity, and peri-trauma responses, were found to explain significantly greater variance in startle responses over and above the influences of concurrently employed emotion regulation strategies. In line with the Gross EM regulation model suppression was found to increase sympathetic electrodermal responses independently of emotional context, however no

support was found for the adaptive influences of reappraisal on reducing negative affect and emotion modulated eye-blink startle responses. These findings suggest that acceptance based reappraisal techniques may act upon mechanisms other than hyperarousal reduction in the treatment of PTSD symptomology, such as alterations in negative core beliefs which were not assessed within the current study.

8 AN ANALOGUE INVESTIGATION OF THE MECHANISMS BY WHICH VIRTUAL REALITY BASED EXPOSURE THERAPY (VRET) ALTERS FEAR RESPONSE HABITUATION: CAN REAPPRAISAL AND SUPPRESSION ALTER VRET RESPONSE TRAJECTORIES?

8.1 ABSTRACT

Virtual reality exposure therapy (VRET) is a relatively new exposure based behavioural treatment for posttraumatic stress disorder (PTSD), affording increased immersion and control compared to traditional imaginal exposure therapy, with preliminary data showing promising recovery outcomes. Although evidence suggests that cognitive interventions are as efficient as traditional behavioural exposure therapies in the treatment of PTSD, research comparing cognitive strategies with VRET is lacking. While acceptance based emotional reappraisal forms a key part of evidenced based cognitive treatments for post traumatic stress disorder, suppression of emotional responses has been widely associated with pathology and poorer recovery rates. Experimental studies have illustrated the successful manipulation of emotion regulation strategies and respective changes in PTSD related symptomology; however less is known about how such strategies differentially influence the course of recovery and anxiety habituation during exposure based therapies and whether differences in trait emotion regulation styles play a role. Furthermore, a number of individual difference traits are known to influence PTSD development following trauma exposure, however little is known about whether or how such pre-trauma risk and resilience traits interact with post-trauma emotion regulation strategies to influence symptom expression and recovery trajectories during trauma re-exposure. This study employed a VR trauma (virtual Iraq) analogue design to elucidate the relative influence of manipulated emotion regulation strategies (acceptance and coping based reappraisal and behavioural suppression, compared to a non-instructed control group), and trait styles (emotion regulation) on post-VR trauma emotional (anxiety, low mood, dissociation) and physiological (skin conductance, heart rate) habituation trajectories during VR re-exposures, following a pre-ER manipulation VR trauma exposure. In addition, the relative influence of individual differences (gender, life events, trait ER styles and anxiety traits) on the course of responding from initial VR trauma exposure to repeated re-exposures, over and above the influence of manipulated ER strategies, was investigated. Results showed that VRET was effective in reducing the emotional and physiological fear responses which were produced by VR-trauma exposure, with female gender and anxiety sensitivity predicting poorer recovery trajectories and trait emotional reappraisal predicting improved trajectories. Interestingly the manipulation of emotion regulation strategies, during and prior to VRET, had no influence on

fear habituation, questioning the increased efficacy of cognitive interventions over behavioural VRET alone; although patient studies would be needed to confirm this. Furthermore, individuals who regularly play computer games reported experiencing reduced state anxiety in response to the virtual Iraq scenario, signifying implications for the inclusion of such individuals within analogue trauma designs. These findings have important implications for VR exposure techniques suggesting that, although pre-trauma factors can influence VR responding and habituation trajectories, emotional and physiological reactivity naturally habituates during immersive VRET and is not influenced by generic post-trauma emotion-regulation manipulations.

8.2 INTRODUCTION

Post traumatic stress disorder imparts a multifaceted range of symptoms including traumatic re-experiencing, generalised hyper arousal and avoidance of trauma reminders; however a common thread across these symptom profiles is their relationship with fear responsivity. Exposure therapy aims to reduce fear responsiveness through stress desensitization and habituation and has proved a strongly evidenced based treatment for anxiety disorders and PTSD specifically (Foa, 2011). Traditional behavioural exposure therapy is divided into three sub-types: in vivo exposure in which the patient confronts feared stimuli in a 'real life' setting, interoceptive exposure which specifically aims at engaging and addressing bodily sensations associated with fear and imaginal exposure therapy in which the client is required to retell their traumatic script to the therapist in a first person narrative. Different theories of PTSD development and maintenance hold differential viewpoints on the specific mechanisms by which exposure therapy acts to produces symptom alleviation. However, it is agreed that repeated re-exposure to the feared stimuli (the trauma and conceptually associated aspects) allows for processing of the trauma memory trace to allow for integration of new learning (e.g. safety information), organisation of the trauma memory into a more coherent autobiographical memory trace and fear response habituation in relation to the trauma memory, reducing its emotional potency (Ehlers & Clark, 2000; Brewin et al., 1996, 2001, 2010; Foa & Riggs, 1993; Foa & Rothbaum, 1998). An important gap in the literature remains in relation to the individual difference markers that can predict fear response habituation in response to PTSD exposure treatments (Shiv, Rusch, Sullivan & Neria, 2013).

Although imaginal re-exposure therapy (IRET) has proved effective in the treatment of a large number of cases of PTSD, there remains a sub-sample of clients for whom IRET does not

facilitate improvement. An issue with traditional IRET is the necessary pre-requisite for prolonged emotional engagement in the trauma memory for treatment gains to be achieved through habituation of activated fear responses (Jaycox & Foa, 1996). As emotional numbing and avoidance are common coping strategies used by clients to detach from the overwhelming feelings of anxiety which are intertwined with the trauma memory, in clients for whom these emotional avoidance patterns are particularly overriding, emotional engagement in the trauma memory cannot be achieved through traditional client based imaginal reliving techniques. A further issue is the requirement for the client to be able to recall the memory in enough detail for imaginal reliving to be feasible (Leskin, Kaloupek and Keane, 1998). With dissociative profiles associated with a sub-group of PTSD sufferers (Ginzburg et al., 2006) and other clients with peri-traumatic injuries and circumstances (e.g. head injury, concussion, drugging) which preclude the full recall of the traumatic event, some PTSD patients will be unable to partake in traditional reliving treatment protocols.

A promising new exposure based treatment for PTSD involving virtual reality (VRET) has been increasingly supported over the last decade. As the client relives their trauma memory through an individually tailored virtual environment, VRET circumvents the problems of avoidance and memory fragmentation which inhibit the use of traditional imaginal reliving in a sub-sample of PTSD cases, enable increased physiological engagement in the traumatic scenario and allow for safe and controlled progressive presentation of trauma stimuli when compared to in vivo exposure (Cosic et al., 2010). However a preliminary review, although supporting the efficacy of VRET, has found VRET to be in general no more efficient than traditional imaginal exposure treatment (Goncalves et al., 2012); though this finding was based on only 10 studies with an unstandardised number of treatment sessions. It appears that the real treatment gains are in regards to individuals with dissociative symptom profiles. VRET has been found to be successful in enabling emotional engagement and a 90% symptom reduction in a case study of a client has shown no improvement with imaginal reliving (Difede & Hoffman, 2002). Although VRET lacks evidence from randomized controlled trials, it has proved an effective treatment for emotional processing in PTSD within a number of case studies and treatment studies in trauma populations including combat personnel, fire fighters and survivors of the motor vehicle accidents and the World Trade Center attacks (for review see Gerardi et al., 2010). Whilst VRET has shown clear PTSD treatment gains larger studies are warranted to facilitate the investigation of potential factors which may respectively enhance or diminish VRET engagement and subsequent fear habituation.

Although some researchers (Foa & Rothbaum, 1998; Foa, 2011) believe that PTSD symptom eradication can be achieved by exposure based treatments alone, with re-living of the trauma memory naturally allowing for the automatic integration of new insights which act to produce cognitive change in negative core beliefs which are believed to maintain symptoms, others (Beck et al., 1985; Resick & Schnicke, 1992) hold that the addition of therapeutic components specifically aimed at addressing maladaptive appraisals and beliefs through cognitive change are necessary for full recovery to occur. Evidence suggests that both behavioural and cognitive interventions are comparable in terms of their clinical efficacy (Marks et al.,1998; Tarrier et al., 1999) and act upon the same symptom clusters (Lovell, Marks, Noshirvani, Thrasher & Livanou, 2001). However the question remains as to whether the combination of such approaches can provide added treatment gains, and despite the prevalence of cognitive-behavioural based treatments for PTSD evidence of the added utility of combined treatment is still inconclusive (Hassija & Gray, 2010). It has been suggested that exposure based treatments may only produce change in fear relevant emotions (Brewin & Holmes, 2003) and cognitive restructuring may be required to achieve treatment success with other emotions such as anger and guilt (Ehlers & Clark, 2000). Treatment trials have found that emotion regulation and interpersonal training skills learnt prior to IRET, predict the effectiveness of IRET treatments at reducing PTSD symptoms and maintaining treatment gains at 3 and 9 months (Cloitre, Koenen, Cohen & Han, 2002). However, to the best of the author's knowledge no research has been carried out to date to explore the added efficiency of emotion regulation strategies over VRET alone. The added emotional and physiological engagement afforded by a virtual environment, compared to imaginal reliving, may be adequate to produce ample fear reduction and prove to make additional cognitive aspects redundant in altering such habituation processes. Indeed VRET has been found to produce greater long term treatment gains when compared to person centred psychotherapy (Ready, Gerardi, Backscheider, Mascaro & Rothbaum, 2010).

Cognitive approaches in the treatment of PTSD focus on the modification of dysfunctional trauma appraisals relating to the world, the self and others. Within analogue trauma research, in which healthy participants are exposed to a trauma-film to simulate an analogue trauma exposure, reappraisal has proved a successful peri-trauma cognitive manipulation in the alleviation of fear arousal responses peri-trauma and subsequent reduction in symptomatic post-trauma responses (Gross, 2002) as well as illustrating symptom reductions when reappraisal training was completed post-trauma film (Woud, Holmes, Postma, Dalgleish & Mackintosh, 2012). Whilst reappraisal has proved an adaptive strategy in promoting reductions in fear and analogue PTSD symptomology (i.e. emotional and reflex startle

responses), suppression has been shown to produce the opposite effect with an increase in emotional and autonomic fear responses (Gross & Levenson, 1997); although the findings relating the detrimental consequences of suppression are less conclusive with regards to autonomic responding and behavioural suppression has been shown to not impact on emotional experience (Gross, 2002). For example, expressive suppression during a negative (disgust inducing) film has been shown to result in a contrasting autonomic reaction of reduced heart rate (HR) together with increased skin conductance (SC) and eye blink responses (EMG), compared to a non-suppression control group (Gross & Levenson, 1993). The role of reappraisal strategies in the facilitation of cognitively focused treatments and the known detrimental consequences of emotional numbing, such as a lack of emotional expression (i.e. suppression), on a reduced efficiency of imaginal exposure therapy lends these two emotion regulation strategies to the investigation of their respective impact upon VRET.

This study will first address the question of whether VRET (over two VR re-exposures) can illustrate fear habituation in an analogue VR trauma exposure design and secondly whether cognitive strategies (reappraisal) and emotional numbing responses (suppression) can respectively facilitate or impede fear habituation trajectories, over and above change produced by VRET alone. Following initial exposure to a VR trauma (virtual Iraq), in which they are involved in a virtual IED road side bomb attack, participants will be instructed in either acceptance based reappraisal, behavioural suppression or receive no explicit instructions apart from the VR scene setting information (control group) and be required to use these strategies through a 45 minute acoustic startle paradigm (See Chapter 7 for write up of these results). Although positive reappraisal manipulations have been widely used in the literature (Gross, 2002), positive reappraisal would appear to be an inappropriate intervention for the elevation of PTSD symptoms which relate directly to a traumatising and distressing experience. As such, the current study will employ acceptance and coping based reappraisal strategies which are more in keeping with the forms of reappraisal an individual may naturally use post-trauma (Tull et al., 2007) or those that would be used during PTSD treatments (NICE, 2005). Emotional and physiological fear responding will be recorded during an initial VRET virtual Iraq re-exposure with no emotion regulation explicitly required (carryover of manipulation effects from the startle regulation task) and during a second VRET virtual Iraq re-exposure in which participants will be explicitly instructed to use their emotion regulation strategy (or receive no instruction as in the case of the control group). Despite the small duration of the VRET within this study, with only two VRET re-exposures, a single one hour session of exposure therapy has been found to produce a reduction in phobia specific startle potentiation, in specific phobic

patients compared to wait list controls (Kashdan, Adams, Read & Hawk Jr, 2012). Furthermore, higher anxiety ratings during the initial session of IRET have been found to be associated with post-treatment non-improvement, and habituation between the first and second exposure has been associated with treatment success (van Minnen & Hagenaars, 2002). It is expected that due to the analogue nature of the design participants fear responses will habituate at a faster rate compared to those seen in patients who suffer from PTSD relating to the trauma to which they are being re-exposed, as such a high number of re-exposures would not be tenable within the current analogue design.

In addition to the expected influence of manipulated emotion regulation strategies on VRET related emotional and physiological fear habituation there are known individual differences in trait styles of emotional suppression and reappraisal and pre-trauma traits and characteristics, which have been previously found to influence responses to negative life events and subsequent anxiety profiles (Garnefski & Spinhoven, 2001). It is further anticipated that such individual difference characteristics will affect the initial response to an analogue VR trauma and the fear habituation trajectory during VRET. A recent review of prospective studies has shown emotional avoidance and trait anxiety to be important factors in the prediction of PTSD symptomology post-trauma (DiGangi et al., 2013), whilst broader meta-analysis and reviews have also highlighted the importance of anxiety related personality traits, female gender and stressful life events in imparting risk for PTSD development (Ozer et al., 2003; Brewin et al., 2000; Stam, 2007). It is believed that the increased prevalence of PTSD among females may be a result of differences in cognitive coping strategies (Garanidou & Rosner, 2003); this begs the question of whether gender or trait emotion regulation strategies are more predictive of trauma and treatment responses. Interestingly however, males have in fact shown a reduced maintenance of treatment gains following imaginal exposure therapy, which is believed to relate to an increased propensity in women to be able to recall emotional memories (Felmingham & Bryant, 2012); importantly the reduced necessity of client emotional recall within VRET may not confer such a female treatment advantage.

Ozer et al. (2003) concluded that peri-trauma risk factors are a stronger predictor of PTSD compared to pre-trauma individual differences, and as pre-trauma characteristic are likely to be associated with such peri-trauma reactions, therefore when investigating the effects of pre-trauma individual difference it seems important to account for the influences they bestow on peri-trauma responses as well as the respective trajectory of emotional and physiological fear habituation during VRET. To explore the contribution of such individual differences, in addition to the measurement of reappraisal and suppression dependent alterations in VRET fear

habituation, pre-trauma individual difference in trait emotion regulation styles will be assessed and controlled for, and additionally the contribution of pre-trauma variables towards the prediction of peri-traumatic responding and the subsequent relative efficiency of VRET will be investigated.

8.2.1 Research Questions and Hypotheses

Q1: What influence do reappraisal and behavioural suppression strategies have on the habituation of physiological and emotional responses to analogue VRET?

H1a: It is hypothesised that reappraisal in comparison to a non-manipulation control will reduce physiological and emotional arousal towards VRET.

H1b: It is hypothesised that suppression in comparison to a non-manipulation control will increase physiological arousal towards VRET, but will have no influence on emotional arousal.

Q2: Are experimental manipulations of reappraisal and suppression associated with differential changes in psychological and emotional responding to analogue VRET when the effects of trait emotion regulation styles (reappraisal and suppression) are controlled for?

Q3. Does analogue VRET show significant reductions in emotional and physiological response profiles compared to initial trauma responses?

H3: It is hypothesised that VRET will confer habituation in fear related emotional (anxiety and dissociation) and physiological stress responses (HR, SC), but will show no direct influence on fear related responses (low mood).

Q4. Do individual differences predict the course of psychological and emotional responding, from initial VR trauma exposure to VRET habituation?

H4: It is hypothesised that individual differences in gender, trait emotion regulation styles and anxiety will influence the efficiency (habituation) of VRET.

8.3 METHOD

8.3.1 Participants

See methods Chapter 4 section 4.2.2.1, and appendix 16 figure A16.1 for a flow chart of participant attrition and group allocation.

8.3.2 Measures

See the following sections within methods Chapter 4:

Screening questionnaires section 4.1.1.1: EEG and VR screening questionnaire, PHQ9 and PC-PTSD.

Trait questionnaires section 4.1.1.2: ASI, STAI, HA, ERQ

Life events questionnaires section 4.1.1.3: SRRS, Traumatic life events checklist from the CAPS

State questionnaires section 4.1.1.4: VAS mood scale and peri-trauma dissociation measure.

Psychophysiological responses section 4.1.3: SC and ECG (i.e. HR).

Computerised tasks section 4.1.4: VR Iraq world.

8.3.3 Procedure

See Methods Chapter 4 Procedure section 1.2.2.3 for an overview of the full study design from which the data within this chapter were collected. The same set of pre-, peri and post--trauma factors will be analysed across this and the preceding Chapter 7; however the outcome measures covered within this chapter relate only to the response and habituation profiles measured during analogue VRET treatment analogue.

As a brief re-cap, participants were split into groups and trained in an emotion regulation strategy which they were required to use during a startle task: emotional reappraisal, behavioural suppression or a control group who received no training in emotion regulation and were instructed to respond naturally and not to try to alter their responses. See appendix 13 for the reappraisal, suppression and control group startle task instructions. Following completion of the startle task (the data for which was analysed within the preceding Chapter 7), participants were given a 10 minute break and then asked to re-view the stressor Iraq VR twice more, whilst SC and HR were recorded; this VR-trauma re-exposure acted as an analogue of VRET. During both viewings participants were re-read the scene setting information, but given the briefing that they were back in the same Iraq city on a different occasion. The VR was as before however with each VR viewing the IED went off at an earlier position in the scenario. During the first re-viewing no further instructions were given, this allowed for

assessment of manipulation carry over effects of emotion regulation from the earlier startle task. For the second re-viewing, participants in the two experimental groups (reappraise/suppress) were asked to use the group specific emotion regulation strategy that they used earlier on regulate trials in the startle task, whilst the control group was given the same instructions as in all previous VR-trauma exposures. A gap of 10 minutes was left between the two VR re-viewings, in which participants filled out the SRRS stressful events measure. State mood measures were taken before and after both VR re-viewings, peri-trauma HR and SC responses were measured concurrently with VR presentation and peri-trauma VR dissociation was measured immediately after each VR. The predictor and outcome variables are depicted in table 8.1.

8.3.3 Data pre-processing

See the following sections within Methods Chapter 4 pre-processing section (*4.2.2.3*):

Physiological measures section 4.2.2.3.2: SC and HR levels Trauma VR scenario

Checks for normal distribution section 4.2.2.3.3.

Table 8.1: Variables included in Chapter 8 analysis of VR re-exposure habituation responses following ER manipulation. Summary of the risk and resilience factors pre- peri and post-trauma and analogue symptom measures.

Pre-trauma	Peri-trauma	Post-trauma	Phenotypic symptom Measure of Stress sensitization
PERSONALITY: ▪ ASI ▪ STAI-T ▪ HA ▪ ERQ **LIFE EVENTS:** ▪ SRRS ▪ Traumatic events checklist **GENDER** *COVARIATES:* ▪ *Computer gaming* ▪ *Smoking(that day)* ▪ *Coffee (that day)* ▪ *Alcohol (last 24hrs)*	**BIOLOGICAL STRESS RESPONSE:** ▪ HR trauma sequence-BL ▪ SC trauma sequence-BL ▪ HR trauma sequence-VR initial sequence ▪ SC trauma sequence- VR initial sequence **VALENCE RESPONSE:** ▪ STAI-S difference score ▪ VAS anxiety difference score ▪ VAS low mood difference score ▪ Dissociation	**EMOTION REGULATION MANIPULATION:** ▪ Suppression vs. Reappraisal vs. Control (No manipulation)	**VR2 AND VR3 RE-EXPOSURE** ▪ HR 0:00-1:08 & 20s post-explosion ▪ SCL 0:00-1:08 & 20s post-explosion

8.3.4 Statistical analysis

The initial analysis used ANOVA and ANCOVA to explore the independent contribution of emotion regulation manipulations to changes in responding towards the carryover Iraq VR viewing following startle emotional processing manipulation task (assessing carryover of group

effects) and the regulation Iraq VR viewing with explicit instruction for participants to use their respective groups manipulation (suppress, reappraise, control: view as normal) throughout the course of this VR exposure. Trait emotion regulation strategies (ERQ suppression and ERQ reappraisal subscales) were controlled for in ANCOVA analysis, to look at the effectiveness of the manipulation when the influences of initial trait preferences were controlled. Covariate effects within ANCOVA analysis are not discussed, as the covariates are used to explain a portion of the variance in existing ER manipulation effects and illustrate unique (covariate independent) relationships with the response outcome variables. All assumptions of ANCOVA were tested prior to running the analysis. Independence of the dependent variable (group manipulation) and the covariates ERQ reappraisal ($F(1,19)=0.74$, $p=.76$) and suppression ($F(1,19)=0.9$, $p=.6$) was found. VR responses during the carryover and regulation Iraq VR viewings were baseline corrected against the pre-manipulation initial Iraq VR viewing responses, to obtain a measure of change post-manipulation and to control for any random group variations pre-manipulation.

Due to the longitudinal nature of the repeated re-exposure to the traumatic Iraq VR scenario multilevel models were run to investigate whether pre-trauma factors (personality traits, gender and any covariate effects) were important in predicting changes in responding over time from initial exposure to repeated exposures following the manipulation, over and above any effects of emotion regulation manipulations (for the use of multilevel modelling methods in personality research see West, Ryu, Kwok & Cham, 2011; Nezlek, 2001). Multilevel modelling employs a nested hierarchical data structure, allowing for subject level variation (individual differences) to be differentially accounted for at each nested unit on another level of analysis. In the case of longitudinal data sets this allows for distinct observations across time to be nested within individual subjects (Hox, 2002). Hierarchical longitudinal modelling therefore allows the elucidation of whether subject level data interacts with data sampling time points to predict responding. Within the current data this allows for subject level individual differences and emotion regulation manipulations to be accounted for at each VR exposure across time.

HR and SC responses were corrected against resting baseline responses, whilst anxiety and low mood change scores were calculated as post-pre, to explore responses specifically induced by the traumatic VR scenarios and reduce effects of individual differences in absolute values. As individual difference traits were posited to have an influence on responding at time one (pre-manipulation VR-trauma exposure), it was felt that creating difference scores in relation to the initial time one VR-trauma responding would remove the variance accounted for by individual

differences and hence not be an appropriate methods for addressing the hypothesis in question. Furthermore this analysis aimed to look at change in responding across trauma re-exposures (VRET) in relation to level of initial trauma responding. For these reasons it was therefore decided to run the multilevel analysis accounting for responses across all three VR viewings (West et al., 2011; Nezlek, 2001).

As the multilevel longitudinal analysis was intended to model change over time, for physiological peri-traumatic measurements responses during each of three VR's were further sub divided into two time points 1) the time window corresponding to the initial minute of VR immersion and 2) the 20 seconds during which the explosion and aftermath was occurring; producing six time points for the longitudinal model allowing for modelling of the change within and across VR exposures. Whilst the multilevel models for self-report affective variables (i.e. pre post change scores) were simply run over three VR time points, assessing change across VR exposures. Zero order correlations were computed between pre-trauma predictor variables and VR responses at each time point. Pre-trauma individual difference variables were included as predictors in a respective model if they correlated significantly with the respective response parameter (outcome) across any of the VR viewings. As it was expected that individual differences could affect responding differentially over time, for all predictors in the model interaction effects with time were also included. ER group manipulations primarily will be entered into the model to allow analysis of how pre-trauma individual differences can affect differential courses of responding over repeated traumatic VR exposures, over and above any influence of the experimental manipulation. However, as the manipulation occurred only after the first exposure, any manipulation effects which do become significant within this analysis could be the result of random chance pre-manipulation group differences during the initial VR Iraq viewing. Therefore, significant manipulation effects within this analysis will be followed up within a model containing VR2 and VR3 responses corrected for VR1 (pre-manipulation) responses.[17]

Prior to model computation extreme univariate outliers, defined as 3 interquartile ranges from either end of the box plot distribution of a variable, were replaced with a value one unit larger or smaller than the next score in the distribution (Tabachnick & Fidell, 2001). Multivariate outliers were sought via inspection of standardised residuals and leverage values. All models were tested with visible multivariate outliers removed, where this made a qualitative change to the model this is noted and the model with outlying cases removed is reported.

[17] However, no ER manipulations were actually found within this study and therefore no follow up tests were run.

All models were found to significantly improve the model fit over the empty model (equation 1.), illustrating that the combined predictors entered in each model significantly improve the prediction of the respective VR response measures.

Equation 1 $Y_{ij}=\beta_{Oij}cons$

It was found that all models better accounted for change in their respective VR response measure when the time course of responding across repeated VR's was allowed to vary across participants, therefore all final models reported here allow for variation in the time course of responding across the VR's between different participants, as well as for variation of the intercept across participants and time points (equation 2.).

Equation 2 $Y_{ij}=\beta_{Oij}cons + \beta_{1j}Time_{ij}$

8.4 RESULTS

8.4.1 Utility of VR-trauma induction: Manipulation check

See chapter 7 Section 7.4.2 for results relating to the effectiveness of the VR-trauma induction.

8.4.2 The contribution of instructed emotion regulation strategies to the efficacy of analogue VRET habituation

The following ANOVA analysis will answer research question 1:

Q1: What influence do reappraisal and behavioural suppression strategies have on the habituation of psychological and emotional responses to analogue VRET?

> *H1a: It is hypothesised that reappraisal in comparison to a non-manipulation control will reduce physiological and emotional arousal towards VRET.*
>
> *H1b: It is hypothesised that suppression in comparison to a non-manipulation control will increase physiological and emotional arousal towards VRET.*

Whilst the ANCOVA analysis reported will answer research question 2:

Q2: Are experimental manipulations of reappraisal and suppression associated with differential changes in psychological and emotional responding to analogue VRET when the effects of trait emotion regulation styles (reappraisal and suppression) are controlled for?

8.4.2.1 Mood

Changes in negative mood across VR viewings was significant when ERQ was not accounted for as a covariate ($F(1,110)=38.38$, $p<.001$) with lower mood reported during the 2rd VR viewing ($M=-0.11$) compared to the 3nd ($M=-0.33$), however with the inclusion of ERQ scores this effect was lost ($F(1,108)=0.04$, $p=.839$).

Changes in VAS anxiety across VR viewings was significant in ANOVA analysis ($F(1,110)=4.41$, $p=.038$) with increased anxiety induced by the 2nd VR viewing ($M=-1.16$) compared to the 3rd ($M=-1.58$), this effect reduced to non-significance when controlling for ERQ sub scale scores ($F(1,108)=1.61$, $p=.21$) , however ANCOVA produced a interaction between VR viewings and group manipulation which approached significance ($F(2,108)=2.45$, $p=.055$). Inspection of plots (figure 8.1) indicated that during the carryover VR viewing, the view *(M=-1.1)* and suppress *(M=-0.76)* groups expressed higher anxiety compared to the reappraise group *(M=-1.6*), whereas during the regulation VR viewing the suppress group *(M=-1.81)* showed lower anxiety compared to the reappraise *(M=-1.5)* and control *(M=-1.41)* groups[18].

No main effects or interactions between the repeated VR viewings and regulation group manipulation were present for analysis of state anxiety or dissociation in ANOVA analysis or when the effects of trait ER styles were accounted for.

[18] As the interaction between VR viewings across time and VAS anxiety only approached significance this was not followed up with further tests

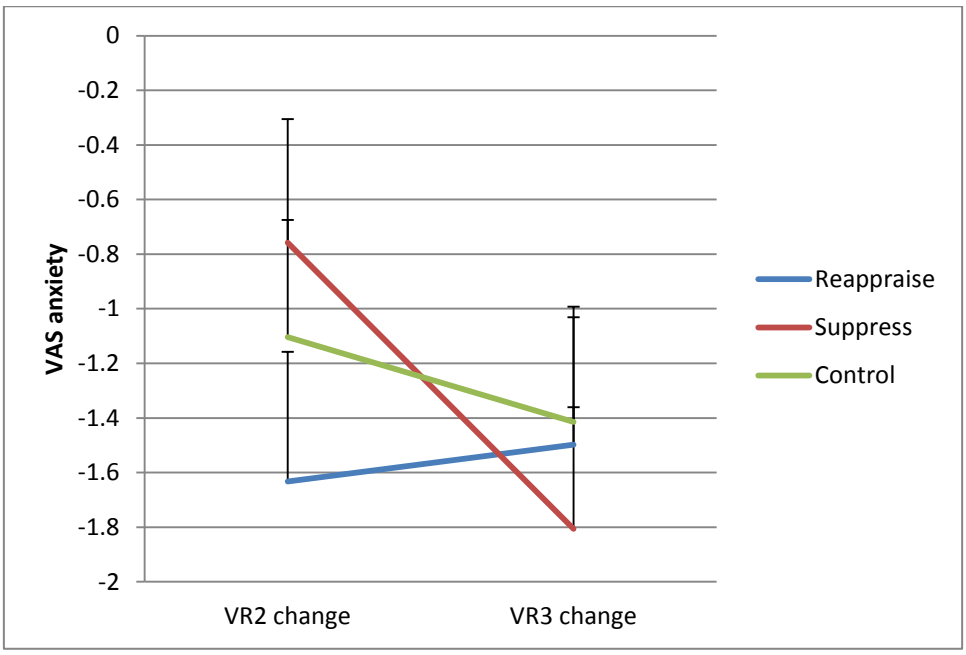


Figure 8.1: VR re-exposure by group interaction for VAS anxiety. Habituation of self-reported VAS anxiety induced by subsequent VR re-exposures (baseline corrected against peri-traumatic VAS anxiety responses during VR1) across the ER manipulation and control groups.

8.4.2.2 Skin Conductance (SC)

A significant change in SC was found within each VR viewing itself ($F(1,110)=23.46$, $p<.001$), with a higher SC response during the initial minute of VR viewing ($M=-0.12$) compared to the section in which the explosive was detonated from ($M=-0.18$), however this effect was no longer significant when the influence of ERQ emotion regulation strategies was accounted for ($F(1,108)=2.2$, $p=.141$). No other main effects or interactions reached significance for SC analysis.

8.4.2.3 Heart Rate (HR)

HR was found to vary within VR viewings ($F(1,106)=21.76$, $p<.001$) with lower HR responding during the traumatic explosion sequence of the VR scenario ($M=1.57$) compared to the first minute of the VR ($M=3.7$); this effect remained when ERQ scores were controlled for ($F(1,104)=4.35$, $p=.04$). An interaction was apparent between HR responses within each VR and the repeated VR's across time ($F(1,106)=17.77$, $p<.001$) (Figure 8.2); this effect remained when ERQ scores were controlled for ($F(1,104)=9.98$, $p=.002$). Inspection of the plots and follow up analysis illustrated that this interaction was driven by HR responses during the explosion segment of the VR ($F(1,106)=8.58$, $p=.004$), for which HR responses were lower during the regulation VR viewing (M=0.64) compared to the carryover VR viewing (M=2.51), with no

significant differences between HR responding within the initial segment of the VR (F(1,106)=0.34, p=.56) (M=3.56; M=3.84, respectively).

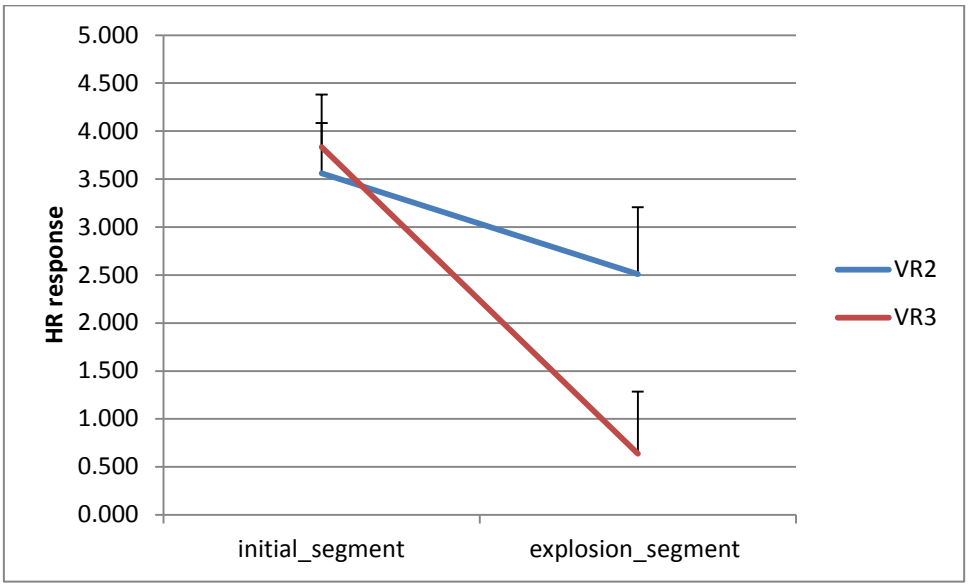


Figure 8.2: VR re-exposure by VR-segment interaction for HR responses. Change in HR responding for initial VR exposure segment to traumatic explosion segment across VR re-exposures (baseline corrected against peri-traumatic HR responses during VR1).

8.4.3 Efficacy of VRET and the influence of individual differences in predicting the responding across repeated VR exposures

The subsequent analysis will answer the following research questions and hypothesis:

Q3. Does analogue VRET show significant reductions in emotional and physiological response profiles compared to initial trauma responses?

H3: It is hypothesised that VRET will confer habituation in fear related emotional (anxiety and dissociation) and physiological stress responses (HR, SC), but will show no direct influence on fear related responses (low mood).

Q4. Do individual differences predict the course of psychological and emotional responding, from initial VR trauma exposure to VRET habituation?

H4: It is hypothesised that individual differences in gender, trait emotion regulation styles and anxiety will influence the efficiency (habituation) of VRET.

8.4.3.1 Mood

8.4.3.1.1 STAI state anxiety

8.4.3.1.1.1 Correlated pre-trauma individual difference variables

Change in state anxiety across all three VR exposures was positively associated with gender (VR1: *r*(114)=.235, p=.011; VR2: *r*(110)=.218, p=.021; VR3: *r*(109)=.288, p=.002) and negatively with currently playing computer games (VR1: *r*(114)=-.234, p=.012; VR2: *r*(110)=-.222, p=.019; VR3: *r*(109)=-.276, p=.003). Additionally ASI was positively associated with state anxiety induced during the initial VR viewing (*r*(114)=.201, p=.031).

8.4.3.1.1.2 Longitudinal prediction of responses and manipulation effects

Gender, current computer gaming, ASI, along with group emotion regulation manipulations (compared to control group) and their interaction terms with time were entered as predictors of change in state anxiety over time. The covariate computer gaming was tested for significance and while the main effect of gaming was retained in the final model the interaction between gaming and VR exposure did not significantly improve the model fit, therefore this interaction term was removed from the final model (Table 8.2).

Induced state anxiety was found to decrease across the three VR exposures, however the addition of a significant quadratic time effect illustrates that anxiety ratings dropped during the ER carry-over VR viewing compared to the initial VR viewing and the explicit ER manipulation VR viewing (figure 8.3). Although state anxiety was not affected by ASI or gender, individuals who play computer games reported less induced anxiety as a result of viewing the VR Iraq scenario. The ER manipulations compared to the control group showed no association with overall STAI anxiety (χ^2=4.13, p= .127) or changes in anxiety over time (χ^2=5.54, p= .063).

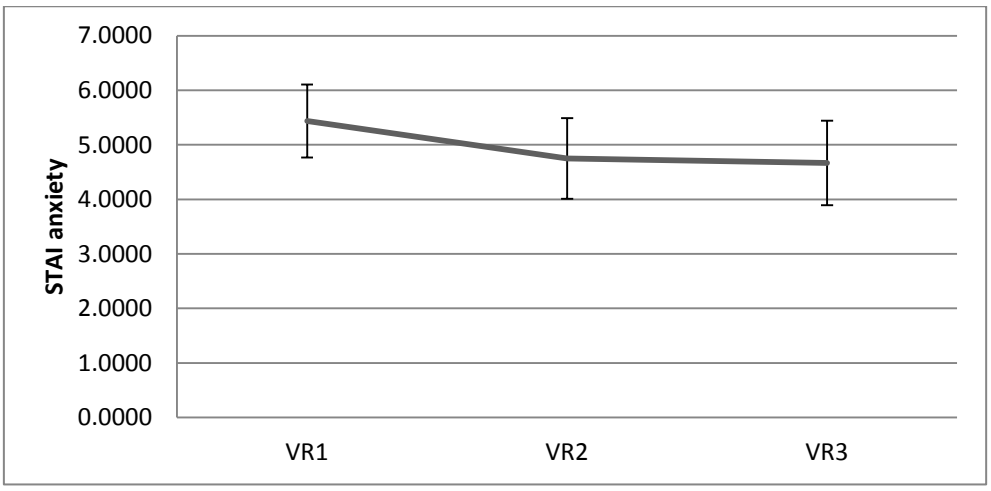


Figure 8.3: State anxiety across VR-exposure and VR re-exposures. Habituation of state anxiety responses from VR trauma exposure to VR re-exposures.

Table 8.2: Beta coefficients for model of changes in STAI anxiety responses over repeated trauma VR re-exposures; comparing ER manipulations to control group responses.

				95% confidence intervals	
Predictor	β	SE	Z score	Lower	Upper
cons	6.843	0.345	19.83*	19.16	20.51
Gender	0.118	0.255	0.46	-0.04	0.96
ASI	2.031	1.132	1.79	-0.42	4.01
Gaming	-0.35	0.161	-2.17*	-2.49	-1.86
reappraise	0.188	0.276	0.68	0.14	1.22
suppress	-0.377	0.277	-1.36	-1.90	-0.82
Time	-1.627	0.275	-5.92*	-6.46	-5.38
TimeSqr	0.314	0.064	4.91*	4.78	5.03
Gender X Time	0.071	0.096	0.74	0.55	0.93
ASI X Time	-0.744	0.447	-1.66	-2.54	-0.79
Reappraise X Time	-0.209	0.11	-1.9	-2.12	-1.68
Suppress X Time	0.031	0.109	0.28	0.07	0.50

*Note: *p>0.05.* gender = males coded '0' and females coded '1'. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control. Cons= Constant.

8.4.3.1.2 Visual analogue scale (VAS) anxiety

8.4.3.1.2.1 Correlated pre-trauma individual difference variables

Change in visual analogue anxiety showed a more varied profile of associations across the three VR exposures. VAS anxiety to initial VR viewing was associated with ASI (r(113)=.191, p=.041) and coffee drinking prior to the experiment (r(113)=.210, p=.024). Whilst anxiety towards the second VR exposure was positively associated with gender (r(113)=.187, p=045) and ERQ reappraisal (r(113)=.207, p=.026) and negatively associated with current computer gaming (r(113)=-.187, p=.046), and the third VR viewing was associated with gender (r(111)=.213, p=.024).

8.4.3.1.2.2 Longitudinal prediction of responses and manipulation effects

Gender, ASI, ERQ reappraisal, current computer gaming, coffee drinking and their interaction terms with time were entered as predictors, along with the group emotion regulation manipulation, in the longitudinal model. The covariates computer gaming and coffee drinking were tested for significance within the model. Both the covariate main effects and their respective interactions were removed from the final model, as their addition was not found to significantly improve the model fit.

Visual analogue reported trauma induced anxiety responses decreased linearly across repeated VR exposures, independently of gender, ASI, ERQ trait reappraisal or the emotion regulation manipulations (Table 8.3). This linear decrease additionally followed a quadratic path with a steeper decline in anxiety reported between the initial VR-exposure and carry-over VR viewing compared to the reduction in anxiety that occurred between the two re-exposure VR's (figure 8.4). Overall anxiety ratings in response to Iraq VR viewings were not found to differ by gender, ASI, ERQ trait reappraisal. In confirmation of prior ANOVA analysis the ER manipulations showed no association with overall VAS anxiety (χ^2=0.18, p= .914) or changes in anxiety over time (χ^2=0.45, p= 0.799).

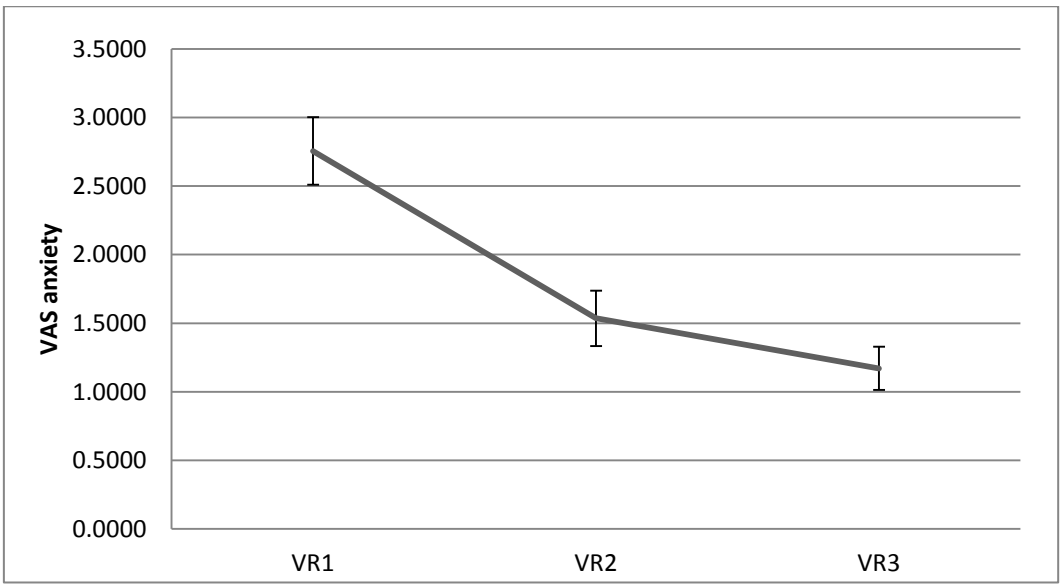


Figure 8.4: VAS anxiety across VR-exposure and VR re-exposures. Habituation of VAS anxiety responses from VR trauma exposure to VR re-exposures.

Table 8.3: Beta coefficients for model of changes in VAS anxiety responses over repeated trauma VR re-exposures; comparing ER manipulations to control group responses.

				95% confidence intervals	
Predictor	β	SE	Z score	Lower	Upper
cons	4.38	0.96	4.57*	2.69	6.44
Gender	0.37	0.71	0.52	-0.87	1.90
ASI	3.37	3.29	1.02	-5.43	7.48
ERQ_reappraisal	0.13	0.07	1.93	1.79	2.06
reappraise	-0.12	0.82	-0.14	-1.75	1.47
suppress	0.24	0.80	0.30	-1.28	1.87
Time	-2.33	0.81	-2.88*	-4.47	-1.30
TimeSqr	0.38	0.19	2.00*	1.63	2.37
Gender X Time	0.14	0.26	0.53	0.01	1.04
ASI X Time	-0.98	1.22	-0.80	-3.19	1.60
ERQ_reappraisal X Time	-0.04	0.03	-1.48	-1.53	-1.43
Reappraise X Time	-0.02	0.31	-0.08	-0.68	0.52
Suppress X Time	-0.19	0.30	-0.63	-1.21	-0.05

*Note: *p>0.05.* gender = males coded '0' and females coded '1'. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control . Cons= Constant.

8.4.3.1.3 Low mood

8.4.3.1.3.1 Correlated pre-trauma individual difference variables

Change in low mood across all three VR exposures was positively associated with gender (VR1: $r(113)=.307$, p=.001; VR2: $r(112)=.399$, p<.001; VR3: $r(102)=.385$, p<.001) and ASI (VR1: $r(113)=.273$, p=.003; VR2: $r(112)=.208$, p=.026; VR3: $r(112)=.220$, p=.019), and negatively with currently playing computer games (VR1: $r(113)=-.233$, p=.012; VR2: $r(112)=-.285$, p=.002; VR3: $r(112)=-.254$, p=.006). Additionally ERQ reappraisal was positively associated with low mood induced during the first two VR viewings (VR1: $r(113)=.342$, p<.001; VR2: $r(112)=.222$, p=.018).

8.4.3.1.3.2 Longitudinal prediction of responses and manipulation effects

Gender, current computer gaming, ASI, ERQ reappraisal and their interaction terms with time were entered as predictors, along with group emotion regulation manipulation, in the longitudinal model (Table 8.4). The covariate computer gaming and its interaction with time were tested for significance, and removed from the model as it did not significantly contribute to the model fit.

Table 8.4: Beta coefficients for model of changes in low mood induction over repeated trauma VR re-exposures; comparing ER manipulations to control group responses.

				95% confidence intervals	
Predictor	β	SE	Z score	Lower	Upper
cons	4.17	0.19	22.08*	21.71	22.46
Gender	0.27	0.16	1.69	1.39	2.00
ASI	1.46	0.74	1.97	0.53	3.42
ERQ_reappraisal	0.06	0.02	4.07*	4.04	4.10
reappraise	-0.35	0.18	-1.91	-2.27	-1.55
suppress	-0.21	0.18	-1.14	-1.49	-0.79
Time	0.02	0.13	0.15	-0.10	0.41
TimeSqr	-0.06	0.03	-1.87	-1.93	-1.81
Gender X Time	0.13	0.05	2.59*	2.50	2.69
ASI X Time	-0.11	0.23	-0.47	-0.92	-0.02
ERQ_reappraisal X Time	-0.02	0.01	-3.00*	-3.01	-2.99
Reappraise X Time	0.00	0.06	-0.03	-0.15	0.08
Suppress X Time	-0.06	0.06	-1.04	-1.15	-0.93

*Note: *p>0.05.* gender = males coded '0' and females coded '1'. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control. Cons= Constant.

The model illustrated that VR induced low mood responses were predicted by increased ASI and increased reappraisal scores. Low mood was found to vary across the three VR viewings as a function of gender and ERQ reappraisal scores. Males showed a steeper reduction in low mood across repeated VR exposures (figure 8.5). At initial VR-exposure scoring high on trait reappraisal was associated with increased low mood scores, however across the 2 re-exposures this relationship became significantly weaker (figure 8.6).

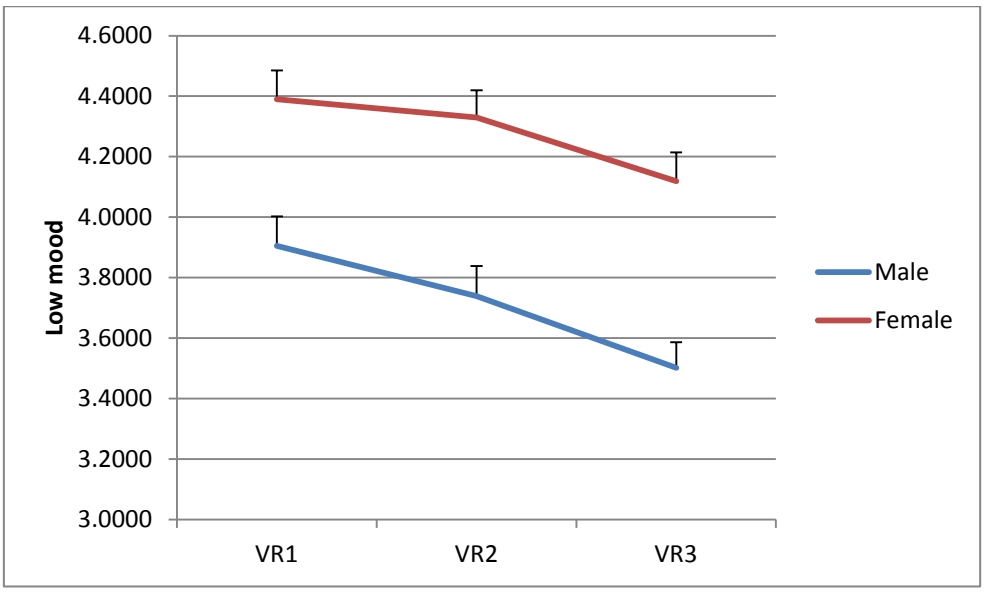


Figure 8.5: Gender by VR-exposure interaction for low mood. Habituation of low mood responses from VR trauma exposure to VR re-exposures across genders.

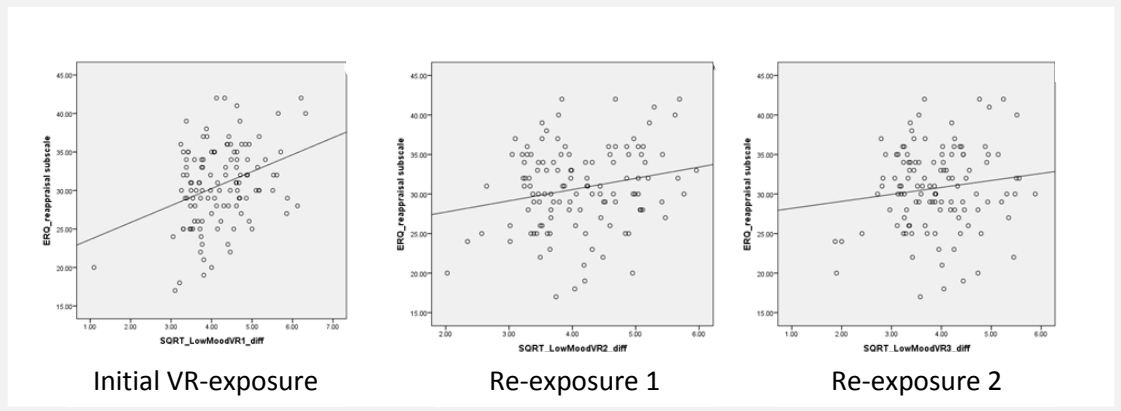


Figure 8.6: Trait reappraisal scores by low mood across VR-exposure. Habituation of low mood responses from VR trauma exposure to VR re-exposure, depending on trait reappraisal scores.

8.4.3.1.4 Dissociation

8.4.3.1.4.1 Correlated pre-trauma individual difference variables

Change in dissociation across all three VR exposures was negatively associated with ERQ reappraisal (VR1: $r(112)=-.260$, p=.005; VR2: $r(113)=-.251$, p=.007; VR3: $r(113)=-.282$, p=.002).

Additionally stressful life events in the past year were positively associated with dissociation induced during the second VR viewing (*r*(113)=.188, p=.044).

8.4.3.1.4.2 Longitudinal prediction of responses and manipulation effects

ERQ reappraisal, stressful life events and their interaction terms with time were entered as predictors, along with group emotion regulation manipulation, in the longitudinal model (Table 8.5).

Changes in peri-traumatic dissociation varied as a function of the individual difference predictor variable ERQ reappraisal; with individuals higher on trait reappraisal showing less dissociation across all VR exposures. Peri-traumatic dissociation was found to increase linearly across repeated VR viewings (figure 8.7). Although, as illustrated in prior ANOVA analysis, the main effect of ER manipulation (χ^2=2.28, p=.32) and its influence over time on peri-traumatic dissociation (χ^2=4.90, p=.086) did not reach significance, change in dissociation over time was found to vary in relation to the direct comparison between the reappraisal and control groups (figure 8.8); individuals who received the reappraise manipulation showed a decrease in dissociation across the 2 repeated VR exposures compared to the non-manipulation control group. This ER manipulation effect was explored further and was confirmed in a simple model containing only time and ER manipulation as predictors. However, analysis correcting for initial dissociation during pre-manipulation initial VR-trauma viewing, showed no differences in dissociation for the reappraisal compared to the control group (χ^2=1.17, p=.28). Follow up analysis confirms the lack of an ER manipulation effect, as found in ANOVA analysis, and shows that the effect here is driven by random differences in groups dissociation scores during initial pre-manipulation VR; illustrating the importance of baseline correction when investigating group differences.

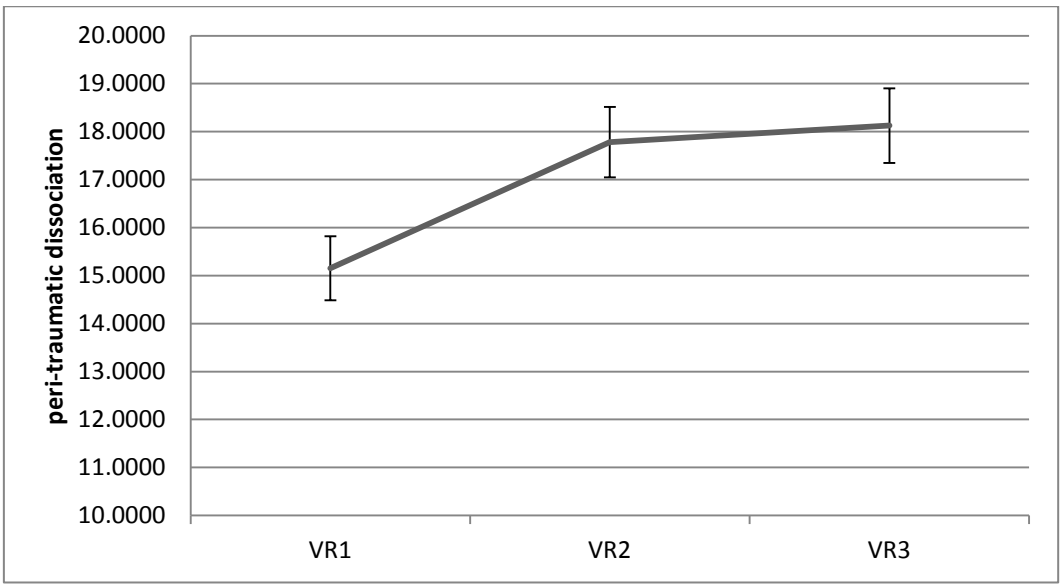
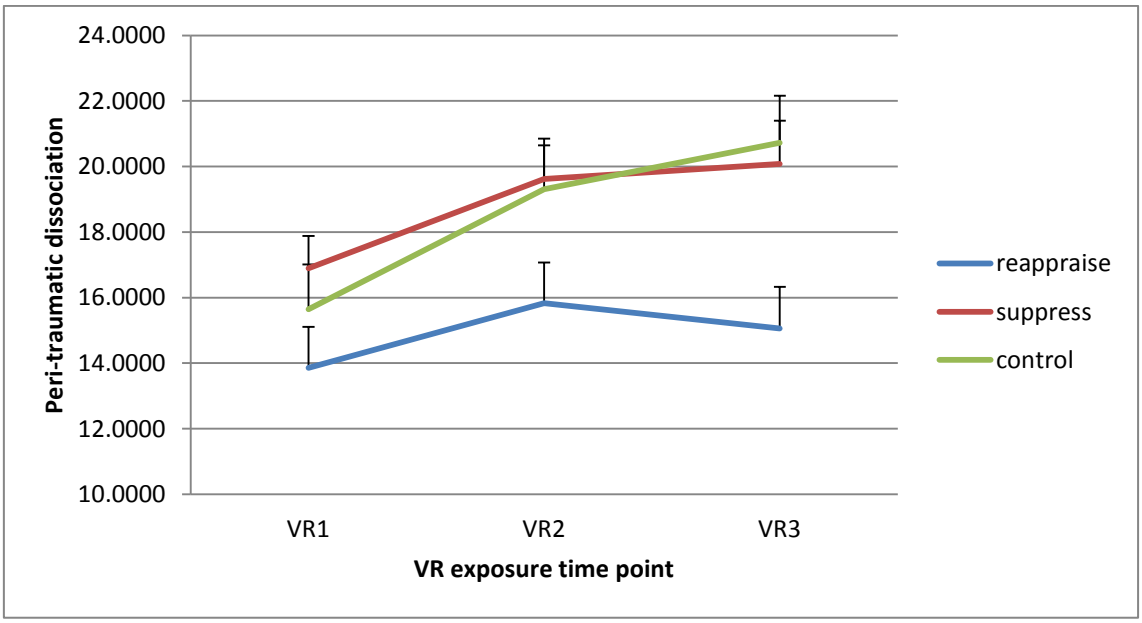


Figure 8.7: Dissociation across VR-exposure and VR re-exposures. Dissociation response profile from VR trauma exposure to VR re-exposures.



Note: This effect was found to be driven by individual differences at time one pre-manipulation scores.

Figure 8.8: Group by VR interaction for dissociation. Dissociation response profile from VR trauma exposure to VR re-exposures across ER manipulation and control groups.

Table 8.5: Beta coefficients for model of changes in peri-traumatic dissociation over repeated trauma VR re-exposures; comparing ER manipulations to control group responses.

				95% confidence intervals	
Predictor	β	SE	Z score	Lower	Upper
cons	8.94	1.80	4.96*	1.42	8.49
ERQ_reappraisal	-0.38	0.16	-2.43*	-2.73	-2.12
SRRS	0.09	0.22	0.40	-0.03	0.83
reappraise	1.94	1.93	1.01	-2.77	4.78
suppress	2.80	1.86	1.50	-2.15	5.15
Time	6.81	1.58	4.31*	1.22	7.41
TimeSqr	-1.12	0.37	-3.02*	-3.74	-2.30
ERQ_reappraisal X Time	0.01	0.06	0.11	-0.02	0.23
SRRS X Time	0.09	0.09	1.03	0.86	1.21
Reappraise X Time	-1.74	0.79	-2.20*	-3.75	-0.66
Suppress X Time	-0.94	0.77	-1.22	-2.73	0.28

*Note: *p>0.05.* reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control. Cons= Constant.

8.4.3.2 Skin conductance (SC)

8.4.3.2.1 Correlated pre-trauma individual difference variables

Skin conductance responses across all six time points were not associated with any hypothesised individual differences. The only significant association was for SC response during the initial minute of the second (carry over) VR exposure which was negatively associated with the covariate alcohol use in the last 24 hours ($r(110)=-.288$, $p=.016$), suggesting larger SC responses in individuals who had not drunk alcohol recently.

8.4.3.2.2 Longitudinal prediction of responses and manipulation effects

The covariate alcohol and its interaction term with time were entered as predictors, along with group emotion regulation manipulation, in the longitudinal model. As a covariate, alcohol use was tested for its importance in the model. The main effect of alcohol use was retained in the final model as it added to the model fit, however the interaction with time was removed from

the final model as its influence on SC responses was not found to vary across repeated trauma re-exposures (table 8.6).

SC responses were found to linearly decrease across repeated VR exposures, independently of the emotion regulation condition or alcohol use in the last 24 hours; however this decrease across VR's also showed an internal quadratic pattern, illustrating an increase in SC responding between initial VR exposure and initial VR explosion sections, and the drastic habituation of SC responding that occurred for the next carry over VR exposure and continued throughout instructed ER manipulation re-exposure (figure 8.9). Furthermore, increased alcohol use was also found to be associated with reduced SC responses across all VR exposures. Confirming the ANOVA results reported previously, the ER manipulations showed no effect on SC responses in general (χ^2=0.83, p=.66) or across VR exposures (χ^2=1.43, p=.489).

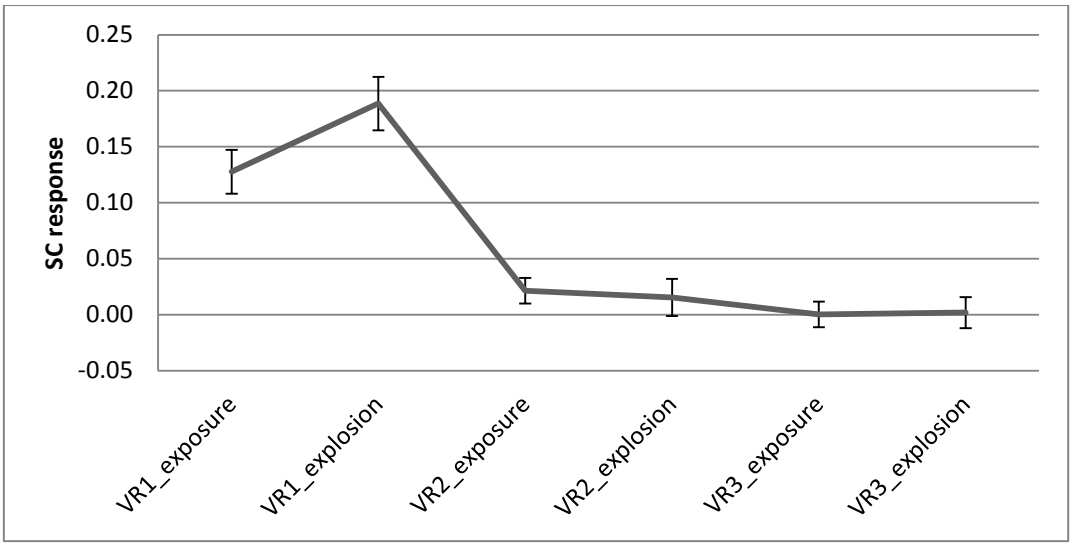


Figure 8.9: SC responses within and across VR-exposure and VR re-exposures. Habituation of SC responses within and between VR trauma exposure and VR re-exposures.

Table 8.6: Beta coefficients for model of changes in SC responses over repeated trauma VR re-exposures; comparing ER manipulations to control group responses.

				95% confidence intervals	
Predictor	β	SE	Z score	Lower	Upper
cons	26.72	4.56	5.85*	-3.09	14.80
Reappraise	-3.32	5.96	-0.56	-12.23	11.11
Suppress	-5.40	6.01	-0.90	-12.68	10.89
alcohol	-4.91	2.41	-2.04*	-6.75	2.67
Time	-7.96	1.74	-4.57*	-7.98	-1.16
TimeSqr	0.53	0.21	2.51*	2.09	2.92
Reappraise X Time	1.07	1.30	0.83	-1.72	3.37
Suppress X Time	1.51	1.31	1.15	-1.41	3.71

*Note: *p>0.05.* reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control. Cons= Constant.

8.4.3.3 Heart rate (HR)

8.4.3.3.1 Correlated pre-trauma individual difference variables

HR responses to the second VR exposure showed no associations with pre-trauma individual difference variables of interest or covariates. Responses towards the first minute of viewing and the 20 seconds post-explosion were negatively associated with ERQ suppression in both the first (first minute: $r(113)=-.199$, p=.033; explosion: $r(113)=-.220$, p=.018) and third VR exposures (first minute: $r(113)=-.206$, p=.027; explosion: $r(113)=-.197$, p=.038), and positively with gender during the first VR exposure (first minute: $r(113)=.260$, p=.005; explosion: $r(113)=.188$, p=.044). Additionally HR responses in the first minute were negatively associated with current computer gaming for the first VR exposure ($r(113)=-.226$, p=.015), and ERQ reappraisal for the third VR exposure ($r(113)=-.221$, p=.018).

8.4.3.3.2 Longitudinal prediction of responses and manipulation effects

Gender, ERQ suppression, ERQ reappraisal, current computer gaming, the group ER manipulation and their interaction terms with time were entered as predictors in the longitudinal model. The removal of four multivariate outlying cases produced qualitative

change in the model, with the covariate computer gaming no longer reaching significance, therefore the model with these cases removed is reported, as they express undue influence on the model fit. The covariate computer gaming was tested for significance and was found to not significantly improve the model fit, therefore gaming and its time interaction term were removed from the final model (table 8.7).

Induced HR responses were found to increase across the three VR exposures both in a linear and quadratic fashion, illustrating the linear increase in HR across the initial and carry-over VR viewings VR's and the respective decrease in HR during ER manipulation instructed VR viewing (figure 8.10). Overall HR was not found to vary according to ERQ subscales, but was generally heightened in females compared to males. Interestingly however the slope of HR responding across VR exposures varied as a function of gender, with males showing a steeper increase in HR responding across initial trauma exposure and first VRET exposure compared to a flatter response slope over time in females (figure 8.11). ER manipulations showed no influence on VR HR responding (χ^2=1.01, p=.604) or changes across VR exposures (χ^2=1.00, p=.607), confirming prior ANOVA results.

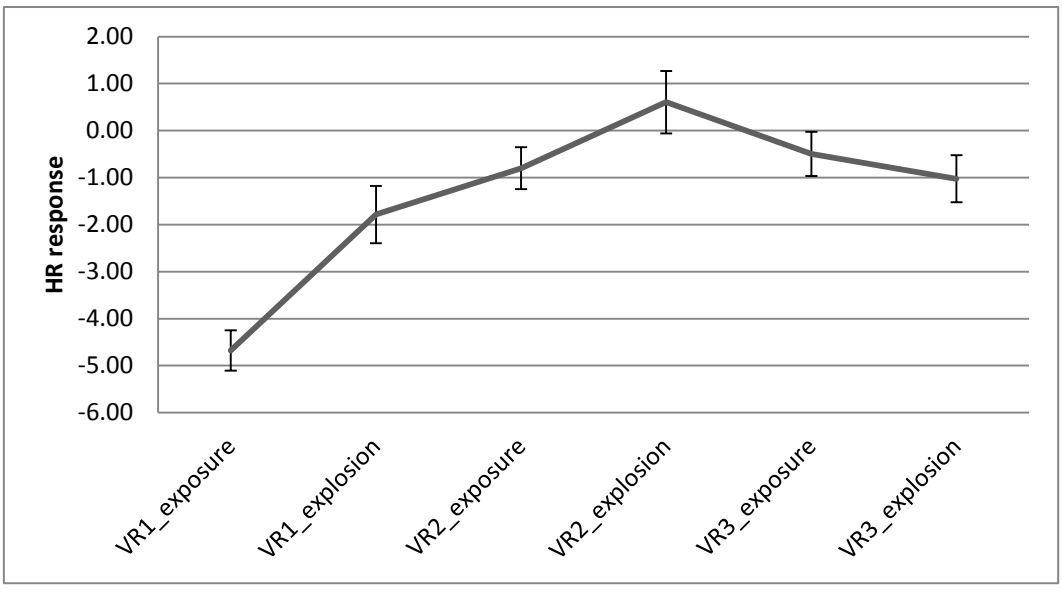


Figure 8.10: HR responses within and across VR-exposure and VR re-exposures. Habituation of HR responses within and between VR trauma exposure and VR re-exposures.

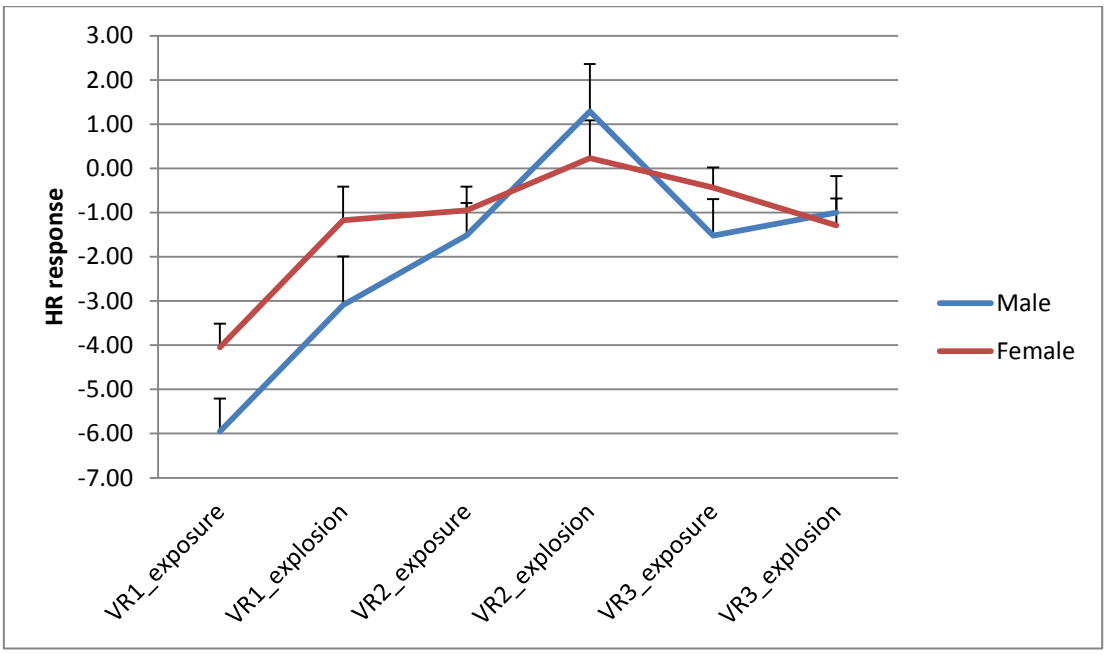


Figure 8.11: HR responses within and across VR-exposure and VR re-exposures by gender. Habituation of HR responses within and between VR trauma exposure and VR re-exposures across genders.

Table 8.7 : Beta coefficients for model of changes in HR responses over repeated trauma VR re-exposures; comparing ER manipulations to control group responses.

				95% confidence intervals	
Predictor	β	SE	Z score	Lower	Upper
cons	-10.26	1.29	-7.94*	-10.48	-5.41
Gender	2.50	1.16	2.16*	-0.10	4.43
ERQ_suppression	-0.15	0.11	-1.42	-1.63	-1.22
ERQ_reappraisal	0.11	0.11	0.98	0.77	1.19
reappraise	0.79	1.31	0.60	-1.97	3.18
suppress	1.40	1.29	1.08	-1.45	3.61
Time	4.29	0.51	8.43*	7.44	9.43
TimeSqr	-0.45	0.06	-7.31*	-7.43	-7.19
Gender X Time	-0.60	0.27	-2.22*	-2.75	-1.68
ERQ_suppression X Time	-0.02	0.03	-0.72	-0.77	-0.67
ERQ_reappraisal X Time	-0.04	0.03	-1.76	-1.81	-1.71
Reappraise X Time	-0.06	0.31	-0.18	-0.79	0.42

Suppress X Time	-0.29	0.30	-0.96	-1.56	-0.36

*Note: *p>0.05.* gender = males coded '0' and females coded '1'. reappraisal = acceptance based reappraisal manipulation group versus control group; suppression = behavioural suppression manipulation group versus control. Cons= Constant.

8.5 DISCUSSION

This study aimed to address the question of whether emotional reappraisal would facilitate, and behavioural suppression would hinder, the habituation of emotional and physiological responses during an analogue VR exposure treatment (VRET) when controlling for the effects of trait reappraisal and suppression styles, in individuals previously exposed to a virtual Iraq trauma scenario (VR) within the same laboratory session. An additional question of interest was the extent to which individual differences in anxiety traits, gender, life events and trait emotion regulation styles predicted initial VR responding and subsequent habituation trajectories, over and above the effects of instructed ER strategies (i.e. regulation group effects).

Interestingly, in contrast to hypothesis 1a and 1b, the emotion regulation manipulations carried out within this study made no influence on the trajectories of VRET response habituation, either independently or when controlling for the influence of trait emotion regulation styles. This finding is in contrast to previous findings showing that both reappraisal and suppression induce measureable changes in emotional and physiological responses during emotional film viewing (Gross, 2002). The results are partially in line with the finding of Gross and Levenson (1993) that behavioural suppression induced no measureable changes in self-reported emotion during an emotional film; however within their study suppression was found to induce physiological alterations in SC and HR, which were not replicated here. Importantly, the design of this study differs from that of many previous analogue ER manipulation designs (with the exception of Woud et al., 2012), in that initial exposure to the emotional VR scenario occurs prior to emotion regulation manipulations, as opposed to ER manipulation prior to or during the emotional event (although concurrent emotion regulation was also manipulated in the final re-exposure, and also illustrated no emotion regulation dependent influences). Although Woud & Holmes (2012) found positive reappraisal afforded a reduction in intrusive memories at one week post-trauma film, their study did not investigate the effects of ER manipulations on response habituation trajectories; it was found within the current study that habituation in anxiety, low mood and SC were influenced by trait differences in ER styles, with main effects lost in covariate analysis. The lack of post-event reappraisals and behavioural

suppression manipulation effect on subsequent VRET habituation has important implications for therapeutic techniques and PTSD models, suggesting that cognitive based reappraisal manipulations may not aid the habituation of emotional fear responses during VRET. This finding is in line with findings that VRET has favourable long term PTSD symptom outcomes compared to present-centred therapy (PCT)[19] (Ready et al., 2010) and with findings suggesting that while exposure based treatments may produce change in fear relevant emotions (such as anxiety and arousal measured within this study) cognitive restructuring may be necessary for amelioration of other emotions such as anger and guilt (which were not assessed in this study). The current finding are however in contrast to the view held by the emotional dysregulation model of PTSD (Lanius et al 2010) that post-trauma emotion regulation responses are key to the development and maintenance of PTSD symptomology (at least in regards to stress sensitization responses, as re-experiencing symptoms were not assessed within the current study). However, as mentioned previously, the role of trait ER styles was highlighted by the fact that habituation effects of low mood, anxiety and SC were all lost when trait ER styles were accounted for. Furthermore, within multilevel analysis it was found that trait differences in ER reappraisal produced generally reduced dissociative responses during all VR exposures and habituation in low mood feelings across VR-trauma exposure; although interestingly trait reappraisal was associated with increases in low mood at initial VR-trauma exposure. As well as supporting the importance of trait ER strategies in altering experiences of negative life events (Garnefski, Kraaij & Spinhoven, 2001) these results suggest that, while reappraisal seems to reduce anxiety responses and dissociation across trauma exposures it can also be associated with self-reported negative mood experiences peri-traumatically (perhaps due to increased engagement in the experience) however across this association reduces significantly, again illustrating trait reappraisal associated adaptive change post-trauma. Further research is needed to investigate the role of trait reappraisal in peri-traumatically induced negative affect, exploring whether these effects are a consequence of adaptive reductions in dissociation. Overall these findings suggests that although manipulated ER styles have no significant influence on the efficacy of analogue-VRET, trait tendencies to reappraise may offer adaptive advantages in the reduction of stress responses and dissociation within VRET.

Significant reductions in low mood, visual analogue rated anxiety and HR were found across VRET when initial levels of VR responding were corrected for. Additionally, when initial VR-trauma responses were modelled in the trajectory of responding to VRET, all fear related

[19] Although PCT omits the use of both exposure and cognitive restructuring, it addresses interpersonal issues, behavioural change and teaches problem solving strategies (Classen et a, 2011).

emotional and physiological outcome variables (anxiety, dissociation, HR, SC) illustrated a linear and quadratic habituation trend; providing support for hypothesis 3. Anxiety states and SC responses showed a steep decline between initial trauma VR exposure and subsequent re-exposures, while HR responses increased between initial trauma exposure and the first VRET exposure and then proceeded to decline between and during the second VRET exposure, suggesting that HR responses may take longer to habituate compared to SC and emotional self report emotional reactions. Findings of a reduction in fear related emotional and physiological responses supports the efficacy of VRET in effective stress desensitisation (Gerardi et al., 2010; Goncalves et al., 2012). Although only two short (2-3 minute) re-exposures were carried out within this study, in comparison with the 4-14 sessions of 90 minute exposures in traditional VRET, limiting the comparison with full VRET protocols, change in responding between the first and second imaginal exposure session has been found to be significantly related to full treatment outcome (van Minnen & Hagenaars, 2002). Although cognitive coping strategies have been shown to be as efficient as imaginal exposure treatments in reducing PTSD symptomology (Hassija et al., 2010; Tarrier et al., 2010), to the best of the authors knowledge the current study is novel in its exploration of the additive value of cognitive emotional reappraisal and acceptance strategies over VRET alone. The presence of VRET induced emotional and physiological response habituation together with a lack of ER manipulation group effects supports the utility of behavioural PTSD treatments, but suggests that interventions addressing cognitive change which focus on acceptance based reappraisal appear to have no added efficacy over pure behavioural VRET in individuals without pathologically developed PTSD. It is possible that the current analogue population sample investigated did not contain individuals with sufficient deficits in emotion regulation, core beliefs or cognitive appraisals, on which reappraisal may impart improvement in engagement with VRET. These results call for investigation and replication of this work within PTSD patient samples to determine under which specific circumstances cognitive reappraisal training can produce added efficiency over VRET treatment alone; such as when maladaptive cognitive appraisals or beliefs are present or when secondary emotions as opposed to primary emotions (which were measured within the current study) require change (Brewin & Holmes, 2003).

Although correlations between increased dissociation and reduced state anxiety were found within each VR exposure an unexpected finding was the relative increase in peri-traumatic dissociation from initial trauma exposure to VRET exposures, in the presence of habituation of all other emotional and physiological responses. This disparity in the overall patterns of dissociation and fear reduction is in contrast to emotional processing theory of PTSD recovery

(Foa & Riggs, 1993), which holds that emotional engagement is a necessary prerequisite to the habituation of emotional responses and successful exposure therapy (Jaycox & Foa, 1996). It is possible that the longitudinal increase in dissociation was driven by fatigue effects due to the long duration of the study (>3 hours); with the VRET exposures taking place at the end of this session where engagement may have been waning. Importantly however this overall pattern, of increased dissociation and reduced anxiety and physiological responses, implies that a reduction in arousal is in fact possible even when individuals are in a state of relatively increased dissociation. Interestingly previous studies have not solely supported the association between peri-traumatic dissociation and PTSD, with Marx and Sloan (2005) showing that peri-traumatic dissociation was not associated with long term PTSD symptom profiles. Due to the analogue nature of this design, findings should be interpreted tentatively but point to a possible disconnection between experiences of dissociation and successful fear response habituation within VRET, compared to traditional imaginal exposure therapy, perhaps due the inherently increased immersion allowed for within VRET.

Investigation of the effects of individual differences on initial responding and subsequent VRET habituation, in accordance with hypothesis 4, illustrated that although manipulated ER group strategies showed no influence over the course of VRET habituation individual differences did influence both overall fear responses and the habituation of these responses. Confirming the findings of earlier covariate analysis, trait emotion regulation appeared an important factor influencing fear responses in general and habituation of these responses with VRET. Trait reappraisal was found to reduce dissociation and therefore facilitate engagement with VRET. Furthermore although trait reappraisal afforded increases in VR induced low mood, perhaps due to the increased engagement with the scenarios, it was also shown to facilitate a reduction in this low mood across VRET (i.e. improved mood habituation). These findings again confirm the adaptive consequences of trait reappraisal (Garnefski et al., 2001) and suggest that trait styles have a greater influence over VRET engagement and habituation than taught reappraisal strategies; although as the time spent teaching these strategies was limited and reappraisal strategies were generic rather than customised, the role of instructed reappraisal in cognitive restructuring is not ruled out. The importance of trait reappraisal is both in line with the emotion dysregulation model of PTSD development which highlights the key role of emotional regulation peri- and post-traumatically, and with cognitive models of PTSD development which highlight the role of individual differences in peri-and post-traumatic core beliefs and appraisals. Gender also was shown to interact with VRET response habituation profiles, with females illustrating a slower habituation response in self-reported low mood and

males experiencing a steeper increase in HR responses between initial trauma VR exposure and the first VRET exposure; however although females illustrated increased HR responses overall compared to males, by the final VRET the HR responses of both genders had habituated to the same level. It is possible that the increased HR responses in males during VRET actually may portray adaptive functions in increasing engagement with the emotional memory of scenario and hence improving long term treatment gains; although previous studies have found reduced maintenance of treatment gains in males following traditional exposure therapy (Felmingham & Bryant, 2012). In addition, trait anxiety sensitivity (ASI) was shown to be associated with a generally increased low mood during VR exposures; however trait anxiety (STAI) was not correlated with any VR re-/exposures response profiles. This suggests that ASI may be a better distinguishing factor, for dysthymic reactions both to the initial trauma and during exposure therapy, than trait STAI. This finding is interesting in light of the research showing that ASI and STAI are distinguishable traits (McNally, 1996) and ASI is a better predictor of panic disorder and distinguished such patients from patients with other anxiety disorders (Taylor, Kock & Crockett, 1991)

Although no stable individual differences were found to be predictive of SC and anxiety responses (STAI and VAS), across VR exposures reduced SC responses were present in individuals who had drank alcohol in the 24 hour period prior to laboratory testing and reduced STAI state anxiety responses were found in individuals who reported playing computer games in their free time. Previous research has long supported the association between alcohol use and reductions in anxiety and fear experiences such as SC responding (Carpenter, 1957). However, a lack of physiological arousal within a VR setting in individuals who have recently drank has implications for the use of VRET in patients with comorbid alcohol abuse, a common co-morbidity in PTSD patients (McFarlane, 1998), especially in military samples (Kozariæ-Kovaèiæ, Ljubin & Grabbe, 2000). It is known that emotional reactivity is a necessary prerequisite to successful exposure therapy (Jaycox & Foa, 1996) and the lack of SC responsivity in recent alcohol users could suggest a poorer engagement in VRET (although no association between dissociation and alcohol use was present, there is a lack of an association between dissociation and response habituation within the current study, so this would not necessarily be expected). Furthermore the reduction in induced state anxiety in gamers puts into question the recent suppositions of Gerardi et al (2010) that an advantage of VRET is that it 'may be more attractive than traditional therapy to a video-savvy generation'. Whilst indeed VR based therapies may seem more acceptable or 'attractive' to such a populations, findings here suggest that regular computer gaming (and hence perhaps

desensitisation to such fear inducing avatar worlds) has detrimental effects on anxiety engagement which have the potential to reduce the efficiency of such VRET treatments.

8.5.1 Limitations and future research directions

Despite promising new directions for further research into the efficacy of VRET over cognitive based reappraisal strategies and the potential influence of stable individual differences and transient state influences (alcohol, computer gaming) on post-trauma recovery and engagement in VRET and habituation of fear responses with exposure treatment, these findings only provide a PTSD and treatment analogue; it is yet to be seen whether such results would be replicated in a PTSD patient population or in a prospective study of survivors of personally relevant psychological trauma. However, as this current study lacked a measure of cognitive change in global beliefs and trauma appraisals (as measured by Dunmore Clark and Ehlers, 1999, and found to be associated with onset and maintenance of PTSD), the efficiency of behavioural VRET and cognitive emotion regulation strategies can only be assessed in regards to their comparative influence on fear extinction and habituation. It is possible that reappraisal instructions act more upon cognitive change than on arousal reduction, especially in the short term. Furthermore the wider experimental design from which these findings were produced involves a 45 minute acoustic startle paradigm prior to the two VR re-exposures which act as the analogue VRET. It is possible that such a stress de-sensitization task prior to analogue VRET could have acted as a pre-VRET fear reducing stimulus, with the vast majority of habituation in fear responses occurring prior to analogue VRET. Although this study provides promising aspects for future investigation, controlled replication of this study within a patient sample is warranted before solid conclusions can be drawn in regards to the respective role of VRET and cognitive based strategies in alleviating PTSD stress sensitization.

8.5.2 Conclusion

Whilst analogue VRET produced effective habituation in a number of fear related emotions, cognitive based emotion regulation strategies of reappraisal and suppression were found to have no influence on the fear reduction. This calls for replication in patient samples, to confirm whether the superior efficiency of VRET over cognitive therapies holds in a population with current PTSD diagnosis, or whether these results were the consequence of only measuring change in primary emotions rather than secondary emotions which may better addressed by emotional reappraisal techniques. Individual differences in gender and trait emotion regulation style were implicated in better outcomes post-trauma and greater improvement in the VRET related fear habituation. Alcohol use and computer gaming were identified as factors

which could impede adequate engagement of emotional responses during VRE, which may consequently hinder efficiency of VRET.

9 GENERAL DISCUSSION

The importance of individual differences in the development of PTSD symptomology and pathology is highlighted by the conditional probability of developing PTSD, following trauma exposure, being estimated at between 3.5-23.6% (McManus et al., 2009, Breslau et al., 1991 & 1998; Helzer et al., 1987). These figures eloquently illustrate the necessary influence of risk and resilience factors in the development of PTSD. Risk and resilience factors predicting PTSD symptom development can originate pre-trauma, peri-trauma and post-trauma, with the potential for dynamic interaction between each of these three levels. Cognitive models hold peri- and post-trauma processing as the key to PTSD development (Ehlers & Clark., 2000; Brewin et al,. 1996, 2001, 2010). Emotional processing models propose peri- and post-trauma fear learning (conditioning) are responsible for PTSD development and as such again highlight the importance of peri- and post-trauma mechanisms (Foa & Riggs, 1993; Foa & Rothbaum, 1998, Lanius, 2010). A diathesis stress conceptualisation of PTSD posits that pre-trauma vulnerabilities are activated by a stressor (critical catalyst) and are key to pathological development; differing from other models of PTSD development in its emphasis on a diverse range of pre-trauma factors and the interaction between pre-trauma vulnerabilities and peri-trauma mechanisms in the development of PTSD (McKeever & Huff, 2003; Elwood et al., 2009). Within the diathesis stress model of PTSD biological vulnerabilities, including genotypes and physiology, and ecological vulnerabilities, including previous life events and personality traits, are posited have a cumulative effect on risk of PTSD development. The more vulnerability factors one has the lower the level of peri-traumatic stress (e.g. arousal) needed to cause PTSD. To date prospective analysis of a range of biological and ecological pre-trauma vulnerabilities together with the assessment of the respective importance of peri- and post-traumatic mechanisms in PTSD symptom development has not been carried out. Such research is important to clarify the influences of pre-trauma factors on PTSD-like responses when a range of implicated risk factors is assessed, as well as allowing for investigation of the possible mediating effects of peri-traumatic responding on the association between pre-trauma risk factors and symptomology; testing the utility of the addition of a diathesis stress conceptualisation to existing models of PTSD development. The exploration and elaboration of this research question formed the primary motive for the current thesis. The traditional analogue design for the investigation of PTSD related symptomology is the trauma-film paradigm; however the increased immersion and first person perspective afforded by VR scenarios was felt to confer increased ecological validity in the measurement of peri-traumatic responses.

This thesis addressed three main research questions and related hypotheses. The first hypothesis, addressed across all empirical chapters (5-8), aimed to confirm the efficacy of VR-trauma scenarios for use in analogue trauma investigations and posited that *VR-trauma exposure will induce significant anxiety, negative mood induction and positive mood reduction*. The second hypothesis was again addressed within all empirical chapters, but was primarily focused on in chapters 5 and 6; it aimed to confirm the relative importance of peri- versus pre-trauma factors in imparting risk and resilience to the development of PTSD related symptomology. It was posited that *a) peri-trauma factors over pre-trauma factors will account for a greater proportion of variance in analogue PTSD symptom development, in line with cognitive, emotional processing and emotion regulation models of PTSD, however, b) pre-trauma factors will be activated to exert their influences on PTSD related symptoms via peri-traumatic mechanisms, in line with the diathesis stress model of PTSD.* The third hypothesis aimed to address the importance of post-trauma processing in the development of PTSD symptoms, chapters 7 and 8 focussed on this topic in relation to the roles of suppression and reappraisal in altering symptom outcomes, it was hypothesised that *a) post-trauma processing manipulations will influence startle responses and re-exposure habituation, in line with cognitive, emotional processing and emotion regulation models of PTSD, however, b) pre-trauma emotion regulation styles will influence how post-trauma emotion regulation manipulations induce symptoms and influence re-exposure habituation, in line with the diathesis stress model of PTSD.* The current chapter will present a summary and critique of the findings in relation to each of these main hypotheses. Within each empirical chapter separate hypotheses were derived in relation to the specific direction of expected effects based on previous studies (see Chapters 5-8 for directional hypotheses based on specific analogue PTSD symptoms tested within each chapter). The theoretical basis for these chapter specific research questions and hypotheses are outlined within Chapter 3 and respective chapter introductions. The findings relating to chapter specific research questions will also be summarised and critiqued within this chapter.

9.1 Effectiveness of VR as a trauma analogue

Hypothesis 1: VR-trauma exposure will induce significant anxiety, negative mood induction and positive mood reduction.

The work within this thesis supports the findings of pilot testing that watching the VR-trauma scenario[20], acts as a negative mood induction and reduces positive affect; supporting hypothesis 1. Whilst pilot testing on a sample of 16 individuals produced significant negative affect induction at a significance level of 0.05 and failed to produce significant change in feelings of anxiety, replication with the larger sample sizes of the studies presented in this thesis showed highly significant ($p<0.001$) negative mood induction, positive mood reduction and increases in anxiety. These findings support the efficacy of VR scenarios to act as an analogue trauma, by inducing anxiety and negative mood within individuals who view the VR scenario.

As well as acting as a mood inductor, in chapter 4 the VR-trauma was found to show the expected habituation in self-reported anxiety and physiological responsivity (HR and SC) across repeated re-exposures. Illustrating that fear and arousal responses elicited by the VR are reduced with each re-exposure as individuals became more accustomed to the VR-trauma environment. This highlights that whilst the VR-Iraq-trauma induces significant negative mood and arousal responses which allow for the measurement of associated individual differences, these responses show adaptive habituation in an undergraduate population and as such will have no long lasting effects that should be of ethical concern for laboratory designs. All participants were debriefed, given information about support lines and asked to contact the experimenter should they have any problems; which no individuals did.

The ease with which peri-traumatic physiological responses could be recorded and prospective associations with pre- and post-trauma factors analysed was a clear advantage to the use of the analogue trauma design. Furthermore, taken together with published findings that VR scenarios elicit immersion and presence as evidenced in self-report, physiological responsivity and neural activation in brain regions involved in spatial navigation (Baumgartner et al., 2006; 2008), the findings presented within this thesis supports the use of VR scenarios as an efficient trauma analogue, which may have advantages over the traditional trauma-film paradigm in realism and immersion within the environment. Findings clarifying the utility of VR-trauma paradigms in analogue individual difference research of PTSD development are in line with the authors previous assertions based on the past literature (Rumball & Karl, 2011; appendix 1).

[20] In the VR scenario the individual appears to be driving through a war torn Iraq city viewing the surroundings from a first person perspective from the drivers' seat in the vehicle and experience a road side explosion which hits their car and injures other civilians

9.1.1 Limitations and future research directions: VR-trauma analogue research

Although VR-trauma related affective induction was assessed within the current studies, no comparison was available to elucidate the respective increased immersion afforded by the first person viewing of a VR scenario as opposed to the traditional analogue trauma-film paradigm, in which a trauma-film is typically observed from a third person perspective as occurring to another individual (Holmes & Bourne, 2008). Future studies need to directly compare the efficacy of VR-trauma and trauma-film paradigms in increasing immersion and presence, as these factors may impact upon the ability of the analogue paradigm to effectively elicit and evaluate ecologically valid peri-trauma responses and their associates. A further limitation with the current VR paradigm was the use of a VR set up in which participants viewed the scenario though table mounted goggles. Despite the advantages of the table mounted VR, in that it allowed for recording of EEG from electrodes mounted on a skull cap and there was no peripheral stimulation from the external environment and as such the VR-scenario was immersive; a VR set up in which participants wear a VR helmet and can move accordingly within the environment would allow for an increased feeling of presence within the VR world (Baumgartner et al., 2006). Future research should explore the advantages of increased involvement within the VR world which would allow for increasingly ecologically valid measurements of peri-traumatic processes in the laboratory. However, an important caveat with the utility of VR helmet software's to PTSD research is that the ability to move independently within the world and view the scenarios from different angles, which allows for increased feelings of presence, inherently results in subtly different traumatic exposures across participants and as such loses the advantage of table mounted VR-paradigm and the traditional trauma-film paradigm, where exposure is carefully controlled across participants. Furthermore, when the measurement of physiological responses is of interest, the typical upright posture in which head mounted VR software is often carried out and the movements in the head associated with viewing, are likely to create movement artifacts in physiological recordings; such artifacts would then require application of more severe filters to the data or could result in data loss. The advantages of increasing immersion and presence over controlling exposure and problems with movement arfifacts within recordings should be carefully considered.

Key recommendations in regards to the use of VR-trauma scenarios in future analogue research have stemmed from the results of this thesis. Firstly, if the experimental paradigm requires the direct comparison of differentially affective scenarios (such as positive and negative states and their consequences on PTSD symptom profiles), both scenarios should be

created within the same VR avatar software to account for differences in imaginal engagement that may occur between real-world and VR-world scenarios and still images; as discussed in section 9.4.1. Secondly, although gaming was assessed and its influence where apparent was accounted for, it was found that individuals who regularly played computer games had a reduced anxiety response towards initial VR-trauma exposure and subsequent re-exposures (Chapter 4). In addition computer gaming was shown to result in a delayed onset latency of frontal brain processing of startling sounds, over and above the effect of gender and post-trauma ER manipulations (Chapter 3). These results implicate computer gaming in alterations in VR-trauma anxiety inductions and neural alterations in startle processing times, indicating that analogue VR-trauma participant samples should be selected from populations who do not game as, similarly to the rationale for excluding individuals with co-morbid PTSD or depression, such individuals may not follow the same pattern of responding as other individuals in the analogue sample.

The current findings in regards to the effects of gaming are also important in themselves; although reductions in VR induced anxiety could be the simple consequence of pre-existing familiarity and habituation with traumatic events within similar avatar worlds. The finding that computer gaming is implicated in alterations in startle related brain processing responses (i.e. ERPs) is intriguing, and in line with research showing that gamers (who play first person violent video games) have reduced brain activation in the medial frontal lobe when processing negative pictures (Montag et al., 2012). Slowed attentional engagement towards the processing of startling sounds and surroundings could have implications for the depth and detail of environmental and emotional processing which occurs, and highlights the plasticity of brain processes in accordance with external factors such as regular gaming. Of course it is also possible that the relationship illustrates the reverse, and difference in neural processing towards startling sounds precede involvement in gaming and instead predicts an increased tendency to want to play computer games. Prospective research is needed to replicate and extend these findings, exploring the mechanisms by which gaming may be associated with altered brain processing speeds towards startling stimuli and testing whether such alterations extend to attentional allocation towards other arousing stimuli.

9.2 Importance of peri-trauma factors, over pre-trauma factors: Prediction of startle responses and memory distortions

Hypothesis 2a: peri-trauma factors over pre-trauma factors will account for a greater proportion of variance in analogue PTSD symptom development, in line with cognitive, emotional processing and emotion regulation models of PTSD

Hypothesis 2b: pre-trauma factors will be implicated in PTSD-like symptom development and will be activated to excerpt their influences on PTSD related symptoms via peri-traumatic mechanisms, in line with the diathesis stress model of PTSD

Support was found for hypothesis 2a, with peri-traumatic responses explaining the most variance in the prediction of physiological startle response, cued trauma recall and the frequency and form of thought suppression induced intrusive trauma memories. Hypothesis 2b was also supported with the prediction of cued trauma recall accuracy and intrusion distress by pre-trauma vulnerabilities found to be mediated by the effects of peri-trauma responses. In addition a number of startle response outcomes (self-reported affect, EMG magnitudes and habituation, HR amplitudes and SC habituation) were predicted by a range of pre-trauma biological and ecological diatheses in combination with peri-trauma emotional responses, providing strong support for the utility of a diathesis stress conceptualisation of PTSD.

Although differential results were found in regards to EMG startle reflex and HR amplitudes across startle chapter 5 and chapter 7, the findings in regards to SC startle response and habituation proved consistent across paradigms. Males and individuals with increased peri-traumatic SC responses consistently showed increased SC habituation towards startling sounds; while SC magnitudes also showed this same profile of predictors in chapter 5, in chapter 7 only peri-traumatic SC remained a predictor of SC magnitudes. In the prediction of EMG reflex and HR startle responses, although chapter 7 found no vulnerability factors to be predictive of these startle response outcomes, in chapter 5 (where genetic risk factors were assessed) pre-trauma gene polymorphisms and increased peri-trauma HR responses illustrated predictive associations; unfortunately there was no means to replicate this effect in Chapter 7 as genotypes were not able to be collected or analysed due to funding restrictions. Whilst augmentation of EMG reflex responding and habituation was associated with the NPS A allele, confirming the role of this gene in modulation of the startle response (Fendt et al., 2010; Okamura et al., 2011; Lennertz et al, 2012), HR startle responding on neutral trials was predicted by ADRA2B s allele, suggesting this allele may be associated with defence responding

within contextually threatening contexts (i.e. neutral startle). These findings support the importance of both pre- and peri-trauma diatheses in the prediction of PTSD-like responses, in line with the diathesis stress model. However, as expected peri-trauma responses were found to explain greater variance in EMG reflex and HR startle responses than biological pre-trauma differences in genetic allele distribution, supporting cognitive and emotional models of PTSD and hypothesis 2a and confirming the findings of meta-analysis which have not included genotypic variables (Brewin et al, 2000; Ozer et al., 2003).

Emotional responses during the startle task were only assessed in chapter 7, due to differences in design, and as such the consistency of such findings cannot be confirmed. However the affect related startle findings also corroborate the importance of a mix of pre-trauma vulnerabilities and peri-trauma responses in predicting alterations in positive mood, but not negative mood, partially supporting the emphasis of diathesis stress conceptualisations on pre- and peri-trauma factors. Interestingly however hypothesis 2a was not supported, with pre-trauma trait differences in ASI (11%) and state differences in recent alcohol use (5%) accounting for a greater proportion of variance in changes in positive affect throughout the startle paradigm, than peri-trauma anxiety and low mood responses (10%). These results indicate that in the prediction of change in positive affect in response to acoustic startle, although altered by peri-traumatic anxiety, is highly dependent on ecological diatheses which precede the trauma.

Peri-trauma anxiety responses were found to be integral in the prediction of cued recall and thought suppression induced intrusions and intrusion characteristics. Whilst only peri-trauma anxiety (self-rated and SC) responses were predictive of the frequency and form of intrusions respectively (supporting hypothesis 2a, and in opposition to hypothesis 2b), the severity of the intrusive thoughts (i.e. self-rated intrusion distress) and trauma cued recall accuracy illustrated pre-trauma risk factors which were mediated by alterations in peri-traumatic HR responding (in support of hypothesis 2b). HR deceleration was shown to mediate the relationship between female gender and development of inaccurate cued recall for the VR-trauma scenario and HR acceleration was found to mediate the relationship between a reduction in trait harm avoidance and the development of distressing intrusive trauma memories during a thought suppression task. The finding that HR deceleration mediates the relationship between female gender and cued recall inaccuracy is in line with previous findings of Holmes et al., (2004) which have implicated peri-traumatic HR reductions in intrusion development, and meta-analytic findings which have illustrated the importance of female gender in risk of PTSD development in civilian populations (Brewin et al., 2000). This mediation illustrates a potential

peri-traumatic mechanism through which female gender may impart risk of PTSD development. The finding that reductions in harm avoidance are associated with risk of intrusion distress is in contrast to the literature illustrating a detrimental effect of increased HA on PTSD development retrospectively (Richman & Frueh, 1997) and prospectively (Gill, 2005), as such this finding is difficult to interpret from these data alone and further research would be necessary to confirm and unpick this relationship. The mediations shown for the development of memory problems are strong support for the utility of a diathesis stress conceptualisation of PTSD symptom development as posited in hypothesis 2b, whilst illustrating the key role of peri-traumatic processes in support of hypothesis 2a. Furthermore, findings that both HR acceleration and deceleration peri-traumatically can mediate different pre-trauma vulnerabilities to produce risk or resilience to different PTSD like symptoms is in line with the emotion regulation model of Lanius (2010) which proposes that different forms of peri-traumatic responding can lead to different post-trauma outcomes.

Although the majority of symptom profiles were predicted by a combination of pre- and peri-trauma factors supporting hypothesis 2a and 2b, or solely by peri-trauma factors supporting hypothesis 2a, results illustrated that free recall distortions, physiological intrusion responses and ERP startle responses were predicted by pre-trauma vulnerability factors alone; highlighting the importance of pre-trauma characteristics in the prediction of PTSD-like responding and the need for full incorporation of such factors within existing models.

Interestingly HR deceleration towards intrusive memories during a thought suppression paradigm, was predicted by 5HTTLPR s allele and NPS T allele gene expression, in line with literature illustrating their pathological associations with PTSD (Lee et al., 2005) and panic disorder (Domschke et al., 2010) respectively. Research to date has not explored the physiological markers during intrusion responses, although peri-traumatic HR reductions have been found to be predictive of later intrusion development (Holmes et al., 2004); although this finding was not replicated within the current thought suppression intrusion paradigm. It has been posited by Holmes et al (2004) that peri-traumatic HR deceleration, as predictive of intrusion frequency, represents a “fear bradycardia” as recorded in animals who freeze in response to threat[21] (Campbell, Wood & McBride, 1997) and may be a physiological correlate of enhanced SAM inputs and reduced VAM inputs, in line with Brewin’s (1996, 2001, 2010)

[21] This perspective was previously argued by Lange et al (1997) to account for findings of HR deceleration towards adversive picture presentations. Moreover, it is unknown whether fear bradycardia responses are related to HR orienting bradycardia responses, although they appear unrelated in non-mammalian vertebrate species (Campbell, Wood & McBride, 1997).

model of PTSD development. The current finding, that HR deceleration occurs during intrusive trauma memories and that peri-traumatic HR deceleration mediates the development of poor trauma cued-recall, adds support to the theory of fear bradycardia and SAM facilitation.

Free recall content accuracy and sequence accuracy were both predicted by female gender and genetic allele distribution, with prior life events also predictive of sequence recall. The current finding that female gender is associated with poorer trauma recall is in line with meta-analytic findings showing that following trauma exposure females are more likely to develop PTSD (Tolin & Foa, 2006; Brewin et al., 2000). The current findings implicate gender differences in memory encoding, storage or retrieval as a potential mechanism by which pathological risk is imparted, in line with the emphasis on memory within dual-processing models of PTSD development (Brewin, 1996, 2001, 2010). A number of models of PTSD development have highlighted the importance of pre-trauma life events in altering peri- and post-trauma processing (Brewin, 1996, 2001; Ehlers & Clark, 2000; Lanius, 2010; McKeever & Huff, 2003; Elwood et al., 2009). The current finding that stressful life events predicted a more organised trauma memory suggests that stressful events can have a protective effect on peri- and post-trauma memory encoding; perhaps by increasing the use of adaptive coping strategies and associated empowerment (Gutierrez, 1994). The protective effects of stressful life events are also in accordance with literature illustrating that a low dose administration of glucocorticoids (a hormone naturally released in responses to stress) weakens the trauma memory trace, showing improvements in memory re-experiencing symptoms in PTSD (Aerni et al., 2004; Schelling et al., 2006; de Quervain & Margraf, 2008). Whilst previous research has shown that prior traumatic events are associated with PTSD risk (Vermetten & Bremner, 2002; Berntsen et al., 2012), the current results suggest that non-traumatic stressful life events may facilitate resilience, and call for further research into the possible resilient responses which may also be associated with exposure to stressful life events. However a possible caveat with the interpretation of the current results is the finding by Mol et al. (2005), that life events can produce as many PTSD symptoms as traumatic events (Mol et al., 2005). Within this thesis individuals with a tentative PTSD diagnosis were excluded, therefore it is possible that in such a sample the presence of heightened stressful life event experiences was artificially associated with resilience via the screening and exclusion processes imposed. Overall however, the findings imply that pre-trauma biological diatheses predict physiological intrusive memory responses and free recall inaccuracies, independently of peri-trauma anxiety responses, potentially via underlying influences on peri- and post-trauma SAM encoding. This would suggest that intense physiological arousal is not a necessary prerequisite for PTSD symptom

development, as posited in emotional and cognitive PTSD models, but rather that the necessary level of arousal is dependent upon the presence of pre-trauma risk diatheses with lower arousal eliciting symptom development when key pre-trauma risk diatheses are present, as posited in the diathesis stress model.

The general findings in relation to ERP startle responses indicate that ERP processing profiles are directly predicted by pre-trauma characteristics, showing no peri-traumatic predictors, apart from on neutral startle trials in the parietal brain region where increased peri-trauma state anxiety predicted earlier ERP responses. No individual difference variables successfully predicted alterations in P2 and P3 responding in chapter 7, however as discussed in section 9.1.1 above gaming did predict delayed ERP processing. When no concurrent emotion regulation manipulations were carried out, prior stressful life events were found to be predictive of a generally later and more P3 maximal ERP response. The importance of pre-trauma life events in altering post-trauma processing supports cognitive models of PTSD development which posit that prior events can alter processing and encoding of the trauma memory in the aftermath of trauma exposure (Ehlers & Clark, 2000; Brewin et al., 1996, 2001, 2010); the current findings implicate prior stressful life events in the alteration of post-trauma processing. Furthermore these findings support the diathesis stress conceptualisation of PTSD which posits that pre-trauma vulnerabilities, including ecological diatheses such as prior life events, are highly associated with symptom development following a critical level of trauma exposure; although a critical level of peri-traumatic anxiety was not found to mediate the influence of stressful life events.

9.2.1 Limitations and future research directions: Importance of peri-trauma factors, over pre-trauma factors

As ERP processes were only assessed following the VR-trauma it is was not possible to conclude whether pre-trauma vulnerability factors (e.g. stressful life events) which predicted post-trauma startle processing, also predicted brain processing patterns peri-traumatically. However, the measurement of ERP's peri-traumatically is complicated by the traditional requirement for an ERP response to be made up of an averaged EEG response towards a comparable set (average of ~30 stimuli required for each ERP) of time-locked stimuli. As a single traumatic event usually initiates PTSD development and as analogue trauma studies work on the principle of a single trauma presentation, such conditions do not allow for traditional analysis of ERP's. Recent work has presented de-noising methods that can allow for single-trial ERP estimation (Quiroga & Garcia, 2003; Blankertz, Lemm, Treder, Haufe & Muller,

2011), however even with such complex analysis protocols PTSD researchers would still experience the problem of not being able to accurately time-lock the ERP response to the exact time of trauma across individuals, as the specific detail of the event which constitute a trauma for one individual can vary for another.

Whilst the current results show that PTSD related genes predict fear bradycardia during (thought suppression induced) VR-trauma related intrusions, no patient studies have assessed physiological responding during the occurrence of intrusions, as such this is an interesting avenue for future clinical research. Future studies should also aim to elucidate whether fear bradycardic responses peri-traumatically and during intrusive memories are respectively representative of SAM encoding and SAM activation and retrieval as was posited in the paper by Holmes et al. (2004). Furthermore, as PTSD related gene polymorphisms were directly predictive of such bradycardic responses during intrusions, it is possible that the mechanisms by which such genes impart PTSD risk is through their influence on SAM versus VAM processing. Analogue research has yet to explore the genetic associations with peri- and post-trauma encoding and memory processing; this seems a fruitful avenue for future research.

9.3 Importance of post-trauma emotion regulation, compared to pre- and peri-trauma factors: Prediction of startle responses and habituation to re-exposure

Hypothesis 3a: post-trauma processing manipulations will influence startle responses and re-exposure habituation, in line with cognitive, emotional processing and emotion regulation models of PTSD

Hypothesis 3b: pre-trauma emotion regulation styles will influence how post-trauma emotion regulation manipulations induce symptoms and influence re-exposure habituation, in line with the diathesis stress model of PTSD

The overall findings in relation to emotion regulation only partially support hypothesis 3a, with post-trauma manipulations having no influence on trauma response habituation and only behavioural suppression manipulations (but not reappraisal manipulations) predicting alterations in startle responses. The importance of pre-trauma trait emotion regulation styles (measured using the ERQ) was also highlighted by the results of chapters 8, with the level of trait reappraisal style proving important in the prediction of negative affect and dissociation responses peri-traumatically and towards trauma re-exposure. However such trait emotion regulation influences did not alter the effectiveness of manipulated emotion regulation strategies; findings are therefore not in line with hypothesis 3b.

The lack of significant reappraisal manipulation effects on startle responding or re-exposure habituation profiles is of particular interest due to the inherent focus on reappraisal within cognitive reframing treatments for PTSD and the posited therapeutic gains of specifically incorporating reappraisal within cognitive therapy (Campbell-Sills & Barlow, 2007). These findings suggest that acceptance based reappraisal may only aid in the alleviation of PTSD in its pathological form, and have no impact on the reduction of PTSD-like symptoms per se in healthy populations. Interestingly, recent research has shown that electrophysiological responses towards threat or non-threat pictures do not reduce in line with symptom reduction during psychotherapy in PTSD patients (Grasso & Simmons, 2012), supporting the lack of reappraisal effects on ERP startle responses within this thesis. However, Grasso and Simmons (2012) failed to find any baseline (i.e.pre-intervention) differences in electrophysiology (ERP, HR, SC) between the PTSD group and control group towards emotional pictures; which is in contrast to the meta-analytic findings of Pole (2007) and Karl et al. (2006), and could explain the lack of electrophysiological alterations with treatment found within their study.

Whilst reappraisal manipulations showed no influence on post-trauma hyperarousal responses, suppression was shown to reduce reflex and affective startle responses but have no influence on trauma re-exposure habituation. The current findings implicate suppression in improvements in startle related affect and reflex eye-blink (EMG) responding, but illustrate increases in arousal with heightened startle SC responses and slower SC habituation. These findings support the work of Gross (see review 2002) in highlighting the role of suppression in augmenting arousal responses as a result of the effortful reduction in behavioural expressions of emotions (i.e. a reduction in EMG startle response), however they extend this body of work by illustrating that suppression can have positive effects on affect regulation. The adaptive influences of suppression on affect were most consistently found within this study when exploring adaptive changes in positive mood as opposed to maladaptive changes in negative mood (which have formed the basis of the suppression regulation findings to date). Furthermore the adaptive influence on affective startle reduction cannot be explained simply by the presence of a dual-task, as found in previous studies (Brewin & Saunders, 2001), as the reappraisal group also completed a concurrent task and showed no alterations in startle responding. These findings extend prior work by illustrating that suppression can have a mix of concurrent adaptive (mood and defence reflex response reduction) and maladaptive (increased sympathetic arousal) influences on post-trauma startle responses.

Although no support was found for the influence of trait emotion regulation techniques on the effectiveness of emotion regulation manipulations (hypothesis 3b), pre-trauma individual

differences in trait reappraisal were found to predict self-reported low mood and dissociation responses peri-traumatically and towards trauma re-exposures; highlighting their independent role in influencing PTSD-like exposure response habituation. Trait reappraisal was shown to exert adaptive influences on reductions in dissociation towards VR-traumas. Interestingly however trait reappraisal positively predicted increased low mood within the initial VR-trauma exposure, with then a habituation of this effect on trauma re-exposures. These findings suggest that although trait reappraisal appears to adaptively reduce dissociation allowing for engagement with the VR-trauma this may also lead to increases in peri-traumatic negative affect. However the overall profile of habituation in low mood and reduced dissociation supports the adaptive role of reappraisal in trauma processing and post-trauma adaption. The importance of pre-trauma trait emotion regulation styles is explicitly specified within Charney's resilience and vulnerability model, and is implicit within cognitive and emotional processing models which state the importance of post-traumatic (Brewin, 1996, 2001, 2010; Foa & Riggs, 1993; Foa & Rothbaum, 1998,; Ehlers & Clark, 2000) and peri-traumatic (Lanius, 2010) emotion regulation in the development of PTSD symptomology; which is presumably influenced to some degree by pre-morbid trait tendencies, although this is not explicitly outlined within the models. Therefore, these findings add support for the explicit integration of the importance of pre-trauma factors within existing models and call for further research into the current findings of differential influences on peri-traumatic affect and post-traumatic affect habituation, which suggest (in line with cognitive and emotional models) that trait reappraisal may predominantly impart its adaptive effects post-traumatically whilst also reducing peri-traumatic dissociation.

9.3.1 Limitations and future research directions: Importance of post-trauma emotion regulation, compared to pre- and peri-trauma factors

Due to the design of the emotion regulation study, in which startle modulation was measured prior to trauma re-exposures, it is possible that the lack of significant emotion regulation dependent influences on trauma re-exposure responses was due to habituation of arousal responses over startle response paradigm which preceded re-exposure. As an analogue-trauma design was employed, it was expected that habituation of responses would occur at a fast rate; the possibility that the reappraisal or suppression manipulation could have exerted an influence on re-exposure response habituation if the design of the paradigm was reversed cannot be ruled out. In addition, Woud et al., 2012 found that post-trauma reappraisal does improve trauma memory and reduce intrusions within an analogue design, illustrating that the effects of reappraisal manipulations are not consistent across the literature, however the

direct comparison of the current findings with those of Woud et al (2012) cannot be properly assessed as the influences of post-trauma emotion regulation strategies on memory disturbances was not measured within this thesis[22]. It may be that the form of acceptance and coping based reappraisal undertaken within the current studies was insufficient to improve analogue PTSD-like symptomology in general, or that reappraisal exerts its beneficial influences only on processing related symptoms (e.g. memory disturbances) but not on hyperarousal symptoms (e.g. startle and re-exposure arousal responses).

Due to the difficulties in measuring ERP's peri-traumatically, as discussed in section 9.2.1, ERP responses were not measured during re-exposure to account for the influence of reappraisal and suppression on trauma processing. However, the lack of emotion regulation effects on startle responding suggests that pathologically related ERP processes may be stable across time and only influence pathological development via inherent pre-trauma individual differences; the measurement of pre-trauma ERP responses towards negative and neutral startle stimuli would have allowed for the investigation of such an interpretation. Future research should prospectively investigate the influences of pre- and post-trauma ERP response profiles in patients with PTSD and trauma-matched controls, and determine if pathological alterations are susceptible to change with cognitive and behavioural PTSD treatments.

9.4 DSM-V PTSD diagnostic criteria: Current implications and critical analysis

Subsequent to the design and completion of the studies carried out within this thesis a number of important changes have been made to the diagnostic criteria for PTSD, with the recent publication of DSM-V (APA, 2013). These changes inevitably have an impact upon the way in which PTSD is conceptualised and discussed, it is therefore necessary to discuss how the current thesis would be interpreted in relation to the amended criteria.

To explicitly account for the pre-requisite traumatic exposure required for a diagnosis of PTSD, which is in contrast to other anxiety related conditions, the recent publication of DSM-V (APA, 2013) has moved PTSD from original classification within the anxiety disorder chapter, to a new chapter 'Trauma- and Stressor-Related disorders' and now contains a clearer specification of events which would constitute traumatic exposure. In addition the distinction between acute and chronic PTSD has been dropped, so that the only stipulation regarding duration of disturbances is that they continue for more than one month. Whilst these changes do not

[22] The decision to not include measurements of memory distortions was made due to the existing duration (~3 hours) of the study and the concern of fatigue effect unduly influencing results were the study to contain additional components.

explicitly affect the rationale or findings within this thesis it does mean that PTSD is now no longer conceptualised as an 'anxiety disorder' per se, or as having separate sub-diagnoses depending on the longevity of disturbances. Inevitably these conceptual changes have an impact upon the way in which PTSD would now be described within the literature, for example reducing the parallels that would have been previously drawn between PTSD and 'other anxiety disorders' and PTSD models no longer having to explicitly account for durational differences in symptom maintenance.

A further alteration relates to the symptom criteria that constitute diagnosis, with the addition of a new criterion accounting for 'negative alterations in cognitions and mood', which has been split off and extended from the 'numbing' aspect of the avoidance criterion from DSM-IV-TR, and an increased emphasis has been placed on behavioural 'flight' responses, with the specification of an 'arousal and reactivity' criterion as opposed to the previous 'hyper-arousal' criterion within DSM-IV-TR. Pre-requisite symptomology pertaining to negative beliefs and affective states within DSM-V highlight the importance of subjective self-report of cognitions and emotional states, with the additional sub-symptoms of negative beliefs, distorted blame and negative trauma-related emotions. Although it would be expected that distortions in blame would not be experienced within an analogue trauma exposure, the assessment of negative beliefs (about the self and the world) within analogue methodology would be of interest, in accordance with their role in predicting PTSD (Bryant & Guthrie, 2007), and it could be postulated that such a symptom cluster may have shown adaptive change with acceptance based reappraisal as used within this thesis. The addition of 'persistent negative trauma-related emotions' as a specific sub-symptom of PTSD, increases the importance of findings illustrating that individual differences in trait emotional styles influence the habituation of negative mood towards trauma re-exposure and affective responses towards acoustic startle. The heightened prominence of behavioural fear reactions within DSM-V also adds further support for the choice to measure physiological startle responses and physiological habituation profiles as PTSD symptom analogues within chapters 5, 7 and 8.

However the most important change in DSM-V criterion in regards to the current thesis is the removal of the DSM-IV-TR A2 criterion, which stipulated that the peri-traumatic response must involve feelings of 'intense fear, helplessness of horror' and was determined to have "no utility" within the current conceptualisation of PTSD (APA,2013). This removal follows from literature illustrating that individual differences in peri-traumatic arousal and dissociation responses are both predictive of PTSD development; as outlined in section 2.4.2 and in

accordance with Brewin (1996, 2001, 2010) and Ehlers & Clark (2000) models of PTSD development, which discuss the role of dissociative, as well as arousal, responses in PTSD development. The results of this thesis show that peri-traumatic responses can have mediating effects on the predictive associations between pre-trauma vulnerabilities and PTSD-like symptomology; illustrating that both cardiac acceleration and deceleration responses to trauma can result in memory distortions. These findings thus support the premise of the DSM-V criterion A2 removal, in as much as both increases and decreases in arousal and engagement appear to be associated with analogue symptom development; supporting the role of both arousal and dissociation in PTSD development. However, the current results and the findings from previous literature suggest that although peri-traumatic arousal reactions may not exclusively predict PTSD, it appears that the two extremes of responses – arousal 'fight/flight' responses or dissociative 'freeze' responses – are integral peri-traumatic responses in the prediction of PTSD. As such, peri-traumatic individual differences in extremes of responding may in fact still carry utility in the prediction of PTSD development and diagnosis.

9.5 Modulation of startle response: Motivational priming hypothesis versus Interrupt hypothesis

The results of the startle paradigms within this thesis illustrate a lack of emotion-modulation of the startle reflex response. Although this was not a main hypothesis within the thesis, the stark contrast of these findings to existing findings within the startle literature (for review see Grillon & Bass, 2003) calls for further explanation of the possible causes of such an anomaly.

9.5.1 Motivational priming hypothesis

Lang et al (1998) developed the motivational priming hypothesis of affective states from the premise that emotional effects represent evolutionary states of motivational readiness. As such emotional states are posited to facilitate appetitive or defensive actions which are congruent with their evolutionary functions; with unpleasant emotions priming defensive responses and pleasant emotions priming appetitive responses. When one motivational state is engaged, this is posited to decrease the activation of the alternate state. Startle reflex responding represents an unconditioned defence reflex, in accordance with the priming hypothesis unpleasant emotional states should therefore facilitate an augmented startle response and pleasant emotional states should inhibit the startle response.

Empirical evidence from acoustic startle paradigms has supported the motivational priming hypothesis of emotional modulation of reflex eye-blink startle responding in healthy controls,

with augmented startle reflexes observed in accordance with negative foreground images and negatively valenced sound presentations, reduced startle reflexes for positively valenced foregrounds and sounds, with neutral contexts showing no effect on startle reflex responses (Bradley &Lang, 2000; Bradley et al., 1993; for review see Grillon & Bass, 2003). Furthermore, research has shown that the emotional modulation effect is apparent in a blocked design, and despite habituation, an increase in emotional modulation is found across repeated blocks (Smith et al., 2001). These findings have been extended to investigate concurrent influences on physiological afferents of startle responding. Studies have shown both emotional modulation, increased SC responses towards unpleasant foregrounds compared to pleasant and neutral foregrounds (Miller et al., 2002) and HR decelaration towards unpleasant foregrounds compared to neutral and pleasant foregrounds (Bradley et al., 1990), and arousal modulation, increased SC responding towards unpleasant and pleasant foregrounds compared to neutral foregrounds (Bradley et al., 1990) and acceleration HR towards unpleasant and pleasant foregrounds compared to neutral (Miller et al., 2002).

The finding in chapter 5 that physiological and reflex startle responding was un-modulated by the emotional valence of the foreground image and congruently valenced sound stimulus, despite the fact that the foregrounds consisted of images of scenarios that had been previously rated as negative and neutral (with slight positive affect) by the same sample of individuals, does not support to the motivational priming hypothesis of emotional states; in as much as the emotional state alone did not facilitate appetitive or defensive motivational states. Moreover, the finding in chapter 3, that neutral startle contexts augmented electrophysiological startle responses (startle component amplitudes, HR and SC) compared to trauma startle contexts, whilst there was no emotion modulation of startle eye-blink reflex, is in direct opposition to responses that would be predicted by the affective motivational priming hypothesis.

The findings within this thesis suggest that the facilitation of motivational states may be more complex than mere emotional priming of associated action programmes. Instead, the inherent judgement of motivational qualities of the context itself may also be integral in the priming of motivational states. For example within contexts in which the individual has no need to personally interact, such as those relating to computer generated scenarios or images (i.e. VR images), motivational states would have little relevance and as such motivational states may be dampened; however when the context is one in which the individual feels they have the potential to interact, such as those constituting real world scenarios or images (i.e. photographs of real cityscapes), motivational states are facilitated. It is possible that the

motivational judgement of a context may act in conjunction with the emotional modulation of the startle response. As such, a real world context could result in augmentation of the startle response and artificial contexts could result in a reduction of the startle response; whilst at the same time emotional priming may be co-occurring, in which negative contexts augment the startle response compared to neutral contexts, and positive contexts reduce the startle response. These dual effects acting in tandem could explain the lack of emotion modulation in reflex eye-blink found within chapter 1 and 3, if effects of trauma augmentation were of a similar influence to the effects of real world context augmentation. As such the increased augmentation of electrophysiological responses in neutral real world contexts compared to the VR-trauma contexts, as found in chapter 3, could be illustrative of the effects of motivational context in action. Such an explanation of co-occurring influences on motivational state modulation has been previously proposed by Graham (1979) in the interrupt hypothesis of startle responding, and extended by Miller et al (2002).

9.5.2 Interrupt hypothesis

The interrupt hypothesis of startle reflex eye-blink holds that the core function of such a response is to clear internal processing to focus attention on the identification of current stimuli and appropriate elicitation of action (Graham, 1979). In support of the behaviourally inhibitory function of the startle reflex, studies have shown that as startle magnitudes increase, reaction time performance becomes longer (Fitzpatrick, 1997). Miller et al (2002) have extended the interrupt hypothesis to propose that 1) due to the function of startle reflex in aiding stimulus identification: startle reflex responding will be augmented in accordance with engagement in mental imagery processing, which co-varies with arousal, 2) due to the function of the startle reflex in disrupting internally focussed processing: startle reflex augmentation co-varies with the magnitude of processing interrupt, and 3) this modulation is independent of the emotion modulation of startle reflex. Therefore in more engaging imagery scenes startle is expected to be augmented, whilst valence-dependent modulation may additionally co-occur. These two co-occurring modulations could explain the lack of startle reflex differentiation across mutually facilitatiing VR-trauma foregrounds (augmentation in accordance with valence) and real world-neutral foregrounds (augmentation in accordance with imagery engagement and increased internal processing), such a comparable profile of augmentation by both modulations could have resulted in the lack of differences in reflex EMG startle responses found towards startle sounds with neutral real-world foreground and trauma related VR-foregrounds in chapters 1 and 3.

Further support for the application of this hypothesis to the current findings is produced by the findings in chapter 3 of increased SC startle responses on neutral trials. As mental imagery processes are believed to co-vary with arousal (Miller et al, 2002: hypothesis 1) the finding of increased SC, an objective measure of autonomic arousal, for neutral real-world foregrounds adds credence to the idea that these trials elicited increased imagery engagement due to their naturalistic content; compared to virtual reality images for which reduced SC startle responses occurred, suggesting reduced imagery engagement. Moreover, Miller et al (2002) additionally proposed that increases in HR responses were an indicator of the degree of imaginal engagement, indeed within chapter 3 HR acceleration was also found on neutral real world startle foregrounds compared to VR-trauma foregrounds. Although HR and SC responses were not found to be facilitated on neutral stimuli within chapter 5 the interpretation of HR and SC responding within this chapter was inhibited by significant effect of the order in which the two blocks of differently valenced foregrounds and startles were presented, and as such the physiological findings in chapter 7 carry the most weight.

9.5.3 Summary and future research directions: Motivational priming and Interrupt

Although further investigation would be needed to confirm the exact nature of the startle response findings within this thesis, the results support a tentative hypothesis that the co-occurrence of valence dependent motivational priming and imagery dependent processing interrupt may have cancelled out respective differences in the modulation of the reflex eye-blink startle responses. Future studies to test the hypothesis of combined imagery and affect based modulations should be carried out. A limitation of the startle paradigms employed within this thesis is that they did not include a pleasant startle and foreground comparison to allow for assessment of differences across all valence sets. As such, future studies to test the combined hypothesis should include foregrounds that vary in their valence (unpleasant, neutral, and pleasant) across different levels of imagery engagement (cartoon image, real world photograph and mental imagery).

9.6 Limitations

The generalisability of the findings within this thesis is limited by the homogeneity of the samples that were tested within the composite studies. All participants were students at the University of Exeter (at a range of academic levels) and the range of ages sampled was somewhat constricted, with a mean age of ~20 years. In addition, all participants received reimbursement for their participations, in the form of university course credits or payment. Although it is common to reimburse participants for their time, it is possible that such

incentives within a university based sample could result in the recruitment of individuals who lack interest or motivation to actively take part in the experiments.

Although within this thesis a measure of dissociation was retrospectively derived using factor analytic techniques, this measure was not tested for reliability and it is possible that the items within the major factor could have tapped both dissociation related components (i.e. 'Did you have moments of losing track of what was going on, that is did you "blank out", "space out", or in some way not feel that you were a part of the experience?'), as well as VR engagement related aspects which were not tapping dissociation in its natural form (i.e 'How much were your senses involved by the virtual reality scenario'). Previous trauma research has employed standardised questionnaires which have been shown to be reliable and valid (Bremner et al., 1998; Birmes et al., 2004) to assess state peri-traumatic dissociative responses; with the clinical administered dissociative states scale (Bremner et al., 1998) being used within a laboratory trauma film paradigm (Holmes et al., 2004) and the peritraumatic dissociative experiences questionnaire (Marmar, Weiss & Metzler, 1997) within patient populations following trauma exposure (Holeva & Tarrier, 2001). The use of a standardised measure of dissociation within this thesis would have greatly improved the reliability of the dissociation findings, and as such the findings relating to peri-traumatic dissociation should be interpreted cautiously and with careful consideration of the specific items which this measure includes (see appendix 7).

The large number of variables that were necessary to assess to answer the primary hypothesis within this thesis meant that, although the numbers of individuals tested were comparatively large for experimental and electrophysiological investigations, there was insufficient power for a thorough examination of variable interactions that would be of interest based on previous literature, such as gene X gene interactions and gene X environment interactions where literature illustrates that epigenetic and epistasis effects can alter functional gene expression and therefore influence respective risk or resilience associated with carrying specific allelic distributions. In a sample of 84 individuals (as constituted the genetic analysis within this thesis) it is likely that individual differences in combinations of genes and life experiences across the sample will increasingly impact upon the genetic results.

9.7 Final conclusions

The aim of this thesis was to address the utility of VR-trauma for the use in analogue designs, investigate the relative importance of peri-trauma responses and post-trauma emotion regulation strategies in the development of hyperarousal and memory disturbances in line

with cognitive (Ehlers & Clark, 2000; Brewin et al., 1996, 2001, 2010) and emotion based models (Foa et al, 1989, 1990; Lanius, 2010) of PTSD development, and explore the contribution of pre trauma factors in line with a diathesis stress conceptualisation of PTSD development (McKeever & Huff, 2003; Charney, 2004). VR-was found to induce significant changes in self-rated arousal and negative mood, supporting its use in analogue trauma paradigms. In general peri-trauma factors were shown to impart the greatest predictive risk of memory distortions and hyperarousal, however pre-trauma factors illustrated the only predictive relationships with ERP startle responses, cued recall and HR intrusion responses. Moreover, peri-traumatic HR responses were found to mediate the influence of pre-trauma vulnerabilities on trauma cued-recall and intrusion distress. Whilst the emotion regulation findings supported the role of manipulated behavioural suppression in increasing arousal, manipulated reappraisal was not shown to exert any influences on alterations in hyperarousal towards startle or trauma re-exposures; although trait reappraisal strategies showed adaptive reductions in peri-traumatic dissociation. The results of this thesis support the key role of peri-traumatic responses in the development of hyperarousal and trauma memory distortions, whilst illustrating that biological and ecological pre-trauma factors additionally exert important influences on hyperarousal and trauma memory and dynamically interact with peri-traumatic responses to explain hyperarousal and memory distortions. The integration of a diathesis stress model, accounting for the importance of biological and ecological pre-trauma vulnerabilities (diatheses), into exciting cognitive and emotion processing accounts of PTSD development would aid in advancement of a fuller understanding of the precise mechanisms of PTSD development and the design of preventative programmes.

APPENDIX 1: Virtual reality as a beneficial tool for experimental research into posttraumatic stress disorder (Rumball & Karl, 2011)

Virtual reality has proved itself as a useful tool for allowing environmental manipulations far beyond those possible in the everyday world. Simulations are effectively used in training programmes of pilots, astronauts and military personnel pre deployment. Virtual films are becoming common place with interactive simulations at major theme parks and IMAX 3D technology widely used in cinema theatres, allowing the viewer an increasingly immersive and realistic viewing experience. With virtual reality technology becoming increasingly accessible and common place, it seems useful to evaluate the benefits of such technology as a potentially valuable tool for experimental research purposes in the field of posttraumatic stress disorder (PTSD).

It is known that imagery plays a special part in the development and persistence of PSTD symptoms (Holmes and Bourne, 2008), with emotionally charged traumatic events causing an increased propensity for visual processing, which can result in automatically triggered vivid intrusions and flashbacks. Processing of traumatic visual images is an important area for further experimental investigation and a target for clinical treatment. Unlike the trauma film paradigm traditionally used for the investigation of maladaptive visual processing in analogue PTSD research, virtual reality worlds allow the presentation of an immersive traumatic environment, experienced from a first person perspective and are easily manipulated for different experimental needs.

As experimental researchers we have been using the 'Iraq world' virtual reality software designed by Hoffman et al. (2008) in our own research for the past two years. Within the academic community we have received mixed opinions about the potential utility of virtual reality for use in experimental studies. Whilst the majority of individuals can clearly see the advantages of having access to an experimental tool which allows the manipulation of an immersive environment beyond the constraints of the real world, a minority have questioned the ability of such an avatar world to impact upon individuals' emotions to a measureable degree. Many participants of experimental research will be used to playing computer animated games with a traumatic nature; individuals who play violent computer games seem easily able to detach themselves from the traumatic nature of these gaming environments and little or no long term psychological carry over is experienced in their everyday lives (Ferguson, 2007). As such can virtual reality worlds induce a measurable emotional impact and allow the investigation of short term individual differences in emotional, physiological and cognitive reactivity before, during and after VR trauma exposure? Our own experimental research as well as treatment based studies of our collaborators (Difede & Hoffman, 2002) and other researchers in the field has clearly illustrated the answer to this question is most definitely YES.

Avoidance of trauma reminders is a core symptom in PTSD and as such some patients are unwilling to engage in imaginal therapy or unable to adequately engage emotions and senses necessary for adequate changes to be made to their maladaptive memory formations. In such

cases VR exposure therapy (VRE) customised to the individual's trauma experience and current level of distress is a valuable treatment tool. VRE has been used to treat PTSD with promising outcomes in road accident survivors (Beck et al., 2007), survivors of World Trade Centre attack (Difede & Hoffman, 2002; Difede et al., 2007) and soldiers both post deployment (Rizzo et al., 2009; Wood et al., 2007) and in the front line (McLay et al., 2010); outcomes in elderly war veterans have been more mixed (Rothbaum et al., 2001; Gamito et al., 2010).

Successful application of VRE in patients with PTSD illustrates that within clinical samples VR induces substantial emotional responses and allows for adequate feelings of immersion and presence in order to change maladaptive trauma related memory traces. Can VR be used to investigate PTSD risk factors in a non clinical sample? It has been suggested that the level of presence felt within the VR world may be reduced in individuals not currently suffering from PTSD and they may experience the VR as a game, rather than an immersive representation of a real life scenario (Spira et al., 2010). However, our own research (Rumball et al., 2011) has shown VR as successful in inducing specific emotional states in non clinical subjects, with individuals with at risk personality types showing differential processing of VR trauma related stimuli compared to neutral stimuli following VR trauma exposure.

It has been found that as the level of presence felt within the VR world increases, the level of emotional state induced by the VR exponentially increases (Riva et al, 2007). This finding highlights the importance of immersion and presence within the VR in inducing measureable emotional responses, especially in non clinical samples. As well as differences in the image quality of the VR world, there are different levels of personal interaction (i.e. table mounted goggles in which the image does not move in accordance with the subjects own movements versus head mounted goggles for which the subject can explore the VR world interactively by moving their head to span the environment and decide upon their own movement within the virtual world) and additional equipment which can stimulate the senses in accordance with the current VR scenario presented (i.e. odour boxes can release smells appropriate for the environment, and platforms and controllers can be programmed to shake when explosives are detonated or shots are fired). Analogue studies of PTSD mechanisms and risk factors may benefit from increased graphical quality, head mounted goggles and stimulation of additional senses, all of which will aid in increasing feelings of immersion and presence within the VR world and so increase the emotional impact of the VR.

VR exposure therapy (VRE) has been successful in substantially reducing PTSD and depression symptoms where in vivo exposure was not possible or traditional imaginal exposure therapy has failed due to patients' inability to recall or recount the painful traumatic memories at the core of the disorder. The continued use of VR in experimental studies will aid in developing a deeper understanding of the cognitive and biological correlates of successful exposure therapy and can elucidate individual differences in emotional, cognitive and physiological reactivity which may impart risk for PTSD development following trauma exposure.

References

Beck, J.G., Palyo, S.A., Winer, E.H., Schwagler, B.E., & Ang, A.J. (2007). Virtual reality exposure therapy for PTSD symptoms after a road accident: an uncontrolled case series. Behaviour Therapy, 38, 39-48.

Difede, J., Cukor, J., Jayasinghe, N., Patt, I., Jedel, S., Spielman, L., Giosan, C., & Hoffman, H.G. (2007). Virtual reality exposure therapy for the treatment of posttraumatic stress disorder following September 11, 2001. Journal of Clinical Psychiatry, 68, 11, 1639-1647.

Difede, J., & Hoffman, H. (2002). Virtual reality exposure therapy for world trade centre post-traumatic stress disorder: A case report. CyberPsychology & Behaviour, 5, 6, 529-535.

Ferguson, C.J. (2007). The good the bad and the ugly: A meta-analytic review of positive and negative effects of violent video games. Psychiatric Quarterly, 78, 4, 309-316.

Gamito, P., Oliveira, J., Rosa, P., Morais, D., Duarte, N., Oliveira, S., & Saraiva, T. (2010). PTSD elderly war veterans: A clinical controlled pilot study. Cyberpsychology & Behaviour, 13, 1, 43-48.

Hoffman, H., Miyahira, S., Hollander, A., & Rose, H. (2008). Iraq World Software. University of Washington.

Holmes, E.A., & Bourne, C. (2008). Inducing and modulating intrusive emotional memories: A review of the trauma film paradigm. Acta Psychologica, 127, 3, 553-566.

Riva, G., Mantovani, F., Capideville, C.S., Preziosa, A., Morganti, F., Villani, D., Gaggioli, A., Botella, C., & Alcaniz, M. (2007). Affective interactions using virtual reality: The link between presence and emotions. CyberPsychology & Behaviour, 10, 1, 45-56.

Rizzo, A.A., Difede, J., Rothbaum, B.O., Johnston, S., McLay, R.N., Reger, G., Gahm, G., Parsons, T., Graap, K., & Pair, J. (2009). VR PTSD exposure therapy results with active duty OIF/OEF combatants. Studies in Health Technology & Informatics, 142, 277-282.

Rothbaum, B.O., Hodges, L.F., Ready, D., Graap, K., & Renato, D. (2001). Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. Journal of Clinical Psychiatry, 62, 617-622.

Rumball, F.R., Lavric, A., Malta, L.S., Hoffman, H., & Karl, A. (2011). Electroencephalographic correlates of the acoustic startle response following virtual reality stress exposure [Abstract]. Psychophysiology, 48 (suppl), 113-114.

Spira, J.L., Johnston, S., McLay. R., Popovic, S., Russoniello, C., & Wood, D. (2010). Expert Panel: Future directions of technological advances in prevention, assessment, and treatment for militart deployment mental health. CyberPsychology & Behaviour, 13, 1, 109-117

Wood, D.P., Murphy, J., Center, K., McLay, R., Reeves, D., Pyne, J., Shilling, R., & Wiederhold, B.K. (2007). Combat-related posttraumatic stress disorder: a case report using virtual reality exposure therapy with physiological monitoring. CyberPsychology & Behaviour, 10, 309-315

APPENDIX 2: EEG & VR Screening Questionnaire

Date: _____

Participant ID: _____

You can withdraw from the study at any time. All of the information that we collect about you will be kept completely confidential. The information that we gather is purely for research purposes.

1. Are you aged 18-35?
    a. □Yes
    b. □ No

2. Are you a right handed?
    a. □Yes
    b. □ No

3. Are you a native English native speaker?
    a. □Yes
    b. □ No

4. Do you regularly take medication?
    a. □ Yes, Which?.....
        1. What for?.....
        2. Since when?.....
    b. □ No

5. Do you have Visual and hearing difficulties which are not corrected for with glasses/contact lenses or a hearing aid?
    a. □Yes
    b. □ No

6. Do you have a diagnosed skin condition such as Eczema?
    a. □Yes
    b. □ No

7. Have you ever had a brain surgery?
    a. □Yes, Why?.....
        1. When?.....
    b. □ No

8. Do you suffer from high blood pressure?
    a. □ Yes
    b. □ No

9. Do you have a pacemaker?
    a. □ Yes
    b. □ No

10. Do you suffer from epilepsy?
    a. □ Yes
    b. □ No

11. Do you have a current mental health condition for which you are being treated (e.g. depression, posttraumatic stress disorder, eating disorder, schizophrenia)?
    a. □ Yes
    b. □ No

12. Do you have a history of military service or a history of war trauma or war-related post traumatic stress disorder?
    a. □Yes
    b. □ No

APPENDIX 3: Traumatic Life Events Questionnaire

1. Have you ever witnessed or been directly involved in a natural disaster such as a flood or hurricane etc.?
    a. □Yes
    b. □ No

2. Have you ever witnessed or been directly involved in a "man-made" disaster such as a train crash, building collapse, robbery, fire etc.?
    a. □Yes
    b. □ No

3. Have you ever been in any other situation in which you feared you might be killed or seriously injured?
    a. □Yes
    b. □ No

4. Have you ever seen someone killed?
    a. □Yes
    b. □ No

5. Has anyone ever made you have intercourse, oral, or anal sex against your will?
    a. □Yes
    b. □ No

6. Has anyone ever touched private parts of your body or made you to touch theirs under threat or force?
    a. □Yes
    b. □ No

7. Has anyone ever attacked you with a weapon?
    a. □Yes
    b. □ No

8. Has anyone ever attacked you **without** a weapon **and caused injury**?
    a. □Yes
    b. □ No

9. Have you experiences any other extraordinary stressful situation or event that is not covered above?
    a. □Yes
    b. □ No

    If yes please specify

    .....

APPENDIX 4: VR Self-assessment manikin (SAM mood)

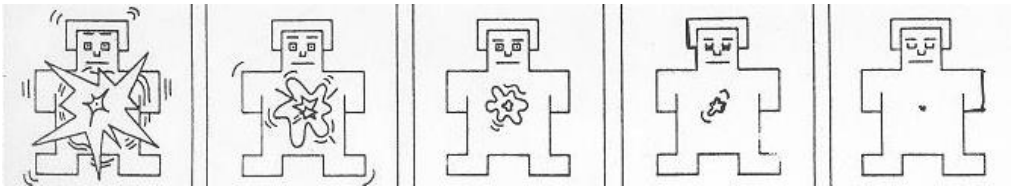
How AROUSED do you feel?

Below you see some manikins in different states of arousal. Please circle the manikin that describes best how aroused you feel at the moment.

For example if you feel stimulated, excited, frenzied, jittery, wide awake or aroused, then you would circle the image at the left end of the scale. If the word makes you feel completely relaxed, calm, sluggish, dull, sleepy, and un-aroused, then you would circle the image at the right end of the scale.

If you feel completely neutral, that is neither excited nor calm; you should circle the image in the centre of the scale. You can also circle anywhere else along the line to indicate varying degrees of arousal.

Aroused Calm



APPENDIX 5: Visual analogue (VAS) mood scale

Mood Scale

Please make a line at the appropriate point along the scale to indicate how you feel at the moment.

At the moment I am feeling:

not at all ◆——————————————◆ extremely

SAD

not at all ◆——————————————◆ extremely

HAPPY

not at all ◆——————————————◆ extremely

ANXIOUS

not at all ◆——————————————◆ extremely

DEPRESSED

not at all ◆——————————————◆ extremely

CALM

not at all ◆——————————————◆ extremely

HOPELESS

not at all ◆——————————————◆ extremely

ANGRY

APPENDIX 6: Peri-trauma dissociation measure

The following 7 questions are meant to help us understand how much you were absorbed by the virtual reality scenario. Read the questions and respond according to your experience using the 10-point scale. Please consider the entire scale when responding, as the intermediate levels may apply.

1. How drawn in or engaged were you by the virtual reality scenario?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

2. How much did the virtual reality scenario simulate how you might feel during a real life experience?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

3. How much were your senses (e.g. sights, sounds) involved by the virtual reality scenario?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

4. How distracted were you by non-related activities (e.g. other people, equipment)?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

5. Did your sense of time change during the scenario – that is, did things seem unusually speeded up or slowed down?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

6. Did you feel emotionally numb during the scenario?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

7. Did you have moments of losing track of what was going on, that is, did you "blank out," "space out," or in some other way not feel that you were a part of the experience?

0 1 2 3 4 5 6 7 8 9 10

Not At All Somewhat Completely

Film Ratings

Please indicate how much attention you have paid to the film you have just seen

0 1 2 3 4 5 6 7 8 9 10

None at all Total attention

Please indicate from what perspective you felt you were watching the film

0 1 2 3 4 5 6 7 8 9 10

Third person (Entirely observing from an external point of view)

First person (Entirely looking out through my own eyes)

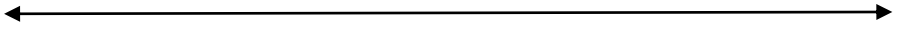
Please indicate how distressing you found the film you have just seen

0 1 2 3 4 5 6 7 8 9 10

Not at all Extremely

Please indicate how anxious the virtual reality world you have just seen made you feel

0 1 2 3 4 5 6 7 8 9 10



Not at all Extremely

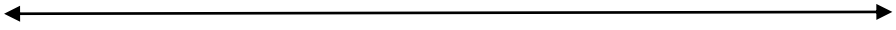
Please indicate how upsetting you found the film you have just seen

0 1 2 3 4 5 6 7 8 9 10

Not at all Extremely

Please indicate how pleasant you found the film you have just seen

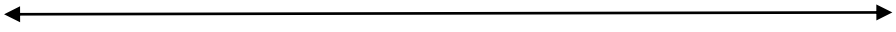
0 1 2 3 4 5 6 7 8 9 10



Not at all Extremely

Please indicate how emotionally arousing you found the film you have just seen

0 1 2 3 4 5 6 7 8 9 10



Not at all Extremely

Please indicate how physically arousing (e.g. increased heart rate, startle response) you found the film you have just seen

0 1 2 3 4 5 6 7 8 9 10

Not at all Extremely

Please indicate how realistic you feel it is that the virtual reality scenario you encountered could occur in the real world

0 1 2 3 4 5 6 7 8 9 10

Not at all Extremely

APPENDIX 7: Dissociation factor loadings

Table A7.1: F*actor loadings for the determination of items tapping dissociation*

Item	Factor loading							
	Study 1				Study 2			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Attention †			-.601			-.634	.440	
Perspective †		.530			.652			
Distress	.697							.986
Anxiety	.705							.822
Upset	.938							.907
Pleasant				.407			.393	-.444
EmotionArousal	.542				.459			.505
PhysioArousal	.315	.615	.354		.476			.406
Realistic		.467			.468			
Engaged †		.628			.671			
Simulate †		.778			.623			
Senses †		.630			.697			
Distracted			.391			.680		
Time	.355			.397			.512	
Numb				.718	-.486		.321	
Blank out †			.510			.516		

Note: †= items used within final dissociation scale

APPENDIX 8: VR-trauma free recall

Date: _____

Participant ID: _____

Please write down all the details that you can remember from the virtual reality scenario; start from the beginning and work through chronologically.

Memory recall for the scenario:

a. On a 0-100 scale, how strong of an effort did you make to recall the scenarios, if 0 = no effort and 100 = 100% effort? _____

b. On a 0-100 scale, how successful do you think you were at recalling the scenarios, if 0 = not at all and 100 = totally successful? _____

APPENDIX 9: Multiple choice cued VR-trauma recall questionnaire

You will now be given some questions about the virtual scenario you watched previously. Please read each question and the choice of responses carefully. After you have read each response, circle the one that you think is the best. If you are not sure of the answer, please make your best guess.

1. The first thing you saw in the scenario was
a) Cars and trucks driving past, civilians walking on the pavement
b) Cars and buses driving past, civilians walking on the pavement
c) Cars and trucks driving past, soldiers walking on the pavement
d) Cars and buses driving past, soldiers walking on the pavement

2. At the beginning of the scenario you could hear
a) civilians yelling b) a man singing a prayer call c) children playing d) a woman screaming

3. Halfway down the first street you passed
a) a burnt out bus on your right c) a burnt out bus on your left
b) a mosque on your right d) a mosque on your left

4. On the first street an individual ran in front of your truck, it was a
a) civilian woman c) soldier
b) civilian man d)child

5. Directly ahead of you, as you reach the end of the first street there was
a) a derelict building with a civilian walking in front of it
b) a derelict building with a soldier walking in front of it
c) a derelict building with a civilian walking through the first floor
d) a derelict building with a soldier walking through the first floor

6. On the pavement towards the end of the second street there was
a) a group of soldiers walking on the right and civilians walking on the left
b) a group of stationary soldiers on your right and civilians walking on your left
c) a group of soldiers walking on the left and civilians walking on the right
d) a group of stationary soldiers on your left and civilians walking on your right

7. As you reach the end of the second street there was
a) a mosque c) a trialer with bombs in it
b) an oil tankard d) a burnt out bus

8. The individual firing the machine gun was

a) driving a truck
b) in the doorway of the mosque
c) in the doorway of a shop
d) driving a car

9. Along the final street you see

a) lots of civilians on either side
b) lots of burned out cars on either side
c) cars driving down the opposite side of the road
d) a bus driving down the opposite side of the road

10. Towards the end of the scenario, on the final street

a) soldiers walk past with machine guns
b) a man runs in front of your car
c) a car drives past and shoots at you
d) a group of children are playing on the pavement

11. At the end of the scenario after the bomb went off you were looking at

a) a mosque
b) a jeep with a man inside it
c) a car with bombs visible in its boot
d) a pile of rubbish bags

12. During the entire scenario how many individuals ran in front of your truck

a) one b) two c) three d) four

13. During the scenario how many bombs exploded?

a) one b) two c) three d) four

14. During the scenario how many mosques did you drive past?

a) one b) two c) three d)four

15. In real time how long was the scenario from beginning to end?

a) between 1-2 minutes
b) between 2-3 minutes
c) between 3-4 minutes
d) between 4-5 minutes

APPENDIX 10: Thought suppression questionnaire

If you experienced intrusions during this task:

1. In what form were they: (Please circle)
a) Verbal
b) Images
c) Mixture of Verbal and Images. If c) which type occurred most often?_____.

2. Please rate the level of distress caused by your intrusions from O (no distress) - 100 (severe distress):
_____

3. Please give specific details about any intrusive thoughts you had (i.e what parts of the virtual reality, what did you see, what did you hear, and what did it make you feel)?
_____

_____

_____

_____

_____

_____

EVERYONE ANSWER ALL QUESTIONS BELOW

1.On a 0-100 scale, how strong of an effort did you make to suppress thoughts about the scenarios, if 0 = no effort and 100 = 100% effort? _____

2. On a 0-100 scale, how successful do you think you were at suppressing thoughts about the scenarios, if 0 = not at all and 100 = totally successful? _____

APPENDIX 11: Iraq VR Script

“One of your lecturers at University has received a grant to go and investigate newly emerging democracies developing in war torn areas. You applied for an internship over the holidays and have been selected as a research assistant, to go and accompany the team during their placement in Iraq.”

“As we begin the scenario you are currently driving around the local town where there have been a number of recent bombings, while your lecturer is at an arranged meeting with local party leaders. So just look at the scenery around you, as you explore the town. Are you ready for me to begin the VR scenario?”

APPENDIX 12: Neutral VR Script

“One of your friends has begun a course at a University near London. They have invited you to stay with them over the holidays, and you have decided go and visit them to do some sightseeing around the University town.”

“As we begin the scenario you are currently driving around the local suburban town exploring the area, while your friend is at a prior engagement. So just look at the scenery around you, as you explore the town. Are you ready for me to begin the VR scenario?”

APPENDIX 13: Group based startle task instructions

Task Instructions – Group 1 Acceptance and coping based reappraisal

Trial:

- RELAX
- VIEW/COPE
- +
- IMAGE
- SOUND
- IMAGE

Introduction

You will now be show a number of pictures of the Iraq town and of the English town that you drove through.

Each time you see a picture of the Iraq town I would like you to imagine you are back in your car in the Iraq town completing your research project.

Each time you see a picture of the English town I would like you to imagine you are back in your car in the English town driving around your friends University town sightseeing.

When each and every picture is presented you will hear a loud sound from outside the vehicle while you are watching the picture. Please sit quietly and listen to each sound as it comes- the sound will happen at different times for different pictures. Keep your eyes open and remain looking at the computer screen for the entire task.

Please watch the pictures and listen to the sounds, concentrate on how they make you feel.

At the beginning of each trial you will see an instruction to relax. This is your cue to relax and to get ready for the instruction.

Cope/View

Before each picture is presented you will be given an instruction to either view or cope for the next picture, which will appear after a fixation cross. I would like you to follow this instruction for the entire time that the next picture is on the screen, while the picture is presented alone before the sound is presented, while the picture is present and the sound is playing and while the picture remains on the screen after the sound. View instructions can be followed only by presentation of an Iraq town image or a London town image. Cope instructions will only ever be followed by an Iraq town image.

View: When the word VIEW is presented, please concentrate on the next town image and listen to the noise from outside, understand its content and allow yourself to feel and experience any

emotional or bodily response which the picture or the sound might naturally elicit. Do not try to alter your feelings or bodily responses in any way; simply respond naturally to viewing the pictures and sounds.

Cope: When the word ***cope*** is presented please concentrate on the next town image and listen to the noise from outside, in this case you should concentrate on how the picture and the sound makes you feel, you might feel afraid, scared or distressed, this is absolutely normal. I would like you to accept the possibility of unwanted or unpleasant thoughts, without them becoming catastrophic. Remember that you have previously managed the situation and remind yourself that you are doing well and can be proud of yourself that you have faced that situation. You may think things such as "This feeling will pass." "I will get through this." "I am safe right now." "I have faced this situation and got through it", "I can cope".

Ratings

After every 9 minutes there will be an instruction to complete a rating. When this instruction appears I would like you to fill in the next available rating slot on this rating questionnaire (show questionnaire), as you can see you will complete 5 ratings in total for the experimental block. For each rating you will fill in your current mood and the technique and thoughts you used when looking at the pictures following an instruction to 'cope' on the last group of trials. If you used a number of different techniques or thoughts then write them all down.

Would you like me to repeat any of the instructions or clarify anything? Do you have any other questions?

Ok so first we will go through a 3 minute practice run of 12 trials, without the sounds, while I sit in the room and then after this you can ask any further questions you may have. Then we will begin the 35 minute experimental block.

Could I ask you to fill out the first rating on the sheet before we begin the practice, so you can get an idea of how to complete the ratings?

Task Instructions – Group 2 Behavioural suppression

Trial:

- RELAX
- VIEW/SUPPRESS
- +
- IMAGE
- SOUND
- IMAGE

Introduction

You will now be show a number of pictures of the Iraq town and of the English town that you drove through.

Each time you see a picture of the Iraq town I would like you to imagine you are back in your car in the Iraq town completing your research project.

Each time you see a picture of the English town I would like you to imagine you are back in your car in the English town driving around your friends University town sightseeing.

When each and every picture is presented you will hear a loud sound from outside the vehicle while you are watching the picture. Please sit quietly and listen to each sound as it comes- the sound will happen at different times for different pictures. Keep your eyes open and remain looking at the computer screen for the entire task.

Please watch the pictures and listen to the sounds, concentrate on how they make you feel.

At the beginning of each trial you will see an instruction to relax. This is your cue to relax and to get ready for the instruction.

Suppress/view

Before each picture is presented you will be given an instruction to either view or suppress for the next picture, which will appear after a fixation cross. I would like you to follow this instruction for the entire time that the next picture is on the screen, while the picture is presented alone before the sound is presented, while the picture is present and the sound is playing and while the picture remains on the screen after the sound. View instructions can be followed only by presentation of an Iraq town image or a London town image. Suppress instructions will only ever be followed by an Iraq town image.

View: When the word VIEW is presented, please concentrate on the next town image and listen to the noise from outside, understand its content and allow yourself to feel and experience any emotional or bodily response which the picture or the sound might naturally elicit. Do not try to alter your feelings or bodily responses in any way; simply respond naturally to viewing the pictures and sounds.

Suppression: When the word 'suppress' is presented, please concentrate on the next town image and listen to the noise from outside, understand its content. We want to see how well you can keep from showing any emotional response on your face and body when you concentrate on the next town image and hear the noise from outside. If you have any feelings before, during or after you look at the picture and hear the sound from outside, please try your best not to let those feelings show on your face or in your body's reactions. In other words, as you concentrate on the picture and hear the sound from outside, try to behave in such a way that a person watching you would not know that you were feeling anything. Look at the picture carefully and listen to the sound, do not try to distract yourself with other thoughts or let your mind wander, but please try to behave (in

your facial and bodily responses) so that someone watching you would not know that you are feeling anything at all.

Ratings

After every 9 minutes there will be an instruction to complete a rating. When this instruction appears I would like you to fill in the next available rating slot on this rating questionnaire (show questionnaire), as you can see you will complete 5 ratings in total for the experimental block. For each rating you will fill in your current mood and the technique and thoughts you used when looking at the pictures following an instruction to 'suppress' on the last group of trials. If you used a number of different techniques or thoughts then write them all down.

Would you like me to repeat any of the instructions or clarify anything? Do you have any other questions?

Ok so first we will go through a 3 minute practice run of 12 trials, without the sounds, while I sit in the room and then after this you can ask any further questions you may have. Then we will begin the 35 minute experimental block.

Could I ask you to fill out the first rating on the sheet before we begin the practice, so you can get an idea of how to complete the ratings?

Task Instructions – Group 3 Control (view as normal)

Trial:

- RELAX
- VIEW
- +
- IMAGE
- SOUND
- IMAGE

Introduction

You will now be show a number of pictures of the Iraq town and of the English town that you drove through.

Each time you see a picture of the Iraq town I would like you to imagine you are back in your car in the Iraq town completing your research project.

Each time you see a picture of the English town I would like you to imagine you are back in your car in the English town driving around your friends University town sightseeing.

When each and every picture is presented you will hear a loud sound from outside the vehicle while you are watching the picture. Please sit quietly and listen to each sound as it comes- the sound will happen at different times for different pictures. Keep your eyes open and remain looking at the computer screen for the entire task.

Please watch the pictures and listen to the sounds, concentrate on how they make you feel.

At the beginning of each trial you will see an instruction to relax. This is your cue to relax and to get ready for the instruction.

View Only

Before each picture is presented you will be given an instruction to view the next picture, which will appear after a fixation cross. I would like you to follow this instruction for the entire time that the next picture is on the screen, while the picture is presented alone before the sound is presented, while the picture is present and the sound is playing and while the picture remains on the screen after the sound.

View: When the word VIEW is presented, please concentrate on the next town image and listen to the noise from outside, understand its content and allow yourself to feel and experience any emotional or bodily response which the picture or the sound might naturally elicit. Do not try to alter your feelings or bodily responses in any way; simply respond naturally to viewing the pictures and sounds.

Ratings

After every 9 minutes there will be an instruction to complete a rating. When this instruction appears I would like you to fill in the next available rating slot on this rating questionnaire (show questionnaire), as you can see you will complete 5 ratings in total for the experimental block. For each rating you will fill in your current mood.

Would you like me to repeat any of the instructions or clarify anything? Do you have any other questions?

Ok so first we will go through a 3 minute practice run of 12 trials, without the sounds, while I sit in the room and then after this you can ask any further questions you may have. Then we will begin the 35 minute experimental block.

Could I ask you to fill out the first rating on the sheet before we begin the practice, so you can get an idea of how to complete the ratings?

APPENDIX 14: Study 1 ethical approval

NHS
National Patient Safety Agency

National Research Ethics Service

South West 2 REC
Research Ethics Service
Royal Devon & Exeter Hospital (Heavitree)
Gladstone Road
Exeter
EX1 2ED

Tel: 0117 342 1328

18 January 2011

Miss Freya Rumball

University of Exeter,
Washington Singer Laboratories,
Perry Road, Exeter, United Kingdom
EX44QG

Dear Miss Rumball

Study title:	**Emotion processing and memory of virtual reality scenarios**
REC reference:	**09/H0206/64**
Protocol number:	**N/A**
Amendment number:	**2**
Amendment date:	**08 December 2010**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Leaflet C	1.0	06 December 2010
Summary	Amendment 2 (6.10.2010) to Protocol V1.9	06 December 2010
Advertisement	POster C	06 December 2010

Letter of invitation to participant	Version 1.0	
Participant Consent Form	C1 V1.0	06 December 2010
Participant Information Sheet	2.0	07 December 2010
Notice of Substantial Amendment (non-CTIMPs)	2.0	07 December 2010
Attendance & Measurement Detail Sheet		08 December 2010
Letter of invitation to participant	1.0	11 October 2010
	C2 V1.0	06 December 2010

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H0206/64:	Please quote this number on all correspondence

Yours sincerely

Ms Mindy Kaur
Committee Co-ordinator

E-mail: mindy.kaur@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Anke Karl*

APPENDIX 15: Study 1 PCA factor loadings showing all components

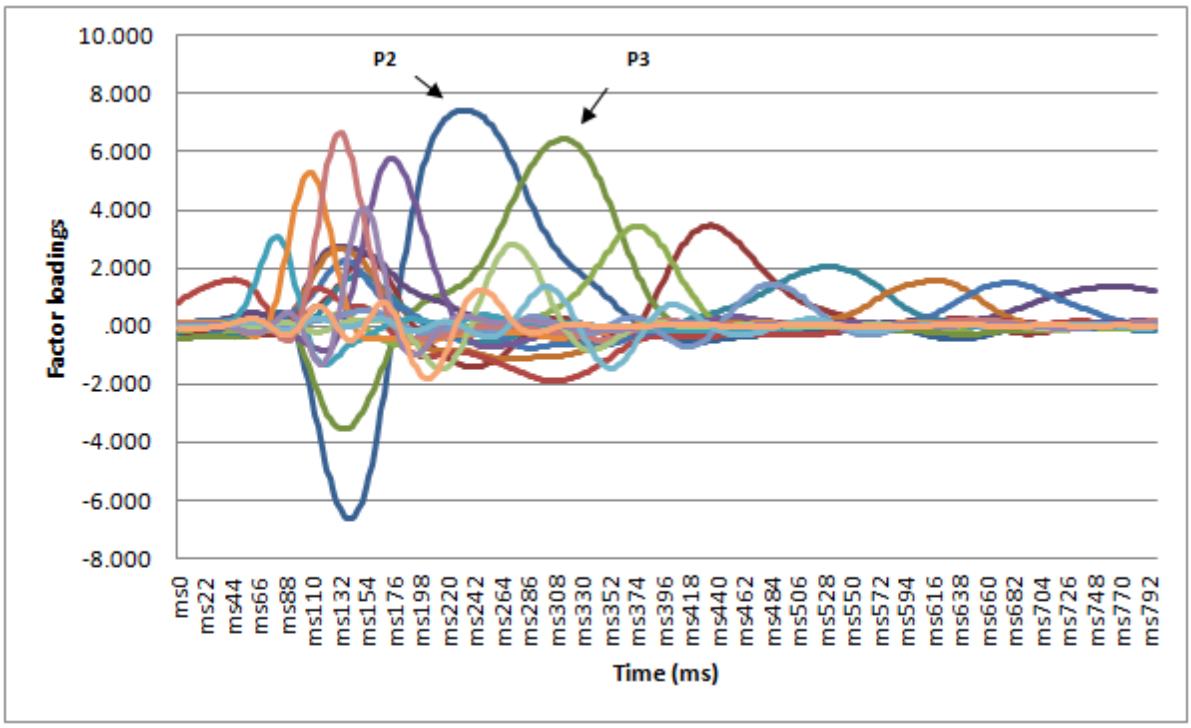


Figure A15.1: Study 1 PCA factor loadings showing all components which explained >1.5% of the total variance in the ERP response.

APPENDIX 16: Participant recruitment and group allocation

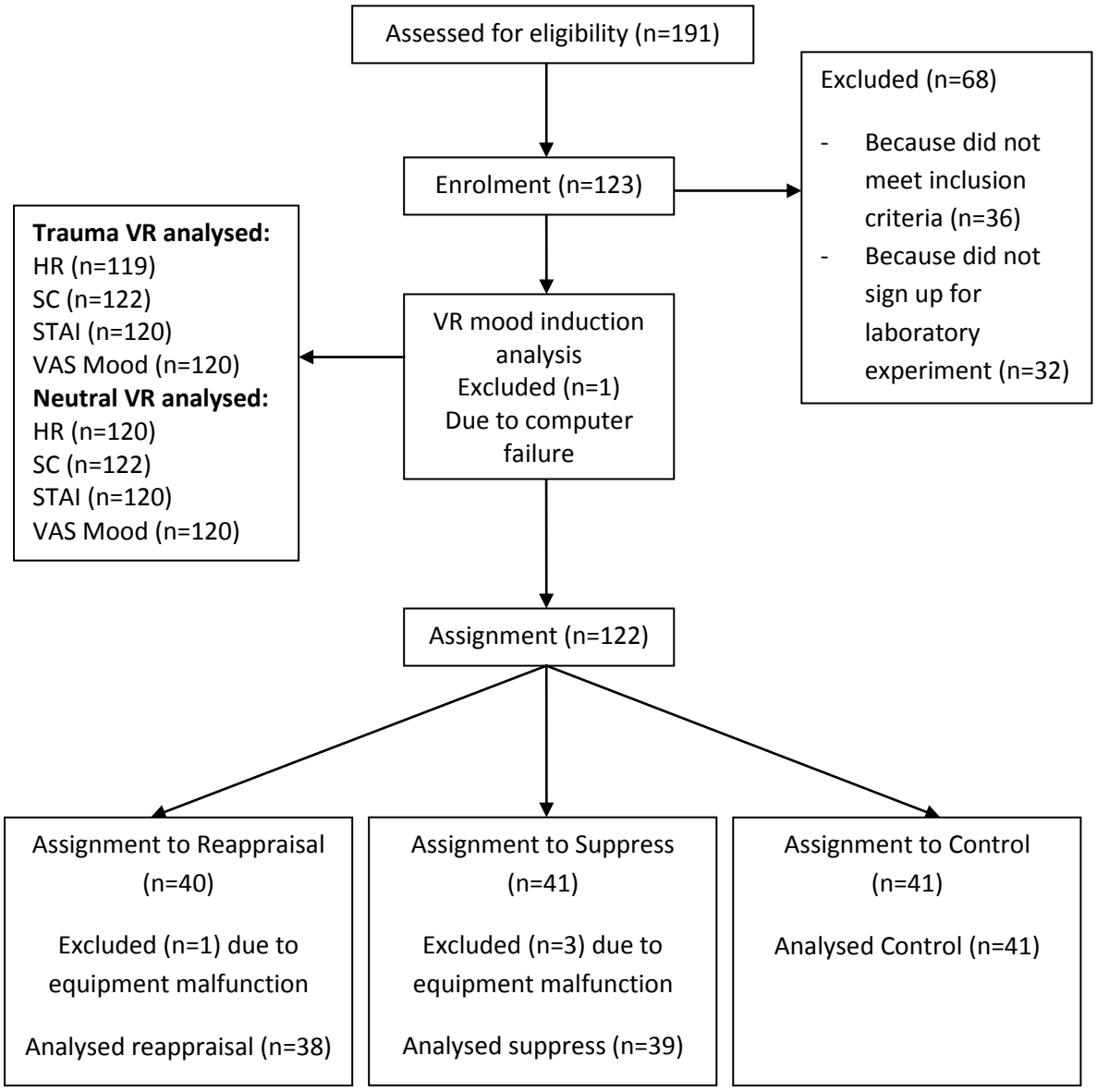


Figure A16.1: Depiction of participant recruitment and exclusion, and subsequent allocation to the manipulation conditions

APPENDIX 17: Ethical approval study 2

To: **Freya Rumball**
From: **Cris Burgess**
CC: **Anke Karl**
Re: **Application 2010/505 to Ethics Committee**

The School of Psychology Ethics Committee met on 26/10/11 and your proposal was discussed. The Committee raised a number of conditions of agreement to this application being accepted. You would be expected to address these before beginning the research but sight of the evidence is not required by the Committee and the project has been approved in principle for the duration of your study.

The conditions are as follows:

- Participants should be told that they may omit individual items if they wish to
- Participants who are selected at the screening stage but decide not to continue should be informed how they may collect the 0.5 credit for participation in the screening process
- Item 9 on the PHQ9 should only be used if deemed necessary to the anticipated outcomes of the research. If item 9 is used, the MDC suicide protocol should be followed. This may be problematic if the PHQ9 is administered online, in which case the researcher should seek advice from the research supervisor and Chair of Psychology REC

In any correspondence with the Ethics Committee about this application, please quote the reference number above or decisions may be delayed.

Yours sincerely,

Cris Burgess
Chair of School Ethics Committee

APPENDIX 18: Study 2 PCA factor loadings showing all components

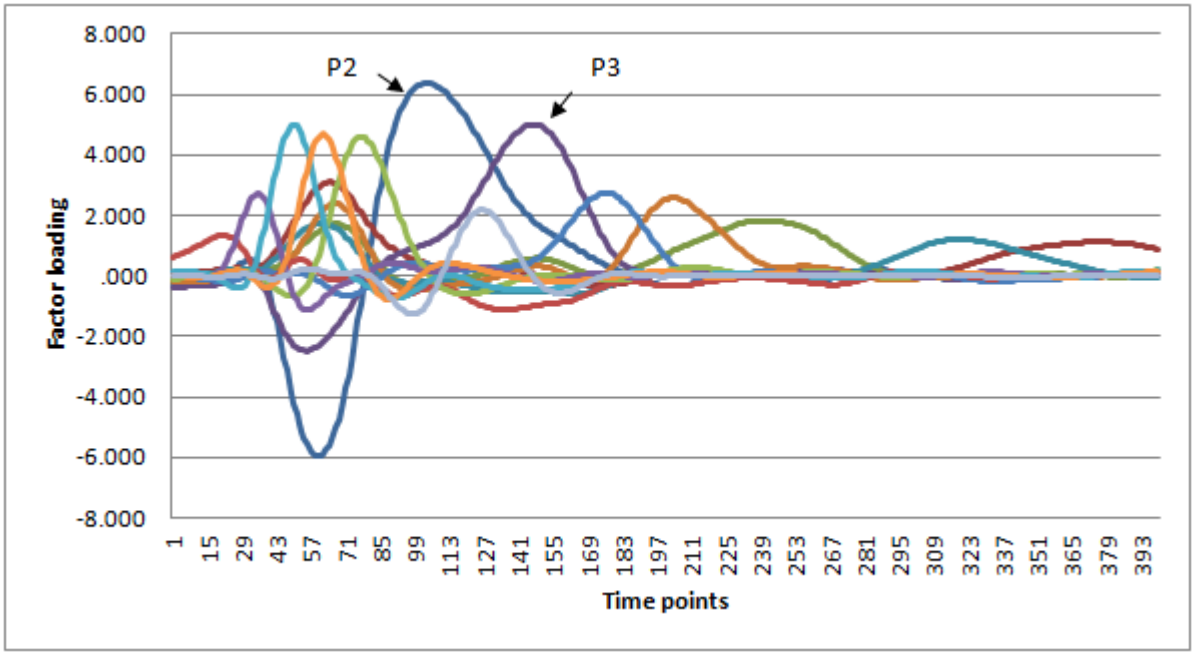


Figure A18.1: Study 2 PCA factor loadings showing all components which explained >1.5% of the total variance in the ERP response. Example for neutral and trauma regulate trials

APPENDIX 19: Post hoc analysis of order by trial interactions

Table A19.1: Order of counterbalancing and effects on startle skin conductance magnitudes towards trauma and neutral trials

Order blocks	Trial type	Mean	F	p
T-N	N	0.14 (0.07)	111.11	<.001
	T	0.21 (0.07)		
N-T	N	0.23 (0.08)	106.54	<.001
	T	0.15 (0.07)		

Note: Standard deviations appear in parenthesis below means.

Table A19.2: Order of counterbalancing and effects on startle skin conductance habituation towards trauma and neutral trials

Order blocks	Trial type	Mean	F	p
T-N	N	6.29 (8.41)	46..44	<.001
	T	14.46 (9.54)		
N-T	N	18.26 (9.71)	44.34	<.001
	T	10.57 (10.54)		

Note: Standard deviations appear in parenthesis below means.

Table A19.3: Order of counterbalancing and effects on startle EMG magnitudes towards trauma and neutral trials

Order blocks	Trial type	Mean	F	p
T-N	N	0.26 (0.2)	61.94	<.001
	T	0.39 (0.17)		
N-T	N	0.42 (0.15)	49.42	<.001
	T	0.35 (0.18)		

Note: Standard deviations appear in parenthesis below means

Table A19.4: Order of counterbalancing and effects on startle EMG habituation towards trauma and neutral trials

Order blocks	Trial type	Mean	F	p
T-N	N	12.32 (12.31)	22.34	<.001
	T	17.66 (10.72)		
N-T	N	19.9 (9.58)	15.30	<.001
	T	15.21 (11.61)		

Note: Standard deviations appear in parenthesis below means.

Table A19.5: Order of counterbalancing and effects on startle ERP (PCA) component amplitudes towards trauma and neutral trials

Order blocks	Trial type	Mean	F	p
T-N	N	174.91 (0.23)	2977.04	<.001
	T	165.26 (0.23)		
N-T	N	164.92 (0.25)	4217.38	<.001
	T	175.09 (0.25)		

Note: Standard errors appear in parenthesis below means.

Table A19.6: Order of counterbalancing and effects on startle ERP onset latencies towards trauma and neutral trials

Order blocks	Trial type	Mean	F	p
T-N	N	0.72 (0.06)	6.40	0.30†
	T	0.84 (0.06)		
N-T	N	0.86 (0.06)	7.23	0.14†
	T	0.92 (0.07)		

Note: Standard errors appear in parenthesis below means. † Bonferroni corrected

REFERENCES

Aardal-Eriksson, E., Eriksson, T. E., Holm, A. C., & Lundin, T. (1999). Salivary cortisol and serum prolactin in relation to stress rating scales in a group of rescue workers. *Biological psychiatry*, *46*(6), 850-855.

Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A., ... & Dominique, J. F. (2004). Low-dose cortisol for symptoms of posttraumatic stress disorder. *American Journal of Psychiatry*,*161*(8), 1488-1490.

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clinical psychology review*, *30*(2), 217-237.

Aleman, A., Swart, M., & van Rijn, S. (2008). Brain imaging, genetics and emotion. *Biological psychology*, *79*(1), 58-69.

Amir, N., Stafford, J., Freshman, M. S., & Foa, E. B. (1998). Relationship between trauma narratives and trauma pathology. *Journal of Traumatic Stress*,*11*(2), 385-392.

Amrhein, C., Mühlberger, A., Pauli, P., & Wiedemann, G. (2004). Modulation of event-related brain potentials during affective picture processing: a complement to startle reflex and skin conductance response?. *International Journal of Psychophysiology*, *54*(3), 231-240.

Andrews, B., Brewin, C. R., & Rose, S. (2003). Gender, social support, and PTSD in victims of violent crime. *Journal of Traumatic Stress*, *16*(4), 421-427.

American Psychiatric Association. (1980*). DSM-III Diagnostic and statistical manual of mental disorders,* 3th Edition. Washington DC: American Psychiatric Association.

American Psychiatric Association. (1994*). DSM-IV Diagnostic and statistical manual of mental disorders,* 4th Edition. Washington DC: American Psychiatric Association.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington DC: American Psychiatric Association.

American Psychiatric Association. (2013*). Diagnostic and statistical manual of mental disorders: DSM-V*. Washington DC: American Psychiatric Association.

Arntz, A., de Groot, C., & Kindt, M. (2005). Emotional memory is perceptual.*Journal of behavior therapy and experimental psychiatry*, *36*(1), 19-34.

Bailey, A., Couteur, A.L., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., Rutter,. M. (1995). Autism as a strongly genetic disorder: evidence from a British twin study. *Psychological Medicine, 25*, 63-77.

Bailey, J. N., Goenjian, A. K., Noble, E. P., Walling, D. P., Ritchie, T., & Goenjian, H. A. (2010). PTSD and dopaminergic genes, DRD2 and DAT, in multigenerational families exposed to the Spitak earthquake. *Psychiatry research*, *178*(3), 507-510.

Baron- Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E. (2001). The autism spectrum quotient (AQ): Evidence from Asperger Syndrome/high functioning autism, males, and females, scientists and mathematicians. Journal of Autism and Developmental Disorders, 31, 5-17.

Barr, C. S., Newman, T. K., Schwandt, M., Shannon, C., Dvoskin, R. L., Lindell, S. G., ... & Higley, J. D. (2004). Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promoter variant in rhesus macaques. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(33), 12358-12363.

Bartussek, D., Becker, G., Diedrich, O., Naumann, E., & Maier, S. (1996). Extraversion, neuroticism, and event-related brain potentials in response to emotional stimuli. *Personality and Individual Differences*, *20*(3), 301-312.

Başoglu, M., Kılıç, C., Şalcıoglu, E., & Livanou, M. (2004). Prevalence of posttraumatic stress disorder and comorbid depression in earthquake survivors in Turkey: an epidemiological study. *Journal of traumatic stress*,*17*(2), 133-141.

Baumgartner, T., Speck, D., Wettstein, D., Masnari, O., Beeli, G., & Jäncke, L. (2008). Feeling present in arousing virtual reality worlds: prefrontal brain regions differentially orchestrate presence experience in adults and children. *Frontiers in Human Neuroscience*, *2*.

Baumgartner, T., Valko, L., Esslen, M., & Jäncke, L. (2006). Neural correlate of spatial presence in an arousing and noninteractive virtual reality: an EEG and psychophysiology study. *CyberPsychology & Behavior*, *9*(1), 30-45.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. F. (1996). Comparison of Beck Depression Inventories-IA and-II in psychiatric outpatients. *Journal of personality assessment*, *67*(3), 588-597.

Beck, A.T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961) An inventory for measuring depression. *Archives of General Psychiatry,* 4, 561-571.

Beck, J. G., Gudmundsdottir, B., Palyo, S. A., Miller, L. M., & Grant, D. M. (2006). Rebound effects following deliberate thought suppression: Does PTSD make a difference?. *Behavior therapy*, *37*(2), 170-180.

Beck, J.G., Palyo, S.A., Winer, E.H., Schwagler, B.E., & Ang, A.J. (2007). Virtual reality exposure therapy for PTSD symptoms after a road accident: an uncontrolled case series. Behaviour Therapy, 38, 39-48.

Bedard-Gilligan, M., & Zoellner, L. A. (2008). The utility of the A1 and A2 criteria in the diagnosis of PTSD. *Behaviour research and therapy*, *46*(9), 1062-1069.

Bedi, U. S., & Arora, R. (2007). Cardiovascular manifestations of posttraumatic stress disorder. *Journal of the National Medical Association*,*99*(6), 642.

Bennice, J. A., Resick, P. A., Mechanic, M., & Astin, M. (2003). The relative effects of intimate partner physical and sexual violence on post-traumatic stress disorder symptomatology. *Violence and Victims*, *18*(1), 87.

Bernat, J. A., Ronfeldt, H. M., Calhoun, K. S., & Arias, I. (1998). Prevalence of traumatic events and peritraumatic predictors of posttraumatic stress symptoms in a nonclinical sample of college students. *Journal of Traumatic Stress*, *11*(4), 645-664.

Bernier, V., Stocco, R., Bogusky, M. J., Joyce, J. G., Parachoniak, C., Grenier, K., ... & Therien, A. G. (2006). Structure-Function Relationships in the Neuropeptide S Receptor. *Journal of Biological Chemistry*, *281*(34), 24704-24712.

Berntsen, D., Johannessen, K. B., Thomsen, Y. D., Bertelsen, M., Hoyle, R. H., & Rubin, D. C. (2012). Peace and War Trajectories of Posttraumatic Stress Disorder Symptoms Before, During, and After Military Deployment in Afghanistan. *Psychological science*, *23*(12), 1557-1565.

Bieling, P. J., Antony, M. M., & Swinson, R. P. (1998). The Stait–Trait Anxiety Inventory, Trait version: Structure and content re-examined. *Behaviour Research and Therapy*.

Birmes, P., Brunet, A., Benoit, M., Defer, S., Hatton, L., Sztulman, H., & Schmitt, L. (2005). Validation of the Peritraumatic Dissociative Experiences Questionnaire self-report version in two samples of French-speaking individuals exposed to trauma. *European Psychiatry*, *20*(2), 145-151.

Blanchard, E. B. (1990). Elevated basal levels of cardiovascular responses in Vietnam veterans with PTSD: A health problem in the making?. *Journal of Anxiety Disorders*, *4*(3), 233-237.

Blanchard, E. B., Hickling, E. J., Buckley, T. C., Taylor, A. E., Vollmer, A., & Loos, W. R. (1996). Psychophysiology of posttraumatic stress disorder related to motor vehicle accidents: replication and extension. *Journal of consulting and clinical psychology*, *64*(4), 742-751.

Blanchard, E. B., Kolb, L. C., Gerardi, R. J., Ryan, P., & Pallmeyer, T. P. (1986). Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post-traumatic stress disorder in Vietnam veterans. *Behavior Therapy*, *17*(5), 592-606.

Blanchard, E. B., Kolb, L. C., Taylor, A. E., & Wittrock, D. A. (1989). Cardiac response to relevant stimuli as an adjunct in diagnosing post-traumatic stress disorder: Replication and extension. *Behavior Therapy*, *20*(4), 535-543.

Blankertz, B., Lemm, S., Treder, M., Haufe, S., & Müller, K. R. (2011). Single-trial analysis and classification of ERP components—a tutorial. *NeuroImage*,*56*(2), 814-825.

Bliese, P. D., Wright, K. M., Adler, A. B., Cabrera, O., Castro, C. A., & Hoge, C. W. (2008). Validating the primary care posttraumatic stress disorder screen and the posttraumatic stress disorder checklist with soldiers returning from combat. *Journal of consulting and clinical psychology*, *76*(2), 272.

Boucsein, W., Fowles, D. C., Grimnes, S., Ben-Shakhar, G., Roth, W. T., Dawson, M. E., & Filion, D. L. (2012). Publication recommendations for electrodermal measurements. *Psychophysiology*, *49*(8), 1017-1034.

Bouton M.E., Mineka, S., Barlow, D.H. (2001). A modern learning theory perspective on the etiology of panic disorder. Psychological Review, 108, 4-32

Bowman, D. A., & McMahan, R. P. (2007). Virtual reality: how much immersion is enough?. *Computer*, *40*(7), 36-43.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: the self-assessment manikin and the semantic differential. *Journal of behavior therapy and experimental psychiatry*, *25*(1), 49-59.

Bradley, M. M., & Lang, P. J. (2000). Affective reactions to acoustic stimuli.*Psychophysiology*, *37*(02), 204-215.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1990). Startle reflex modification: Emotion or attention?. *Psychophysiology*, *27*(5), 513-522.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1993). Pictures as prepulse: Attention and emotion in startle modification. *Psychophysiology*, *30*(5), 541-545.

Brailey, K., Vasterling, J.J, Proctor, S.P., Constans, J.I., Friedman, M.J. (2007). PTSD symptoms, life events, and unit cohesion in U.S. soldiers: Baseline findings from the neurocognition deployment health study. *Journal of Traumatic Stress, 20,* 4, 495-503.

Bramsen, I., Dirkzwager, A.J.E.., van der Ploeg, H. M. (2000). Predeployment personality traits and exposure to trauma as predictors of posttraumatic stress symptoms: A prospective study of former peacekeepers*. American Journal of Psychiatry 157,* 1115-1119.

Brandesab, D., Ben-Schacharb, G., Gilboaa, A., Bonnea, O., Freedmana, S., Shaleva , A.Y. (2002). PTSD symptoms and cognitive performance in recent trauma survivors. *Psychiatry Research, 110, 3*, 231-238.

Bremner, J. D., Krystal, J. H., Putnam, F. W., Southwick, S. M., Marmar, C., Charney, D. S., & Mazure, C. M. (1998). Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS). *Journal of Traumatic Stress*, *11*(1), 125-136.

Bremner, J. D., Vythilingam, M., Vermetten, E., Adil, J., Khan, S., Nazeer, A., ... & Charney, D. S. (2003). Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse.*Psychoneuroendocrinology*, *28*(6), 733-750.

Breslau, N., & Davis, G. C. (1992). Posttraumatic stress disorder in an urban population of young adults: Risk factors for chronicity. *The American Journal of Psychiatry*, 149, (5), 671-675.

Breslau, N., Davis, G. C., Andreski, P., & Peterson, E. (1991). Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Archives of general psychiatry*, *48*(3), 216.

Breslau, N., Davis, G.C ., Andreski, P. (1995). Risk factors for PTSD-related traumatic events: a prospective analysis. *American Journal of Psychiatry, 152,* 529-535.

Breslau, N., Kessler, R. C., Chilcoat, H. D., Schultz, L. R., Davis, G. C., & Andreski, P. (1998). Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Archives of general psychiatry*, *55*(7), 626.

Brewin, C. R. (2001). Memory processes in post-traumatic stress disorder.*International Review of Psychiatry*, *13*(3), 159-163.

Brewin, C. R., & Holmes, E. A. (2003). Psychological theories of posttraumatic stress disorder. *Clinical psychology review*, *23*(3), 339-376.

Brewin, C. R., & Saunders, J. (2001). The effect of dissociation at encoding on intrusive memories for a stressful film. *British Journal of Medical Psychology*, *74*(4), 467-472.

Brewin, C. R., Andrews, B., & Rose, S. (2000). Fear, helplessness, and horror in posttraumatic stress disorder: Investigating DSM-IV Criterion A2 in victims of violent crime. *Journal of Traumatic Stress*, *13*(3), 499-509.

Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of consulting and clinical psychology*, *68*(5), 748.

Brewin, C. R., Gregory, J. D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders: characteristics, neural mechanisms, and treatment implications. *Psychological review*, *117*(1), 210.

Brewin, C. R., Kleiner, J. S., Vasterling, J. J., & Field, A. P. (2007). Memory for emotionally neutral information in posttraumatic stress disorder: A meta-analytic investigation. *Journal of Abnormal Psychology*, *116*(3), 448.

Brewin, C. R., Lanius, R. A., Novac, A., Schnyder, U., & Galea, S. (2009). Reformulating PTSD for DSM-V: Life after Criterion A. *Journal of Traumatic Stress*, *22*(5), 366-373.

Brewin, C.R. (2001). A cognitive neuroscience account of posttraumatic stress disorder and its treatment. *Behaviour Research and Therapy, 39*, 378-393.

Brewin, C.R. (2003). *Post-traumatic stress disorder: malady or myth?* New Haven: Yale University press.

Brewin, C.R., Dalgleish, T., & Joseph, S. (1996). A dual representation theory of post traumatic stress disorder. *Psychological Review, 103*, 670-686.

Brewin, C.R., Smart, L. (2005) Working memory capacity and suppression of intrusive thoughts. *Journal of Behavior Therapy and Experimental Psychiatry, 36, 1*, 61-68.

Broekman, B.F.P., Olff, M., & Boer, F. (2007). The genetic background to PTSD. Neuroscience and *biobehavioural reviwew, 31*, 348-362.

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of psychiatric research*, *42*(6), 503-506.

Brunetti, M., Sepede, G., Mingoia, G., Catani, C., Ferretti, A., Merla, A., ... & Babiloni, C. (2010). Elevated response of human amygdala to neutral stimuli in mild post traumatic stress disorder: neural correlates of generalized emotional response. *Neuroscience*, *168*(3), 670-679.

Brunoni, A.R., Lopes, M., Fregni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *The International Journal of Neuropsychopharmacology, 11*, 1169-1180.

Bryant, R. A. (2003). Early predictors of posttraumatic stress disorder.*Biological Psychiatry*, *53*(9), 789-795.

Bryant, R. A., & Guthrie, R. M. (2007). Maladaptive self-appraisals before trauma exposure predict posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, *75*(5), 812.

Bryant, R. A., Harvey, A. G., Guthrie, R. M., & Moulds, M. L. (2000). A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. *Journal of Abnormal Psychology*, *109*(2), 341.

Buckley, T. C., & Kaloupek, D. G. (2001). A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosomatic Medicine*, *63*(4), 585-594.

Bueller, J.A., Aftab, M., Sen, S., Gomez-Hassan, D., Burmeister, M., & Zubieta, J. (2006). BDNF *Val^{66}Met* Allele Is Associated with Reduced Hippocampal Volume in Healthy Subjects. Biological Psychiatry, *59,* (9), 812-815.

Butler, L.D, & Nolen-Hoeksema, S. (1994). Gender differences in response to depressed mood in a college sample. *Sex roles, 30*, 331-346.

Butler, R. W., Braff, D. L., Rausch, J. L., Jenkins, M. A., Sprock, J., & Geyer, M. A. (1990). Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. *Am J Psychiatry*,*147*(10), 1308-1312.

Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). β-Adrenergic activation and memory for emotional events. *Nature*, *371*(6499), 702-704.

Cameron, A., Palm, K., & Follette, V. (2010). Reaction to stressful life events: What predicts symptom severity?. *Journal of anxiety disorders*, *24*(6), 645-649.

Campbell, B. A., Wood, G., & McBride, T. (1997). Origins of orienting and defensive responses: An evolutionary perspective. *Attention and orienting: Sensory and motivational processes*, 41-67.

Campbell-Sills, L., & Barlow, D. H. (2007). Incorporating emotion regulation into conceptualizations and treatments of anxiety and mood disorders.

Carleton, R. N., Sikorski, J., & Asmundson, G. J. (2010). Terrifying movie stimuli: A new design for investigating precursors for posttraumatic stress.*Psychological Trauma: Theory, Research, Practice, and Policy; Psychological Trauma: Theory, Research, Practice, and Policy*, *2*(3), 206.

Carlson, J. G., Singelis, T. M., & Chemtob, C. M. (1997). Facial EMG responses to combat-related visual stimuli in veterans with and without posttraumatic stress disorder. *Applied psychophysiology and biofeedback*,*22*(4), 247-259.

Carlson, S., & Willott, J. F. (1998). Caudal pontine reticular formation of C57BL/6J mice: responses to startle stimuli, inhibition by tones, and plasticity. *Journal of neurophysiology*, *79*(5), 2603-2614.

Carpenter, J. A. (1957). Effects of alcoholic beverages on skin conductance: An exploratory study. *Quarterly Journal of Studies on Alcohol*.

Carretié, L., Hinojosa, J.A., Martín-Loeches, M., Mercado, F., Tapia, M. (2004). Automatic attention to emotional stimuli: neural correlates. *Human Brain Mapping. 22(4),290-9.*

Carson, M. A., Metzger, L. J., Lasko, N. B., Paulus, L. A., Morse, A. E., Pitman, R. K., & Orr, S. P. (2007). Physiologic reactivity to startling tones in female Vietnam nurse veterans with PTSD. *Journal of traumatic stress*,*20*(5), 657-666.

Cartwright-Hatton, S., McNicol, K., & Doubleday, E. (2006). Anxiety in a neglected population: prevalence of anxiety disorders in preadolescelnct children. *Clinical Psychology Review. 26* (7), 817-833.

Casada, J. H., Amdur, R., Larsen, R., & Liberzon, I. (1998). Psychophysiologic responsivity in posttraumatic stress disorder: generalized hyperresponsiveness versus trauma specificity. *Biological psychiatry*, *44*(10), 1037-1044.

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Focus*, *8*(3), 398.

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., & Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science Signalling*, *301*(5631), 386.

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *FOCUS: The Journal of Lifelong Learning in Psychiatry*, *2* (3), 368-391.

Charney, D. S., Deutch, A. Y., Krystal, J. H., Southwick, S. M., & Davis, M. (1993). Psychobiologic mechanisms of posttraumatic stress disorder.*Archives of General Psychiatry*, *50*(4), 294.

Chen ZY, Bath K, McEwen B, Hempstead B, Lee F. (2008). Impact of genetic variant BDNF (Val66Met) on brain structure and function. Novartis Foundation Symposia. 289,180-195.

Chen, Z., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C., Herrara, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead B.L., Lee, F.S. (2006). Genetic variant BDNF (Val66Met) Polymorphism alters anxiety-related behaviour. *Science, 314*, 140-143.

Christiansen, D., & Elklit, A. (2012). Sex differences in PTSD, Post Traumatic Stress Disorders in a Global Context, Ovuga, E (Ed.), p.127. InTech: Rijeka, Croatia.

Chung, H., & Breslau, N. (2008). The latent structure of post-traumatic stress disorder: tests of invariance by gender and trauma type. *Psychological medicine*, *38*(4), 563-574.

Classen, C. C., Palesh, O. G., Cavanaugh, C. E., Koopman, C., Kaupp, J. W., Kraemer, H. C., ... & Spiegel, D. (2011). A comparison of trauma-focused and present-focused group therapy for survivors of childhood sexual abuse: A randomized controlled trial. *Psychological Trauma: Theory, Research, Practice, and Policy*, *3*(1), 84.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants. *Archives of General Psychiatry, 44* 573–588; Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry*, *50*, 975–990

Cohen, H., Benjamin, J., Geva, A. B., Matar, M. A., Kaplan, Z., & Kotler, M. (2000). Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of

power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Research, 96 (1*), 1-13.

Comings, D. E., Muhleman, D., & Gysin, R. (1996). Dopamine D< sub> 2</sub> receptor (DRD2) gene and susceptibility to posttraumatic stress disorder: A study and replication. *Biological psychiatry*, *40*(5), 368-372.

Conway, M.A. (1997). Introduction: what are memories? In M.A Conway, *Recovered memories and false memories* (pp. 1-22). Oxford, UK: Oxford University Press.

Conway, M.A., Pleydell-Pearce, C.W. (2000). The construction of autobiographical memories in the self-memory system. *Psychological Review, 107,* 2, 261-288.

Cook, E. W., Hawk, L. W., Davis, T. L., & Stevenson, V. E. (1991). Affective individual differences and startle reflex modulation. *Journal of Abnormal Psychology*, *100*(1), 5.

Cornelis, M. C., Nugent, N. R., Amstadter, A. B., & Koenen, K. C. (2010). Genetics of post-traumatic stress disorder: review and recommendations for genome-wide association studies. *Current psychiatry reports*, *12*(4), 313-326.

Corr, P. J., Kumari, V., Wilson, G. D., Checkley, S., & Gray, J. A. (1997). Harm avoidance and affective modulation of the startle reflex: A replication.*Personality and Individual Differences*, *22*(4), 591-593.

Ćosić, K., Popović, S., Kukolja, D., Horvat, M., & Dropuljić, B. (2010). Physiology-driven adaptive virtual reality stimulation for prevention and treatment of stress related disorders. *CyberPsychology, Behavior, and Social Networking*, *13*(1), 73-78.

Couper, M. P., Tourangeau, R., Conrad, F. G., & Singer, E. (2006). Evaluating the Effectiveness of Visual Analog Scales A Web Experiment.*Social Science Computer Review*, *24*(2), 227-245.

Croll, S.D., Ip, N.Y., Lindsay, R.M., Wiegand, S.J. (1998). Expression of BDNF and trkB as a function of age and cognitive performance. *Brain Research, 812*, 1-2, 200-208.

Cuthbert, B. N., Schupp, H. T., Bradley, M. M., Birbaumer, N., & Lang, P. J. (2000). Brain potentials in affective picture processing: covariation with autonomic arousal and affective report. *Biological psychology*, *52*(2), 95-111.

Cuthbert, B. N., Schupp, H. T., Bradley, M., McManis, M., & Lang, P. J. (1998). Probing affective pictures: Attended startle and tone probes.*Psychophysiology*, *35*(3), 344-347.

Dannlowski, U., Kugel, H., Franke, F., Stuhrmann, A., Hohoff, C., Zwanzger, P., ... & Domschke, K. (2011). Neuropeptide-S (NPS) receptor genotype modulates basolateral amygdala responsiveness to aversive stimuli.*Neuropsychopharmacology*, *36*(9), 1879-1885.

Darves-Bornoz, J. M., Alonso, J., de Girolamo, G., Graaf, R. D., Haro, J. M., Kovess-Masfety, V., ... & Gasquet, I. (2008). Main traumatic events in Europe: PTSD in the European study

of the epidemiology of mental disorders survey.*Journal of traumatic stress*, *21*(5), 455-462.

Davidson, J.R.T., Hughes, D., Blazer, D.G., George, L.K. (1991). Post-traumatic stress disorder in the community: an epidemiological study. *Psychological Medicine, 21*, 713-721.

Davies, M. I., & Clark, D. M. (1998a). Thought suppression produces a rebound effect with analogue post-traumatic intrusions. *Behaviour Research and Therapy*, *36*(6), 571-582.

Davies, M. I., & Clark, D. M. (1998b). Predictors of analogue post-traumatic intrusive cognitions. *Behavioural and Cognitive Psychotherapy*, *26*, 303-314.

De Kloet, C. S., Vermetten, E., Geuze, E., Kavelaars, A., Heijnen, C. J., & Westenberg, H. G. M. (2006). Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *Journal of psychiatric research*. 40, (6), 550-567.

De Kloet, E.R., Joe¨ls, M., Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nat Rev Neurosci, 6,* 463–475.

de Quervain, D. J. F., & Margraf, J. (2008). Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: a novel therapeutic approach.*European journal of pharmacology*, *583*(2), 365-371.

De Quervain, D. J., Kolassa, I. T., Ertl, V., Onyut, P. L., Neuner, F., Elbert, T., & Papassotiropoulos, A. (2007). A deletion variant of the α2b-adrenoceptor is related to emotional memory in Europeans and Africans. *Nature neuroscience*,*10*(9), 1137-1139.

Dębiec, J., Bush, D. E., & LeDoux, J. E. (2011). Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats—a possible mechanism for the persistence of traumatic memories in PTSD.*Depression and anxiety*, *28*(3), 186-193.

Den, S., Nesse, R.M., Stoltenberg, S.F,m Li, S., Gleiberman, L., Chakravarti, A., Weber, A.B., Burmeister, M. (2003). A BDNF Coding Variant Is Associated with the NEO Personality Inventory Domain Neuroticism, a Risk Factor for Depression. *Neuropsychopharmacology* 28 , 397–401.

Department of Defense (2004). VA/DoD Clinical practice guideline for the management of post-traumatic stress. Version 1.0. Retrieved from http://www.healthquality.va.gov/ptsd/ptsd_full.pdf

Dietz, L. J., Stoyak, S., Melhem, N., Porta, G., Matthews, K. A., Walker Payne, M., & Brent, D. A. (2012). Cortisol Response to Social Stress in Parentally Bereaved Youth. *Biological Psychiatry*.

Difede, J., & Hoffman, H. (2002). Virtual reality exposure therapy for world trade centre post-traumatic stress disorder: A case report. CyberPsychology & Behaviour, 5, 6, 529-535.

Difede, J., Cukor, J., Jayasinghe, N., Patt, I., Jedel, S., Spielman, L., Giosan, C., & Hoffman, H.G. (2007). Virtual reality exposure therapy for the treatment of posttraumatic stress disorder following September 11, 2001. Journal of Clinical Psychiatry, 68, 11, 1639-1647.

DiGangi, J. A., Gomez, D., Mendoza, L., Jason, L. A., Keys, C. B., & Koenen, K. C. (2013). Pretrauma risk factors for posttraumatic stress disorder: A systematic review of the literature. *Clinical Psychology Review*.

DiGangi, J., Guffanti, G., McLaughlin, K. A., & Koenen, K. C. (2013). Considering trauma exposure in the context of genetics studies of posttraumatic stress disorder: a systematic review. *Biol. Mood Anxiety Disord*,*3*(2).

Doerfel, D., Strobel, A., Moser, D., Werner, A., von Kummer, R., & Karl, A. (submitted). BDNF and 5-HTT interaction association with lower grey matter volume in emotional memory circuitry. *Biological Psychiatry.*

Domschke, K., Reif, A., Weber, H., Richter, J., Hohoff, C., Ohrmann, P., ... & Deckert, J. (2010). Neuropeptide S receptor gene—converging evidence for a role in panic disorder. *Molecular psychiatry*, *16*(9), 938-948.

Donchin, E., Heffley, E.F. (1978). Multivariate analysis of event-related potential data: a tutorial review. In Otto, D. (Ed.), Multidisciplinary Perspectives in Event-Related Brain Potential Research. Government Printing Office, Washington, DC, p. 555–572.

Donner, J., Haapakoski, R., Ezer, S., Melén, E., Pirkola, S., Gratacòs, M., ... & Hovatta, I. (2010). Assessment of the neuropeptide S system in anxiety disorders. *Biological psychiatry*, *68*(5), 474-483.

Du, L., Bakish, D., & Hrdina, P. D. (2000). Gender differences in association between serotonin transporter gene polymorphism and personality traits.*Psychiatric genetics*, *10*(4), 159.

Duggan, C., Sham, P., Lee, A., Minne, C., & Murray, R. (1995). Neuroticism: a vulnerability marker for depression evidence from a family study. *Journal of affective disorders*, *35*(3), 139-143.

Dunmore, E., Clark, D. M., & Ehlers, A. (1999). Cognitive factors involved in the onset and maintenance of posttraumatic stress disorder (PTSD) after physical or sexual assault. *Behaviour research and therapy*, *37*(9), 809-829.

Edwards, V. J., Holden, G. W., Felitti, V. J., & Anda, R. F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents:

results from the adverse childhood experiences study.*American Journal of Psychiatry*, *160*(8), 1453-1460.

Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell, 112*, 2, 257-269.

Ehlers, A., Mayou, R.A., & Bryant, B. (2003). Cognitive predictors of posttraumatic stress disorder in children: results of a prospective longitudinal study. *Behaviour Research and Therapy, 41*, 1, 1-10.

Ehlers, A., Clark, D.M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy, 38*, 319-345.

Ehlers, A., Mayou, R. A., & Bryant, B. (1998). Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *Journal of abnormal psychology*, *107*(3), 508.

Ehlers, A., Mayou, R. A., & Bryant, B. (1998b). Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *Journal of abnormal psychology*, *107*(3), 508.

Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., & Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Human brain mapping*, *28*(5), 409-423.

El-Hage, W,. Gaillard, P., Isingrini, M., Belzung, C. (2006). Trauma-related deficits in working memory. *Cognitive Neuropsychiatry, 11*, 1, 33-46.

Elwood, L.S., Hahn, K.S., Olatunji, B.O., Williams, N.L. (2009). Cognitive vulnerabilities to the development of PTSD: A review of four vulnerabilities and the proposal of an integrative vulnerability model. *Clinical Psychology Review, 29*, 87-100.

Elzinga, B. M., Schmahl, C. G., Vermetten, E., van Dyck, R., & Bremner, J. D. (2003). Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. *Neuropsychopharmacology*, *28*(9), 1656-1665.

Engelhard, I. M., Van Den Hout, M. A., Kindt, M., Arntz, A., & Schouten, E. (2003). Peritraumatic dissociation and posttraumatic stress after pregnancy loss: A prospective study. *Behaviour Research and Therapy; Behaviour Research and Therapy*.

Engelhard, I.M., van den Hout, M.A., Smeets, M.A.M. (2011). Taxing working memory reduces vividness and emotional intensity of images about the Queen's Day tragedy. Journal of Behaviour Therapy and Experimental psychiatry, 42, 1, 32-37.

Enns, M. W., & Cox, B. J. (1997). Personality dimensions and depression: review and commentary. *Canadian Journal of Psychiatry*, *42*(3), 274-284.

Epstein, R. S., Fullerton, C. S., & Ursano, R. J. (1998). Posttraumatic stress disorder following an air disaster: a prospective study. *American Journal of Psychiatry*, *155*(7), 934-938.

Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., & Walter, H. (2010). Acute and sustained effects of cognitive emotion regulation in major depression. *The Journal of neuroscience*, *30*(47), 15726-15734.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R., & Hirsch, J. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces.*Neuron*, *44*(6), 1043-1055.

Eysenck, H. J., & Eysenck, S. B. G. (1968). Eysenck personality inventory manual. San Diego, California: Educational and Industrial Testing Service.

Eysenck, H. J., & Eysenck, S. B.G (1975). *Eysenck Personality Questionnaire (Junior & Adult)*. Hodder & Stoughton,London.

Eysenck, H.J., Eysenck, S.B.G. (1991). Manual of the Eysenck Personality Scales. Hodder & Stoughton, London.

Farmer, A., Redman, K., Harris, T., Mahmood, A., Sadler, S., Pickering, A., & McGUFFIN, P. E. T. E. R. (2002). Neuroticism, extraversion, life events and depression The Cardiff Depression Study. *The British Journal of Psychiatry*,*181*(2), 118-122.

Feeny, N.C.. Zoellner, L.A Fitzgibbons, L. A.. Foa E.B (2000). Exploring the roles of emotional numbing, depression, and dissociation in PTSD. *Journal of Traumatic Stress, 13, 3,* 489–498.

Feldner , M. T., Zvolensky, M.J., Schmidt, N. B., Smith, R. C. (2008). A prospective test of anxiety sensitivity as a moderator of the relation between gender and posttraumatic symptom maintenance among high anxiety sensitive young adults. *Depression and Anxiety, 25, 3,* 190–199.

Feldner, M.T., Lewis, S. F., Leen-Feldner, E.W., Schnurr, P.P., Zvolensky, M. J (2006). Anxiety sensitivity as a moderator of the relation between trauma exposure frequency and posttraumatic stress symptomatology. *Journal of Cognitive Psychotherapy, 20, 2*, 201-213.

Felmingham, K. L., & Bryant, R. A. (2012). Gender differences in the maintenance of response to cognitive behavior therapy for posttraumatic stress disorder. *Journal of consulting and clinical psychology*, *80*(2), 196.

Felmingham, K. L., Dobson-Stone, C., Schofield, P. R., Quirk, G. J., & Bryant, R. A. (2013). The Brain-Derived Neurotrophic Factor Val66Met Polymorphism Predicts Response to Exposure Therapy in Posttraumatic Stress Disorder. *Biological psychiatry*.

Felmingham, K. L., Williams, L. M., Kemp, A. H., Rennie, C., Gordon, E., & Bryant, R. A. (2009). Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in Posttraumatic Stress Disorder. *Psychiatry Research: Neuroimaging*, *173*(1), 59-62.

Felmingham, K., Kemp, A., Williams, L., Das, P., Hughes, G., Peduto, A., & Bryant, R. (2007). Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. *Psychological Science*,*18*(2), 127-129.

Fendt, M., & Koch, M. (2013). Translational value of startle modulations. *Cell and tissue research*, 1-9.

Fendt, M., Buchi, M., Bürki, H., Imobersteg, S., Ricoux, B., Suply, T., & Sailer, A. W. (2011). Neuropeptide S receptor deficiency modulates spontaneous locomotor activity and the acoustic startle response. *Behavioural brain research*, *217*(1), 1-9.

Fendt, M., Imobersteg, S., Bürki, H., McAllister, K. H., & Sailer, A. W. (2010). Intra-amygdala injections of neuropeptide S block fear-potentiated startle.*Neuroscience letters*, *474*(3), 154-157.

Ferguson, C.J. (2007). The good the bad and the ugly: A meta-analytic review of positive and negative effects of violent video games. Psychiatric Quarterly, 78, 4, 309-316.

Fink, G. (2011). Stress controversies: Post-traumatic stress disorder, hippocampal volume, gestrodenal ulceration*. Journal of Neuroendocrinology, 23*, 107-117.

Fitzpatrick, D.F. (1997). The effects of startle on interval timing and reaction time tasks. *Dissertation Abstracts International: Section B: The sciences and Engineering,* 57, 4769.

Foa, E. B. (2011). Prolonged exposure therapy: past, present, and future.*Depression and anxiety*, *28*(12), 1043-1047.

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological bulletin*, *99*(1), 20.

Foa, E. B., & Riggs, D.S. (1993). Post-traumatic stress disorder in rape victims. In J. Oldman, M.B. Riba, & A. Tasman (Eds.), *American Press Review of Psychiatry, vol. 12* (pp.273-303). Washington DC: American Psychiatric Press.

Foa, E. B., & Rothbaum, B.O. (1998). *Treating the trauma of rape: cognitive behavioural therapy for PTSD.* New York: Guildford Press.

Foa, E. B., Riggs, D. S., Massie, E. D., & Yarczower, M. (1995). The impact of fear activation and anger on the efficacy of exposure treatment for posttraumatic stress disorder. *Behavior Therapy*, *26*(3), 487-499.

Foa, E. B., Steketee, G., & Rothbaum, B. O. (1989). Behavioral/cognitive conceptualizations of post-traumatic stress disorder. *Behavior therapy*, *20*(2), 155-176.

Foa, E.B., Molnar, C., & Cashman, L. (1995). Change in rape narratives during exposure therapy for posttraumatic stress disorder. Journal of Traumatic Stress, 8, 675-690.

Foa, E.B., Steketee, G., Rothbaum, B.O. (1989).Behavioral/cognitive conceptualizations of post-traumatic stress disorder. *Behavior Therapy, 20, 2*, 155-176.

Folkins, C. H., Lawson, K. D., & OPTON Jr, E. M. (1968). Desensitization and the experimental reduction of threat. *Journal of Abnormal Psychology*, *73*(2), 100.

Folstein, S., Rutter, M. (1977). Infantile Autism: A genetic study of 21 twin pairs. *The Journal of child psychology and psychiatry, 18*, 4, 297-321.

Frielingsdorf, H., Bath, K.G., Soliman, F., DiFede, J., Casey., B.J., & Lee, F.S. (2010). Variant brain-derived neurotropic factor Val66Met endophenotypes: implications for posttraumatic stress disorder. *Annuals of the new York academy of sciences, 1208*, 150-157.

Frodl, T., Schüle, C., Schmitt, G., Born, C., Baghai, T., Zill, P., ... & Meisenzahl, E. M. (2007). Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Archives of General Psychiatry*, *64*(4), 410-416.

Fydrich, T., Dowdall, D., & Chambless, D. L. (1992). Reliability and validity of the Beck Anxiety Inventory. *Journal of Anxiety Disorders*, *6*(1), 55-61.

Gadow, K.D., DeVincent, C.J., Pomeroy, J., & Azizian, A. (2004). Psychiatric symptoms in preschool children with PDD and clinic and comparison samples. *Journal of Autism and Developmental Disorders, 34* (4), 379-393.

Gadow, Roohi, DeVincent, Kirsch, Hatchwell, (2009). Association of COMPT (Val158Met) and BDNF (Val66Met) gene polymorphisms with anxiety, ADHD and tics in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 39, 1542-1551*.

Gadow, Roohi, DeVincent, Kirsch, Hatchwell, (2009). Association of COMPT (Val158Met) and BDNF (Val66Met) gene polymorphisms with anxiety, ADHD and tics in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 39, 1542-1551*.

Galea, S., Tracy, M., Norris, F., & Coffey, S. F. (2008). Financial and social circumstances and the incidence and course of PTSD in Mississippi during the first two years after Hurricane Katrina. *Journal of Traumatic Stress*, *21*(4), 357-368.

Galletly, C., Clark, C.R., McFarlane, A.C., Weber, D.L. (2001). Working memory in posttraumatic stress disorder - An event-related potential study. Journal of Traumatic Stress, 14, 2, 295-309.

Gamito, P., Oliveira, J., Rosa, P., Morais, D., Duarte, N., Oliveira, S., & Saraiva, T. (2010). PTSD elderly war veterans: A clinical controlled pilot study. Cyberpsychology & Behaviour, 13, 1, 43-48.

Ganong, W.F (2005). Review of Medical Physiology (22nd Ed). The McGraw-Hill Medical: ^ eNew York: NY.

Garnefski, N., Kraaij, V., & Spinhoven, P. (2001). Negative life events, cognitive emotion regulation and emotional problems. *Personality and Individual differences*, *30*(8), 1311-1327.

Gatt, J. M., Nemeroff, C. B., Dobson-Stone, C., Paul, R. H., Bryant, R. A., Schofield, P. R., ... & Williams, L. M. (2009). Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular psychiatry*, *14*(7), 681-695.

Gavranidou, M., & Rosner, R. (2003). The weaker sex? Gender and post-traumatic stress disorder. *Depression and Anxiety*, *17*(3), 130-139.

Gaylord, K., Hoffman, H.G., Maiers, A., Maani, C., Miyahira, S.D, Garcia-Palacios, A., Rothbaum, B., Difede, J. (2009). VR exposure therapy and þD-cycloserine (DCS) for treating PTSD in patients with combat-related burn injuries. Frontiers in Neuroengineering. Conference Abstract: Annual CyberTherapy & CyberPsychology conference. DOI:10.3389=conf.neuro.14.2009.06.034.

Gelernter, J., Southwick, S., Goodson, S., Morgan, A., Nagy, L., & Charney, D. S. (1999). No association between D2 dopamine receptor (DRD2) "A" system alleles, or DRD2 haplotypes, and posttraumatic stress disorder. *Biological Psychiatry*, *45*(5), 620-625.

Gerardi, M., Cukor, J., Difede, J., Rizzo, A., & Rothbaum, B. O. (2010). Virtual reality exposure therapy for post-traumatic stress disorder and other anxiety disorders. *Current psychiatry reports*, *12*(4), 298-305.

Gerst, M. S., Grant, I., Yager, J., & Sweetwood, H. (1978). The reliability of the Social Readjustment Rating Scale: Moderate and long-term stability. *Journal of psychosomatic research*, *22*(6), 519-523.

Gil, S. (2005). Pre-traumatic personality as a predictor of post-traumatic stress disorder among undergraduate students exposed to a terrorist attack: A prospective study in Israel. *Personality and individual differences*, *39*(4), 819-827.

Ginzburg, K., Koopman, C., Butler, L. D., Palesh, O., Kraemer, H. C., Classen, C. C., & Spiegel, D. (2006). Evidence for a dissociative subtype of post-traumatic stress disorder among help-seeking childhood sexual abuse survivors. *Journal of trauma & dissociation*, *7*(2), 7-27.

Glover, E. M., Phifer, J. E., Crain, D. F., Norrholm, S. D., Davis, M., Bradley, B., ... & Jovanovic, T. (2011). Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. *Depression and anxiety*, *28*(12), 1058-1066.

Gold, P.W., Goodwin, F.K., Chrousos, G.P. (1988): Clinical and biochemical manifestations of depression. *N Engl J Med,* 319, 413-420.

Gonçalves, R., Pedrozo, A. L., Coutinho, E. S. F., Figueira, I., & Ventura, P. (2012). Efficacy of Virtual Reality Exposure Therapy in the Treatment of PTSD: A Systematic Review. *PloS one*, *7*(12), e48469.

Gootjes, L., Fanken, I.H.A., Van Strien, J.W. (2011). Cognitive emotion regulation in yogic meditative practitioners: Sustained modulation of electrical brain potentials. Journal of Psychophysiology, 25, 2, 87-94.

Grabe, H. J., Schwahn, C., Mahler, J., Appel, K., Schulz, A., Spitzer, C., Fenske, K., Barnow, S., Freyberger, H.J., Teumer, A., Petersmann, A., Biffar, R., Rosskopf, D., John, U., & Völzke, H. (2012). Genetic epistasis between the brain-derived neurotrophic factor Val66Met polymorphism and the 5-HTT promoter polymorphism moderates the susceptibility to depressive disorders after childhood abuse.*Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 36 (2), 264-270.

Grabe, H., Spitzer, C., Schwahn, C., Marcinek, A., Frahnow, A., Barnow, S., Lucht, M., Freyberger, H.J., John, U., Wallaschofski, H., Volzke, H., & Rosskopf, D. (2009). Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population. *American Journal of Psychiatry*, *166*(8), 926-933.

Graham, F. K. (1979). Distinguishing among orienting, defense, and startle reflexes. *The orienting reflex in humans*, 137-167.

Grasso, D. J., & Simons, R. F. (2012). Electrophysiological responses to threat in youth with and without Posttraumatic Stress Disorder. *Biological psychology*, *90*(1), 88-96.

Gratacos M, Gonzalez JR, Mercader JM, Cid RD, Urretavizcaya M, Estivill X. (2007).Brain-Derived Neurotrophic Factor Val66Met and Psychiatric Disorders: Meta-Analysis of Case-Control Studies Confirm Association to Substance-Related Disorders, Eating Disorders, and Schizophrenia. *Biological Psychiatry, 61,*911–922

Gregurek, R., Vukušić, H., Baretić, V., Potrebica, S., Krbot, V., Džidić, I., ... & Sliepčević, B. (1996). Anxiety and post-traumatic stress disorder in disabled war veterans. *Croatian Med J ,37 (1), 38-41*.

Griffin, M. G. (2008). A prospective assessment of auditory startle alterations in rape and physical assault survivors. *Journal of traumatic stress*, *21*(1), 91-99.

Griffin, M. G., Resick, P. A., & Mechanic, M. B. (1997). Objective assessment of peritraumatic dissociation: psychophysiological indicators. *The American journal of psychiatry*, *154*(8), 1081.

Grillon, C., & Baas, J. (2003). A review of the modulation of the startle reflex by affective states and its application in psychiatry. *Clinical Neurophysiology*, *114*(9), 1557-1579.

Grillon, C., & Morgan, C. A. (1999). Fear-potentiated startle conditioning to explicit and contextual cues in Gulf War veterans with posttraumatic stress disorder. *Journal of abnormal psychology*, *108*(1), 134-142.

Grillon, C., Ameli, R., Foot, M., & Davis, M. (1993). Fear-potentiated startle: relationship to the level of state/trait anxiety in healthy subjects. *Biological Psychiatry*, *33*(8), 566-574.

Grillon, C., Morgan, C. A., Davis, M., & Southwick, S. M. (1998a). Effect of darkness on acoustic startle in Vietnam veterans with PTSD. *American Journal of Psychiatry*, *155*(6), 812-817.

Grillon, C., Morgan III, C. A., Davis, M., & Southwick, S. M. (1998b). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry*, *44*(10), 1027-1036.

Grillon, C., Morgan, C. A., Southwick, S. M., Davis, M., & Charney, D. S. (1996). Baseline startle amplitude and prepulse inhibition in Vietnam veterans with posttraumatic stress disorder. *Psychiatry Research*, *64*(3), 169-178.

Grillon, C., Morgan, C.A., Davis, M., Southwick, S.M. (1998b). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychology, 44*, 1027-1036.

Grös, D. F., Antony, M. M., Simms, L. J., & McCabe, R. E. (2007). Psychometric properties of the State-Trait Inventory for Cognitive and Somatic Anxiety (STICSA): comparison to the State-Trait Anxiety Inventory (STAI). *Psychological assessment*, *19*(4), 369.

Gross, J. J. (2001). Emotion regulation in adulthood: Timing is everything.*Current directions in psychological science*, *10*(6), 214-219.

Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*, *39*(3), 281-291.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being.*Journal of personality and social psychology*, *85*(2), 348.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being.*Journal of personality and social psychology*, *85*(2), 348-362.

Gross, J. J., & Levenson, R. W. (1993). Emotional suppression: physiology, self-report, and expressive behavior. *Journal of personality and social psychology*, *64*(6), 970.

Gross, J.J (1998a). Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology. Journal of Personality and Social Psychology, 74, 224-237.

Gross, J.J., & Levenson, R.W. (1997). Hiding feelings: The acute effects of inhibiting positive and negative emotions. Journal of Abnormal Psychology, 106, 95-103.

Grossman, R., Yehuda, R., New, A., Schmeidler, J., Silverman, J., Mitropoulou, V., ... & Siever, L. (2003). Dexamethasone suppression test findings in subjects with personality disorders: associations with posttraumatic stress disorder and major depression. *American Journal of Psychiatry*, *160*(7), 1291-1298.

Guthrie, R. M., & Bryant, R. A. (2005). Auditory startle response in firefighters before and after trauma exposure. *American Journal of Psychiatry*, *162*(2), 283-290.

Gutierrez, L. M. (1994). Beyond coping: An empowerment perspective on stressful life events. *J. Soc. & Soc. Welfare*, *21*, 201.

Hagemann, T., Levenson, R. W., & Gross, J. J. (2006). Expressive suppression during an acoustic startle. *Psychophysiology*, *43*(1), 104-112.

Halligan, S. L., Clark, D. M., & Ehlers, A. (2002). Cognitive processing, memory, and the development of PTSD symptoms: two experimental analogue studies. *Journal of Behavior Therapy and Experimental Psychiatry*, *33*(2), 73-89.

Halligan, S.L., Michael, T., Clark, D.M., Ehlers, A. (2003). Posttraumatic stress disorder following assault: the role of cognitive processing, trauma memory, and appraisals. *Journal of Consulting and Clinical Psychology, 71,* 3, 419-431.

Hardy, G. H. (1908). Mendelian proportions in a mixed population. *Science*,*28*(706), 49-50.

Hare, R. D. (1973). Orienting and defensive responses to visual stimuli. *Psychophysiology*, *10*(5), 453-464.

Hariri, A. R., Goldberg, T. E., Mattay, V. S., Kolachana, B. S., Callicott, J. H., Egan, M. F., & Weinberger, D. R. (2003). Brain-derived neurotrophic factor val66met polymorphism

affects human memory-related hippocampal activity and predicts memory performance. *The Journal of neuroscience*, *23*(17), 6690-6694.

Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science, 297*, 400–403.

Harvey, A.G. & Bryant, R.J. (1999). A qualitative investigation of the organization of traumatic memories. British Journal of Clinical Psychology, 38, 401-405.

Hashimoto, K. (2007). BDNF variant linked to anxiety-related behaviors. Bioessays, 29, 116-119.

Hassija, C. M., & Gray, M. J. (2010). Are cognitive techniques and interventions necessary? A case for the utility of cognitive approaches in the treatment of PTSD. *Clinical Psychology: Science and Practice*, *17*(2), 112-127.

Hawk, L. W., & Cook, E. W. (1997). Affective modulation of tactile startle.*Psychophysiology*, *34*(1), 23-31.

Hawk, L. W., Dougall, A. L., Ursano, R. J., & Baum, A. (2000). Urinary catecholamines and cortisol in recent-onset posttraumatic stress disorder after motor vehicle accidents. *Psychosomatic Medicine*, *62*(3), 423-434.

Heils, A., Teufel, A., Petri, S., Seemann, M., Bengel, D., Balling, U., Riederer, P., & Lesch, K. P. (1995). Functional promoter and polyadenylation site mapping of the human serotonin (5-HT) transporter gene. *Journal of neural transmission*,*102*(3), 247-254.

Heim, C., Ehlert, U., Hellammer, D.H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders*. Psychoneuroendocrinology, 25*, 1-35.

Heim, C., Newport, D. J., Wagner, D., Wilcox, M. M., Miller, A. H., & Nemeroff, C. B. (2002). The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. *Depression and anxiety*, *15*(3), 117-125.

Heldt, S.A., Stanek, L., Chhatwal, J.P., Ressler, K.J. (2007). Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Molecular Psychiatry, 12, 656-670.

Heller, W. (1993). Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology*, *7*(4), 476.

Hellhammer, D. H., & Wade, S. (1993). Endocrine correlates of stress vulnerability. *Psychotherapy and Psychosomatics*, *60*(1), 8-17.

Helzer, J. E., Robins, L. N., & McEvoy, L. (1987). Post-traumatic stress disorder in the general population. *New England Journal of Medicine*, *317*(26), 1630-1634.

Hensley, L., & Varela, R. E. (2008). PTSD symptoms and somatic complaints following Hurricane Katrina: The roles of trait anxiety and anxiety sensitivity.*Journal of Clinical Child & Adolescent Psychology*, *37*(3), 542-552.

Herbert, C., Kissler, J., Junghöfer, M., Peyk, P., & Rockstroh, B. (2006). Processing of emotional adjectives: Evidence from startle EMG and ERPs.*Psychophysiology*, *43*(2), 197-206.

Hirano, C., Russel, A.T., Ornitz, E.M., Liu, M. (1996). Habituation of the P300 and reflex motor (startle blink) responses to repetitive startling stimuli in children. *International Journal of Psychophysiology, 22*, 97-109.

Hodes, R. L., Cook, E. W., & Lang, P. J. (1985). Individual differences in autonomic response: Conditioned association or conditioned fear?.*Psychophysiology*, *22*(5), 545-560.

Hoffman, H., Miyahira, S., Hollander, A., & Rose, H. (2008). Iraq World Software. University of Washington.

Holeva, V., & Tarrier, N. (2001). Personality and peritraumatic dissociation in the prediction of PTSD in victims of road traffic accidents. *Journal of Psychosomatic Research*, *51*(5), 687-692.

Holmes, E. A., James, E. L., Coode-Bate, T., & Deeprose, C. (2009). Can playing the computer game "Tetris" reduce the build-up of flashbacks for trauma? A proposal from cognitive science. *PLoS One*, *4*(1), e4153.

Holmes, E.A., & Bourne, C. (2008). Inducing and modulating intrusive emotional memories: A review of the trauma film paradigm. Acta Psychologica, 127, 3, 553-566.

Holmes, E.A., Brewin, C.R., Hennesy, R.G. (2004). Trauma films, information processing , and intrusive. *Journal of Experimental Psychology: General, 133*, 1, 3-22.

Holmes, T. H., & Rahe, R. H. (1967). The social readjustment rating scale. *Journal of psychosomatic research*, 11, 213-218.

Horowitz , M.J. (1986). *Stress response syndromes* (2nd ed.). Northvale, NJ: Jason Aronson.

Horowitz, M.J. (1976). *Stress response syndromes*. New York: Aronson.

Hu, X., Oroszi, G., Chun, J., Smith, T. L., Goldman, D., & Schuckit, M. A. (2005). An expanded evaluation of the relationship of four alleles to the level of response to alcohol and the alcoholism risk. *Alcoholism: Clinical and Experimental Research*, *29*(1), 8-16.

Inslicht, S. S., Otte, C., McCaslin, S. E., Apfel, B. A., Henn-Haase, C., Metzler, T., ... & Marmar, C. R. (2011). Cortisol awakening response prospectively predicts peritraumatic and acute stress reactions in police officers. *Biological psychiatry*, *70*(11), 1055-1062.

Jackson, D.C., Malmstadt, J.R., Larson, C.L., & Davidson, R.J. (2000). Suppression and enhancement of emotional responses to unpleasant pictures. Psychophysiology, 37, 515-522.

Janoff-Bulman, R. (1992). *Shattered assumptions: towards a new psychology of trauma*. New York: free Press.

Jansen, D. M., & Frijda, N. H. (1994). Modulation of the acoustic startle response by film-induced fear and sexual arousal. *Psychophysiology*, *31*(6), 565-571.

Jaycox, L. H., & Foa, E. B. (1996). Obstacles in implementing exposure therapy for PTSD: Case discussions and practical solutions. *Clinical Psychology & Psychotherapy*, *3*(3), 176-184.

Jennings, J. R., Bberg, W. K., Hutcheson, J., Obrist, P., Porges, S., & Turpin, G. (1981). Publication guidelines for heart rate studies in man.*Psychophysiology*, *18*(3), 226-231.

Jiang, X., Xu, K., Hoberman, J., Tian, F., Marko, A.J., Waheed, F., Harris, C.R., Marini, A.M., Enoch, M., Lipsky, R.H. (2005). BDNF variation and mood disorders: A novel functional promoter polymorphism and Val66met are associated with anxiety but have opposing effects. *Neuropsychopharmacology, 30,* 1353-1362.

John, O. P., & Gross, J. J. (2004). Healthy and unhealthy emotion regulation: Personality processes, individual differences, and life span development.*Journal of personality*, *72*(6), 1301-1334.

Jones, J. C., Barlow D.H. (1990). The etiology of posttraumatic stress disorder. *Clinical Psychology Review, 10, 3,* 299-328

Joseph, S., Mynard, H., Mayall, M. (2000) Life-event and post-traumatic stress in a sample of English adolescents. *Journal of Community and Applied Social Psychology*, *10*, 475 - 482.

Jovanovic, T., Blanding, N. Q., Norrholm, S. D., Duncan, E., Bradley, B., & Ressler, K. J. (2009). Childhood abuse is associated with increased startle reactivity in adulthood. *Depression and anxiety*, *26*(11), 1018-1026.

Junghöfer, M., Sabatinelli, D., Bradley, M. M., Schupp, H. T., Elbert, T. R., & Lang, P. J. (2006). Fleeting images: rapid affect discrimination in the visual cortex. *Neuroreport*, *17*(2), 225-229.

Jüngling, K., Seidenbecher, T., Sosulina, L., Lesting, J., Sangha, S., Clark, S. D., ... & Pape, H. C. (2008). Neuropeptide S-mediated control of fear expression and extinction: role of intercalated GABAergic neurons in the amygdala. *Neuron*, *59*(2), 298-310.

Jüngling, K., Seidenbecher, T., Sosulina, L., Lesting, J., Sangha, S., Clark, S. D., ... & Pape, H. C. (2008). Neuropeptide S-mediated control of fear expression and extinction: role of intercalated GABAergic neurons in the amygdala. *Neuron*, *59*(2), 298-310.

Kalia, M. (2005). Neurobiological basis of depression: an update. Metabolism, 54, 24-27.

Kalueff, A. V., Olivier, J. D. A., Nonkes, L. J. P., & Homberg, J. R. (2010). Conserved role for the serotonin transporter gene in rat and mouse neurobehavioral endophenotypes. *Neuroscience & Biobehavioral Reviews*,*34*(3), 373-386.

Kana,R.K., Keller, T.A., Minshew, N.J., Just, M.A. (2007). Inhibitory control in high-functioning autism: decreased activation and underconnectivity in inhibition networks. *Biological Psychiatry, 62,* 198-206.

Karakaya, I., Agaoglu, B., Coskun, A., Sismanlar, S. G., & Yildiz Oc, O. (2004). The symptoms of PTSD, depression and anxiety in adolescent students three and a half years after the Marmara earthquake. *Turk Psikiyatri Derg*,*15*(4), 257-263.

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry*, *68*(5), 444.

Karl, A., Malta, L. S., Alexander, J., & Blanchard, E. B. (2004). Startle responses in motor vehicle accident survivors: A pilot study. *Applied psychophysiology and biofeedback*, *29*(3), 223-231.

Karl, A., Malta, L.S., Maercker, A. (2006). Meta-analytic review of event-related potential studies in post-traumatic stress disorder. *Biological Psychology*, *71*(2), 123-147

Karl, A., Rabe, S., Pohnitzsch, K., Zollner, T., Maercker, A., Lesch, K.P., & Strobel, A. (2007). Biopsychological Risk Factors and Correlates of PTSD and its Successful CBT Treatment [Abstract]. *Psychophysiology, 44*, S9.

Karl, A., Schaefer, M., Malta, L.S., Dörfel, D., Rohleder, N., Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience Biobehavioral Review*, *30*(7), 1004-1031.

Kaufman, J., Yang, B-Z., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., Krystal, J.H., & Gelernter, J. (2006). Brain-Derived Neurotrophic Factor–5-HTTLPR Gene Interactions and Environmental Modifiers of Depression in Children. Biological Psychiatry, 59, 673-680.

Kaysen, D., Morris, M. K., Rizvi, S. L., & Resick, P. A. (2005). Peritraumatic responses and their relationship to perceptions of threat in female crime victims. *Violence against women*, *11*(12), 1515-1535.

Keane, T. M. & Kaloupek, D. G. (1996). Cognitive behavior therapy in the treatment of posttraumatic stress disorder. *The Clinical Psychologist, 49*(1), 7-8.

Keane, T. M., & Wolfe, J. (1990). Comorbidity In Post-Traumatic Stress Disorder An Analysis of Community and Clinical Studies1. *Journal of Applied Social Psychology*, *20*(21), 1776-1788.

Keane, T. M., Kolb, L. C., Kaloupek, D. G., Orr, S. P., Blanchard, E. B., Thomas, R. G., ... & Lavori, P. W. (1998). Utility of psychophysiological measurement in the diagnosis of posttraumatic stress disorder: results from a Department of Veterans Affairs Cooperative Study. *Journal of consulting and clinical psychology*, *66*(6), 914-923.

Keil, A., Bradley, M. M., Hauk, O., Rockstroh, B., Elbert, T., & Lang, P. J. (2002). Large-scale neural correlates of affective picture processing.*Psychophysiology*, *39*(5), 641-649.

Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B. (1995). Posttraumatic Stress Disorder in the National Comorbidity Survey. *Arch Gen Psychiatry, 52, 12,* 1048-1060.

Kiesel, A., Miller, J., Jolicœur, P., & Brisson, B. (2008). Measurement of ERP latency differences: A comparison of single-participant and jackknife-based scoring methods. *Psychophysiology*, *45*(2), 250-274.

Kilpatrick, D., Koenen, K., Ruggiero, K., Acierno, R., Galea, S., Resnick, H., Roitzsch, J., Boyle, J., & Gelernter, J. (2007). The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *American Journal of Psychiatry*, *164*(11), 1693-1699.

Kim, J. M., Stewart, R., Kim, S. W., Yang, S. J., Shin, I. S., Kim, Y. H., & Yoon, J. S. (2007). Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. *Biological psychiatry*,*62*(5), 423-428.

Kim, J.A., Szatmari, P., Bryson, S.E., Streiner, D.L., & Wilson, F.J. (2000). The prevalence of anxiety and mood problems amoung children with autism and Asperger syndrome. *Autism, 4* (2), 117-132.

Kleim, B., Ehlers, A., Glucksman, E. (2007). Early predictors of chronic post-traumatic stress disorder in assault survivors. *Psychol Med, 37*, 10, 1457–1467.

Knight, R. G., Waal-Manning, H. J., & Spears, G. F. (1983). Some norms and reliability data for the State-Trait Anxiety Inventory and the Zung Self-Rating Depression scale. *British Journal of Clinical Psychology*, *22*(4), 245-249.

Koch, M. (1999). The neurobiology of startle. *Progress in neurobiology*,*59* (2), 107-128.

Koch, M., Lingenhöhl, K., & Pilz, P. K. D. (1992). Loss of the acoustic startle response following neurotoxic lesions of the caudal pontine reticular formation: possible role of giant neurons. *Neuroscience*, *49*(3), 617-625.

Koenen, K. C., Aiello, A. E., Bakshis, E., Amstadter, A. B., Ruggiero, K. J., Acierno, R., ... & Galea, S. (2009). Modification of the association between serotonin transporter genotype and

risk of posttraumatic stress disorder in adults by county-level social environment. *American journal of epidemiology*,*169*(6), 704-711.

Koenen, K. C., Nugent, N. R., & Amstadter, A. B. (2008). Gene-environment interaction in posttraumatic stress disorder. *European archives of psychiatry and clinical neuroscience*, *258*(2), 82-96.

Koopman, C., Classen, C., & Spiegel, D. A. (1994). Predictors of posttraumatic stress symptoms among survivors of the Oakland/Berkeley, Calif., firestorm.*The American journal of psychiatry*.

Korte, M., Carroll, P., Wolf, E., Brem, G., Thoenen, H., & Bonhoeffer, T. (1995). Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proceedings of the National Academy of Sciences*, *92*(19), 8856-8860.

Kozariæ-Kovaèiæ, D., Ljubin, T., & Grappe, M. (2000). Comorbidity of posttraumatic stress disorder and alcohol dependence in displaced persons.*differences*, *6*, 14.

Kraemer, B., Moergeli, H., Roth, H., Hepp, U., & Schnyder, U. (2008). Contribution of initial heart rate to the prediction of posttraumatic stress symptom level in accident victims. *Journal of psychiatric research*, *42*(2), 158-162.

Kraemer, B., Wittmann, L., Jenewein, J., Maier, T., & Schnyder, U. (2009). Is the stressor criterion dispensable?. *Psychopathology*, *42*(5), 333-336.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9. *Journal of general internal medicine*, *16*(9), 606-613.Primary Care PTSD screening

Kuhn, E., Blanchard, E. B., Fuse, T., Hickling, E. J., & Broderick, J. (2006). Heart rate of motor vehicle accident survivors in the emergency department, peritraumatic psychological reactions, ASD, and PTSD severity: A 6-month prospective study. *Journal of traumatic stress*, *19*(5), 735-740.

Kunihira, Y., Senju, A., Dairoku, H., Wakabayashi, A., Hasegawa, T. (2006). 'Autistic' Traits in Non-Autistic Japanese Populations: Relationships with Personality Traits and Cognitive Ability. *Journal of Autism and Developmental Disorders, 36, 4*, 553-566.

LaGarde, G., Doyon, J., & Brunet, A. (2010). Memory and executive dysfunctions associated with acute posttraumatic stress disorder.*Psychiatry Research*, *177*(1), 144-149.

Lang, P. J. (1977). Imagery in therapy: An information processing analysis of fear. *Behavior Therapy*, *8*(5), 862-886.

Lang, P. J. (1979). A bio-informational theory of emotional imagery. *Psychophysiology, 16*, 495-512.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological review*, *97*(3), 377-395.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). Motivated attention: Affect, activation, and action. *Attention and orienting: Sensory and motivational processes*, 97-135.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1998). Emotion, motivation, and anxiety: Brain mechanisms and psychophysiology. *Biological psychiatry*,*44*(12), 1248-1263.

Lang, P.J. (1980). Behavioural treatment and bio-behavioural assessment: computer applications. In J.B. Sidowski, J.H. Johnson, & T.A. Williams (Eds.). Technology in mental health care delivery systems (pp 119-137). Norwood, NJ: Ablex.

Lang, U. E., Hellweg, R., Kalus, P., Bajbouj, M., Lenzen, K. P., Sander, T., ... & Gallinat, J. (2005). Association of a functional BDNF polymorphism and anxiety-related personality traits. *Psychopharmacology*, *180*(1), 95-99.

Lanius, R. A., Bluhm, R., Lanius, U., & Pain, C. (2006). A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *Journal of psychiatric research*, *40*(8), 709-729.

Lanius, R. A., Vermetten, E., Loewenstein, R. J., Brand, B., Schmahl, C., Bremner, J. D., & Spiegel, D. (2010). Emotion modulation in PTSD: clinical and neurobiological evidence for a dissociative subtype. *The American journal of psychiatry*, *167*(6), 640.

Laposa, J. M., & Alden, L. E. (2003). Posttraumatic stress disorder in the emergency room: exploration of a cognitive model. *Behaviour Research and Therapy*, *41*(1), 49-65.

Laposa, J. M., & Rector, N. A. (2012). The prediction of intrusions following an analogue traumatic event: Peritraumatic cognitive processes and anxiety-focused rumination versus rumination in response to intrusions.*Journal of behavior therapy and experimental psychiatry*, *43*(3), 877-883.

Laposa, J.M., Alden, L.E. (2008). The effect of pre-existing vulnerability factors on a laboratory analogue trauma experience. *Journal of Behaviour Therapy and Experimental Psychiatry, 39*, 4, 424-435.

Landis, C., & Hunt, W. (1939). The startle pattern. New York, NY: Farrar and Rinehart.

Larson, C. L., Ruffalo, D., Nietert, J. Y., & Davidson, R. J. (2000). Temporal stability of the emotion-modulated startle response. *Psychophysiology*,*37*(1), 92-101.

Lau, J. Y., Goldman, D., Buzas, B., Fromm, S. J., Guyer, A. E., Hodgkinson, C., Monk, C.S., Nelson, E.E., Shen, P.H., Pine, D.S., & Ernst, M. (2009). Amygdala function and 5-HTT gene variants in adolescent anxiety and major depressive disorder. *Biological psychiatry*, *65*(4), 349.

Lawford, B. R., Young, M., Noble, E. P., Kann, B., Arnold, L., Rowell, J., & Ritchie, T. L. (2003). D2 dopamine receptor gene polymorphism: paroxetine and social functioning in posttraumatic stress disorder. *European neuropsychopharmacology*, *13*(5), 313-320.

Lawford, B. R., Young, R., Noble, E. P., Kann, B., & Ritchie, T. (2006). The D< sub> 2</sub> dopamine receptor (DRD2) gene is associated with co-morbid depression, anxiety and social dysfunction in untreated veterans with post-traumatic stress disorder. *European psychiatry*, *21*(3), 180-185.

Lawrence, J.W., Fauerbach, J.A. (2003). Personality, Coping, Chronic Stress, Social Support and PTSD Symptoms Among Adult Burn Survivors: A Path Analysis. *Journal of Burn Care & Rehabilitation, 24, 1,* 63-72.

Lazarus, R. S., Opton, E. M., Nomikos, M. S., & Rankin, N. O. (2006). The principle of short-circuiting of threat: further evidence1. *Journal of Personality*,*33*(4), 622-635.

Lee, H., Lee, M.S., Kang, R., Kim, H., Kim, S., Kee, B., Kim, Y., Kim, Y., Kim, J., Yeon, B., Oh, K., Oh, B., Yoon, J., Lee, C., Jung, H.J., Chee, I., Paik, I.H. (2005). Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. *Depression and Anxiety, 21, 3,* 135–139.

Leen-Feldner, E. W., Feldner, M. T., Reardon, L. E., Babson, K. A., & Dixon, L. (2008). Anxiety sensitivity and posttraumatic stress among traumatic event-exposed youth. *Behaviour research and therapy*, *46*(4), 548-556.

Lennertz, L., Quednow, B. B., Schuhmacher, A., Petrovsky, N., Frommann, I., Schulze-Rauschenbach, S., ... & Mössner, R. (2012). The functional coding variant Asn107Ile of the neuropeptide S receptor gene (NPSR1) is associated with schizophrenia and modulates verbal memory and the acoustic startle response. *The International Journal of Neuropsychopharmacology*, *15*(09), 1205-1215.

Leonard, S. K., Dwyer, J. M., Sukoff Rizzo, S. J., Platt, B., Logue, S. F., Neal, S. J., ... & Ring, R. H. (2008). Pharmacology of neuropeptide S in mice: therapeutic relevance to anxiety disorders. *Psychopharmacology*, *197*(4), 601-611.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H.,& Murphy, D. L. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*,*274*(5292), 1527-1531.

Leskin, G. A., Kaloupek, D. G., & Keane, T. M. (1998). Treatment for traumatic memories: Review and recommendations. *Clinical Psychology Review*, *18*(8), 983-1001.

Levenson, R. W., Ekman, P., & Ricard, M. (2012). Meditation and the startle response: A case study. *Emotion*, *12*(3), 650.

Levy, M. N. (1990). Autonomic Interactions in Cardiac Controla. *Annals of the New York Academy of Sciences*, *601*(1), 209-221.

Lewine, J. D., Thoma, R. J., Provencal, S. L., Edgar, C., Miller, G. A., & Canive, J. M. (2002). Abnormal stimulus-response intensity functions in posttraumatic stress disorder: an electrophysiological investigation.*American Journal of Psychiatry*, *159*(10), 1689-1695.

Liberzon, I., Abelson, J. L., Flagel, S. B., Raz, J., & Young, E. A. (1999). Neuroendocrine and Psychophysiologic Responses in PTSD:: A Symptom Provocation Study. *Neuropsychopharmacology*, *21*(1), 40-50.

Lidberg, L., & Wallin, B. G. (1981). Sympathetic skin nerve discharges in relation to amplitude of skin resistance responses. *Psychophysiology*,*18*(3), 268-270.

Linley, P. A., & Joseph, S. (2004). Positive change following trauma and adversity: A review. *Journal of traumatic stress*, *17*(1), 11-21.

Litz, B. T., Orsillo, S. M., Kaloupek, D., & Weathers, F. (2000). Emotional processing in posttraumatic stress disorder. *Journal of Abnormal Psychology*,*109*(1), 26-39.

Longmore, R. J., & Worrell, M. (2007). Do we need to challenge thoughts in cognitive behavior therapy?. *Clinical psychology review*, *27*(2), 173-187.

Lovallo, W. R., Farag, N. H., Sorocco, K. H., Cohoon, A. J., & Vincent, A. S. (2012). Lifetime adversity leads to blunted stress axis reactivity: Studies from the Oklahoma Family Health Patterns Project. *Biological psychiatry, 71,* 344-349.

Lovell, K., Marks, I. M., Noshirvani, H., Thrasher, S., & Livanou, M. (2001). Do cognitive and exposure treatments improve various PTSD symptoms differently? A randomized controlled trial. *Behavioural and Cognitive Psychotherapy*, *29*(1), 107-112.

Luck, S. J. (2005). An Introduction to the Event-Related Potential Technique. Cambridge, MA: MIT Press.

Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behavior and cognition. *Nature Reviews Neuroscience, 10,* 434–445.

Lykken, D. T., & Venables, P. H. (1971). Direct measurement of skin conductance: A proposal for standardization. *Psychophysiology*, *8*(5), 656-672.

Marian, A. J. (2012). Elements of 'missing heritability'. *Current opinion in cardiology*, *27*(3), 197-201.

Marks, I., Lovell, K., Noshirvani, H., Livanou, M., & Thrasher, S. (1998). Treatment of posttraumatic stress disorder by exposure and/or cognitive restructuring: a controlled study. *Archives of general Psychiatry*, *55*(4), 317.

Marmar, C. R., Weiss, D. S., & Metzler, T. J. (1997). The peritraumatic dissociative experiences questionnaire. *Assessing psychological trauma and PTSD*, 412-428.

Marmar, C. R., Weiss, D. S., Metzler, T. J., & Delucchi, K. (1996). Characteristics of emergency services personnel related to peritraumatic dissociation during critical incident exposure. *The American journal of psychiatry*. 153, 94-102.

Marmar, C. R., Weiss, D. S., Metzler, T. J., Delucchi, K. L., Best, S. R., & Wentworth, K. A. (1999). Longitudinal course and predictors of continuing distress following critical incident exposure in emergency services personnel. *The journal of nervous and mental disease*, *187*(1), 15-22.

Marshall, G. N., Miles, J. N., & Stewart, S. H. (2010). Anxiety sensitivity and PTSD symptom severity are reciprocally related: Evidence from a longitudinal study of physical trauma survivors. *Journal of abnormal psychology*, *119*(1), 143-150.

Martin, G. F., Holstege, G., & Mehler, W. R. (1990). Reticular formation of the pons and medulla. *The human nervous system. Academic Press, New York*, 203-220.

Martínez-Sánchez, F., Ortiz-Soria, B., & Ato-García, M. (2001). Subjective and autonomic stress responses in alexithymia. *Psicothema*, *13*(1), 57-62.

Marx, B. P., & Sloan, D. M. (2005). Peritraumatic dissociation and experiential avoidance as predictors of posttraumatic stress symptomatology. *Behaviour Research and Therapy*, *43*(5), 569-583.

Mason, J. W., Wang, S., Yehuda, R., Lubin, H., Johnson, D., Bremner, J. D., ... & Southwick, S. (2002). Marked lability in urinary cortisol levels in subgroups of combat veterans with posttraumatic stress disorder during an intensive exposure treatment program. *Psychosomatic medicine*, *64*(2), 238-246.

Mason, J.W., Giller, E.L., Kosten, T.R., Ostroff, R.B., Podd, L. (1986) Urinary free-cortisol levels in posttraumatic stress disorder patients. *J Nerv Ment Dis, 174*, 145–149.

Mason, J.W., Wang, S., Yehuda, R., Lubin, H., Johnson, D., Bremner, J.D., Charney, D., Southwick, S. (2002) Marked lability in urinary cortisol levels in subgroups of combat veterans with posttraumatic stress disorder during an intensive exposure treatment program. *Psychosom Med, 64*, 238–246.

Mayou, R.A., Ehlers, A., & Byrant, B. (2002). Posttraumatic stress disorder after motor vehicle accidents: 3-year follow-up of a prospective longitudinal study. *Behaviour Research and Therapy, 40*, 6, 665-675.

McFarlane, A. C. (1988). The aetiology of post-traumatic stress disorders following a natural disaster. *The British Journal of Psychiatry*, *152*(1), 116-121.

McFarlane, A. C. (1998). Epidemiological evidence about the relationship between PTSD and alcohol abuse: the nature of the association. *Addictive Behaviors*, *23*(6), 813-825.

McFarlane, A.C. (1989). The aetiology of post-traumatic morbidity: predisposing, precipitating and perpetuating factors British Journal of Psychiatry, 154, 221–228.

McFarlane, A.C., Yehuda, R., Clark, C.R. (2002). Biologic models of traumatic memories and post-traumatic stress disorder: The role of neural networks. *The Psychiatric Clinics of north America, 25, 2,* 253-270.

McHugh, P. R., & Treisman, G. (2007). PTSD: a problematic diagnostic category. *Journal of anxiety disorders*, *21*(2), 211-222.

McKee-Ryan, F. M., Song, Z., Wanberg, C. R., & Kinicki, A. J. (2005). Psychological and physical well-being during unemployment: A meta-analytic study. *Journal of Applied Psychology,90*(1), 53-76.

McKeever, V.M., Huff, M.E. (2003). A Diathesis-stress model of posttraumatic stress disorder: Ecological, Biological, and residual stress pathways. *Review of General Psychology, 7*, 3, 237-250.

McManus, S., Meltzer, H., Brugha, T., Bebbington, P., Jenkins, R. (2009). Adult Psychiatric Morbidity in England 2007: Results of a household survey. Leeds: The Information Centre.

McNally, (1996). Anxiety sensitivity is distinguishable from trait anxiety. In: R. M. Rapee (Ed.), *Current controversies in the anxiety disorders* (pp. 214–227). New York: The Guilford Press.

McNally, R. J. (2003). Progress and controversy in the study of posttraumatic stress disorder. *Annual review of psychology*, *54*(1), 229-252.

McNally, R. J., & Ricciardi, J. N. (1996). Suppression of negative & neutral thoughts. *Behavioural and Cognitive Psychotherapy*, *24*, 17-26.

McNally, R.J., Shin, L.M. (1995) Association of intelligence with severity of posttraumatic stress disorder symptoms in Vietnam Combat veterans. *American Journal of Psychiatry, 152*, 936-938.

McPherson, W. B., Newton, J. E., Ackerman, P., Oglesby, D. M., & Dykman, R. A. (1997). An event-related brain potential investigation of PTSD and PTSD symptoms in abused children. *Integrative Physiological and Behavioral Science*, *32*(1), 31-42.

McTeague, L. M., Lang, P. J., Laplante, M. C., Cuthbert, B. N., Shumen, J. R., & Bradley, M. M. (2010). Aversive imagery in posttraumatic stress disorder: trauma recurrence, comorbidity, and physiological reactivity. *Biological Psychiatry*, *67*(4), 346-356.

Meewisse, M.L., Reitsma, J.B., de Vries, G.J., Gersons, B.P., Olff, M. (2007) Cortisol and post-traumatic stress disorder in adults: systematic review and metaanalysis. *British Journal of Psychiatry, 191*, 387–392.

Metzger, L. J., Carson, M. A., Paulus, L. A., Lasko, N. B., Paige, S. R., Pitman, R. K., & Orr, S. P. (2002). Event-related potentials to auditory stimuli in female Vietnam nurse veterans with posttraumatic stress disorder.*Psychophysiology*, *39*(1), 49-63.

Metzger, L. J., Orr, S. P., Berry, N. J., Ahern, C. E., Lasko, N. B., & Pitman, R. K. (1999). Physiologic reactivity to startling tones in women with posttraumatic stress disorder. *Journal of Abnormal Psychology*, *108*(2), 347.

Metzger, L. J., Pitman, R. K., Miller, G. A., Paige, S. R., & Orr, S. P. (2008). Intensity dependence of auditory P2 in monozygotic twins discordant for Vietnam combat: associations with posttraumatic stress disorder. *Journal of rehabilitation research and development*, *45*(3), 437-450.

Michael, T., Ehlers, A., Halligan, S. L., & Clark, D. M. (2005). Unwanted memories of assault: what intrusion characteristics are associated with PTSD?. *Behaviour Research and Therapy*, *43*(5), 613-628.

Middeldorp, C.M., de Geus, E.J.C., Beem, A.L., Lakenberg, N., Hottenga, J-J., Slagboom P.E., & Boomsma, D.J. (2007). Family based association analysis between the serotonin transporter gene polymorphism (5-HTTLPR) and neuroticism, anxiety and depression. *Behaviour Genetics, 37, 2*, 294-301.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans.*Psychological bulletin*, *133*(1), 25.

Miller, M. W., Patrick, C. J., & Levenston, G. K. (2002). Affective imagery and the startle response: Probing mechanisms of modulation during pleasant scenes, personal experiences, and discrete negative emotions.*Psychophysiology*, *39*(4), 519-529.

Mol, S.L., Arntz, A., Metsemakers, J.F.M., Dinant, G-J., Vilters-Van Monfort, P.A.P., Knottnerus, A. (2005). Symptoms of post-traumatic stress disorder after non-traumatic events: evidence from an open population study. *The British Journal of Psychiatry, 186,* 494-499.

Montag, C., Basten, U., Stelzael, C., Fiebach, C., Reuter, M. (2010). The BDNF Val66Met polymorphism and anxiety: Support for animal knock-in studies from a genetic association study in humans. *Psychiatry Research, 179*, 1, 86-90.

Montag, C., Reuter, M., Newport, B., Elger C., & Weber, B. (2008). The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: Evidence from a genetic imaging study. *NeuroImage, 42,* 1554-1559.

Montag, C., Weber, B., Trautner, P., Newport, B., Markett, S., Walter, N. T., ... & Reuter, M. (2012). Does excessive play of violent first-person-shooter-video-games dampen brain activity in response to emotional stimuli?.*Biological psychology*, *89*(1), 107-111.

Morgan, C. A., Grillon, C., Southwick, S. M., Davis, M., & Charney, D. S. (1996). Exaggerated acoustic startle reflex in Gulf War veterans with posttraumatic stress disorder. *American Journal of Psychiatry*, *153*(1), 64-68.

Morgan, C.A., Grillon, C., Southwick, S.M., Davis, M., Charney, D.S (1995). Fear-potentiated startle in posttraumatic stress disorder. *Biological Psychology, 38,* 6, 378-385.

Morgan, I. A., Matthews, G., & Winton, M. (1995). Coping & Personality as Predictors of Post-Traumatic Intrusions, Numbing, Avoidance & General Distress: A Study of Victims of the Perth Flood. *Behavioural and Cognitive Psychotherapy*, *23*, 251-251.

Munafò, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological psychiatry*, *63*(9), 852-857.

Munafo, M. R., Clark, T., & Flint, J. (2005). Does measurement instrument moderate the association between the serotonin transporter gene and anxiety-related personality traits? A meta-analysis. *Molecular psychiatry*, *10*(4), 415-419.

Munafò, M. R., Durrant, C., Lewis, G., & Flint, J. (2009). Gene× environment interactions at the serotonin transporter locus. *Biological psychiatry*, *65*(3), 211-219.

Munafò, M. R., Freimer, N. B., Ng, W., Ophoff, R., Veijola, J., Miettunen, J., Järvelin, M.R., Taanila., A., & Flint, J. (2008). 5-HTTLPR genotype and anxiety-related personality traits: A meta-analysis and new data. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150*(2), 271-281.

Muris, P., Sterrneman, P., Merckelbach, H., Holdrinet, I., & Meesters, C. (1998). Comorbid anxiety symptoms in children with pervasive developmental disorders. *Journal of Anxiety Disorders, 12* (4), 387-393.

Murray, J., Ehlers, A., & Mayou, R. A. (2002). Dissociation and post-traumatic stress disorder: two prospective studies of road traffic accident survivors. *The British Journal of Psychiatry*, *180*(4), 363-368.

Nakahachi, T., Iwase, M., Takahasi, H., Honaga, E., Seikiyama, R., Ukai, S., Ishii, R., Ishigami, W., Kajimoto, O., Yamashita, K., Hashimoto, R., Yamashita, K., Hashimoto, R, Tanii, H., Shimizu, A., Takeda, M. (2006). Discrepancy of performance among working memory-related tasks in autism spectrum disorders was caused by task characteristics, apart from working memory, which could interfere with task execution. *Psychiatry and clinical neurosciences, 60*, 3, 312-318.

Nakamura, M., Ueno, S., Sano, A., & Tanabe, H. (2000). The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants. *Molecular psychiatry*, *5*(1), 32-38.

Nalloor, R., Bunting, K., & Vazdarjanova, A. (2011). Predicting impaired extinction of traumatic memory and elevated startle. *PloS one*, *6*(5), e19760.

Naragon-Gainey, K. (2010). Meta-analysis of the relations of anxiety sensitivity to the depressive and anxiety disorders. *Psychological bulletin*, *136*(1), 128.

Nederhof, E., Bouma, E. M. C., Riese, H., Laceulle, O. M., Ormel, J., & Oldehinkel, A. J. (2010). Evidence for plasticity genotypes in a gene–gene–environment interaction: the TRIALS study. *Genes, Brain and Behavior*, *9*(8), 968-973.

Nemeroff, C. B., Bremner, J. D., Foa, E. B., Mayberg, H. S., North, C. S., & Stein, M. B. (2006). Posttraumatic stress disorder: a state-of-the-science review. *Journal of psychiatric research*, *40*(1), 1-21.

Nestler, J. M., Ploskey, G. R., Pickens, J., Menezes, J., & Schilt, C. (1992). Responses of blueback herring to high-frequency sound and implications for reducing entrainment at hydropower dams. *North American Journal of Fisheries Management*, *12*(4), 667-683.

Nezlek, J. B. (2001). Multilevel random coefficient analyses of event-and interval-contingent data in social and personality psychology research.*Personality and social psychology bulletin*, *27*(7), 771-785.

NICE (2005). Clinical Guideline 26. Post-traumatic stress disorder (PTSD): the management of PTSD in adults and children in primary and secondary care. Retrieved from http://www.nice.org.uk/CG026NICEguideline

Nishimura, K., Nakamura, K., Anitha, A., Yamada, K., Tsujii, M., Iwayama, Y., Hattori, E., Toyota, T., Takei, N., Miyachi, T., Iwata, Y., Suzuki, K., Matsuzaki, H., Kawai, M., Sekine, Y., Tsuchiya, K., Sugihara, G., Suda, S., Ouchi, Y., Sugiyama, T., Yoshikawa, T., & Mori, N. (2007). Genetic analysis of the brain-derived neurotropic factor (BDNF) gene in autism. *Biochemical and Biophysical Research Communications, 356, 200-206*.

Nitschke, J. B., Larson, C. L., Smoller, M. J., Navin, S. D., Pederson, A. J., Ruffalo, D., ... & Davidson, R. J. (2002). Startle potentiation in aversive anticipation: evidence for state but not trait effects. *Psychophysiology*, *39*(2), 254-258.

Nitschke, W. H. J. B. (1998). The puzzle of regional brain activity in and anxiety: the importance of subtypes and comorbidity. *Cognition & Emotion*,*12*(3), 421-447.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptom. Journal of Abnormal Psychology, 109, (3), 504-511.

Nørby, S., Lange, M., & Larsen, A. (2010). Forgetting to forget: On the duration of voluntary suppression of neutral and emotional memories. *Acta psychologica*, *133*(1), 73-80.

Norris, F. H. (1992). Epidemiology of trauma: frequency and impact of different potentially traumatic events on different demographic groups. *Journal of consulting and clinical psychology*, *60*(3), 409.

North, C. S. (2001). The course of post-traumatic stress disorder after the Oklahoma City bombing. *Military Medicine*.

North, C. S., Pfefferbaum, B., Tivis, L., Kawasaki, A., Reddy, C., & Spitznagel, E. L. (2004). The course of posttraumatic stress disorder in a follow-up study of survivors of the Oklahoma City bombing. *Annals of Clinical Psychiatry*.

O'donnell, T., Hegadoren, K. M., & Coupland, N. C. (2004). Noradrenergic mechanisms in the pathophysiology of post-traumatic stress disorder.*Neuropsychobiology*, *50*(4), 273-283.

O'Carroll, R. E., Drysdale, E., Cahill, L., Shajahan, P., & Ebmeier, K. P. (1999). Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. *Psychological Medicine*, *29*(5), 1083-1088.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Journal of cognitive neuroscience*, *14*(8), 1215-1229.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down-and up-regulation of negative emotion.*Neuroimage*, *23*(2), 483-499.

O'Connor, M., & Elklit, A. (2008). Attachment styles, traumatic events, and PTSD: A cross-sectional investigation of adult attachment and trauma. *Attachment & human development*, *10*(1), 59-71.

Okamura, N., & Reinscheid, R. K. (2007). Neuropeptide S: a novel modulator of stress and arousal. *Stress: The International Journal on the Biology of Stress*,*10*(3), 221-226.

Olatunji, B. O., & Wolitzky-Taylor, K. B. (2009). Anxiety sensitivity and the anxiety disorders: a meta-analytic review and synthesis. *Psychological bulletin*,*135*(6), 974.

Olff, M., Langeland, W., & Gersons, B. P. (2005). The psychobiology of PTSD: coping with trauma. *Psychoneuroendocrinology*, *30*(10), 974-982.

Olofsson, J. K., & Polich, J. (2007). Affective visual event-related potentials: Arousal, repetition, and time-on-task. *Biological psychology*, *75*(1), 101-108.

Orr SP, Claiborn JM, Altman B, Forgue DF, deJong JB, Pitman RK, Herz LR. Psychometric profile of posttraumatic stress disorder, anxious, and healthy Vietnam veterans: correlations with psychophysiologic responses. J Consult Clin Psychol. 1990;58:329–335.

Orr SP, Pitman RK, Lasko NB, Herz LR. Psychophysiological assessment of posttraumatic stress disorder imagery in World War II and Korean combat veterans. J Abnorm Psychol. 1993;102:152–159.

Orr, S. P., Lasko, N. B., Shalev, A. Y., & Pitman, R. K. (1995). Physiologic responses to loud tones in Vietnam veterans with posttraumatic stress disorder. *Journal of Abnormal Psychology*, *104*(1), 75.

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Hu, F. B., Shalev, A. Y., & Pitman, R. K. (2003). Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: association with posttraumatic stress disorder. *Archives of General Psychiatry*, *60*(3), 283.

Orr, S. P., Solomon, Z., Peri, T., Pitman, R. K., & Shalev, A. Y. (1997). Physiologic responses to loud tones in Israeli veterans of the 1973 Yom Kippur War. *Biological Psychiatry*, *41*(3), 319-326.

Orr, S.P, Pitman, R.K, Lasko, N.B, Herz, L.R. (1993). Psychophysiological assessment of posttraumatic stress disorder imagery in World War II and Korean combat veterans. *Journal of Abnormal Psychology, 102*, 152–159.

Otter, C., Huber, J., & Bonner, A. (1995). Cloninger's Tridimensional Personality Questionnaire: reliability in an English sample. *Personality and Individual Differences*, *18*(4), 471-480.

Ouimette, P., Wade, M., Prins, A., & Schohn, M. (2008). Identifying PTSD in primary care: comparison of the Primary Care-PTSD screen (PC-PTSD) and the General Health Questionnaire-12 (GHQ). *Journal of anxiety disorders*, *22*(2), 337-343.

Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis.*Psychological bulletin*, *129*(1), 52.

Paige, S. R., Reid, G. M., Gwyn Allen, M., & Newton, J. E. (1990). Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans. *Biological Psychiatry*, *27*(4), 419-430.

Patterson S, Abel T, Deuel T, Martin K, Rose J, Kandel E. (1996). Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron. 16*, 1137–1145

Pattwell, S. S., Bath, K. G., Perez-Castro, R., Lee, F. S., Chao, M. V., & Ninan, I. (2012). The BDNF Val66Met polymorphism impairs synaptic transmission and plasticity in the infralimbic medial prefrontal cortex. *The Journal of Neuroscience*, *32*(7), 2410-2421.

Perkonigg, A., Kessler, R. C., Storz, S., & Wittchen, H. U. (2000). Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity. *Acta psychiatrica scandinavica*, *101*(1), 46-59.

Pezawas, L., Verchinski, B.A., Mattay, V.S., Callicott, J.H., Kolachana, B.S., Straub, R.E., Egan, M.F., Meyer-Lindenberg, A., & Weinberger, D.R. (2004). The brain-derived neutropic factor val66met polymorphism and variation in human cortical morphology. *The journal of Neuroscience, 24,* 10099-10102.

Pitman, R. K., Orr, S. P., Forgue, D. F., Altman, B., de Jong, J. B., & Herz, L. R. (1990). Psychophysiologic responses to combat imagery of Vietnam veterans with posttraumatic stress disorder versus other anxiety disorders.*Journal of Abnormal Psychology*, *99*(1), 49.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B., Cahill, L., & Orr, S. P. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological psychiatry*, *51*(2), 189-192.

Pocock, G., & Richards, C.D. (2006). Human Physiology: The basis of Medicine 3rd Ed. Oxford university press: NY.

Pole, N. (2007). The psychophysiology of posttraumatic stress disorder: A meta-analysis. *Psychological Bulletin*, *133*(5), 725-746.

Pole, N., Neylan, T. C., Best, S. R., Orr, S. P., & Marmar, C. R. (2003). Fear-potentiated startle and posttraumatic stress symptoms in urban police officers.*Journal of Traumatic Stress*, *16*(5), 471-479.

Pole, N., Neylan, T. C., Otte, C., Henn-Hasse, C., Metzler, T. J., & Marmar, C. R. (2009). Prospective prediction of posttraumatic stress disorder symptoms using fear potentiated auditory startle responses. *Biological psychiatry*, *65*(3), 235-240.

Prins, A., Ouimette, P., Kimerling, R., Camerond, R. P., Hugelshofer, D. S., Shaw-Hegwer, J., ... & Sheikh, J. I. (2003). The primary care PTSD screen (PC-PTSD): development and operating characteristics. *International Journal of Psychiatry in Clinical Practice*, *9*(1), 9-14.

Putnam, F. W., & Trickett, P. K. (1997). Psychobiological effects of sexual abuse. *Annals of the New York Academy of Sciences*, *821*(1), 150-159.

Quevedo, K., Smith, T., Donzella, B., Schunk, E., & Gunnar, M. (2010). The startle response: Developmental effects and a paradigm for children and adults.*Developmental psychobiology*, *52*(1), 78-89.

Quiroga, R. Q., & Garcia, H. (2003). Single-trial event-related potentials with wavelet denoising. *Clinical Neurophysiology*, *114*(2), 376-390.

Rady, A., Elsheshai, A., Mokhtar, M., Abou el Wafa, H., & Elkholy, O. (2011). The A1 allele of the DRD2 TaqA1/A2 polymorphism as risk factor for PTSD. *The European Journal of Psychiatry*, *25*(3), 144-149.

Raiteri, L., Luccini, E., Romei, C., Salvadori, S., & Calò, G. (2009). Neuropeptide S selectively inhibits the release of 5-HT and noradrenaline from mouse frontal cortex nerve endings. *British journal of pharmacology*,*157*(3), 474-481.

Rasch, B., Spalek, K., Buholzer, S., Luechinger, R., Boesiger, P., Papassotiropoulos, A., & de Quervain, D. F. (2009). A genetic variation of the noradrenergic system is related to differential amygdala activation during encoding of emotional memories. *Proceedings of the National Academy of Sciences*, *106*(45), 19191-19196.

Rattiner, L.M., Davis, M., & Ressler, K.J. (2004). Differential regulation of brain-derived neurotrophic factor transcripts during the consolidation of fear learning. Learning and Memory, 11, 727-731.

Rattiner, L.M., Davis, M., & Ressler, K.J. (2005). Brain-derived neurotrophic factor in amygdala-dependent learning. *Neuroscientist, 11,* 323-333.

Rattiner, L.M., Davis, M., French, C.T., Ressler, K.J. (2004). Brain-derived neurotrophic factor and tyrosine kinase receptor B involvement in amygdala-dependent fear conditioning. Journal of Neuroscience, 24, 4796-806.

Ray, R. D., McRae, K., Ochsner, K. N., & Gross, J. J. (2010). Cognitive reappraisal of negative affect: converging evidence from EMG and self-report.*Emotion*, *10*(4), 587.

Ready, D. J., Gerardi, R. J., Backscheider, A. G., Mascaro, N., & Rothbaum, B. O. (2010). Comparing virtual reality exposure therapy to present-centered therapy with 11 US Vietnam veterans with PTSD. *Cyberpsychology, Behavior, and Social Networking*, *13*(1), 49-54.

Reinscheid, R. K., & Xu, Y. L. (2005). Neuropeptide S as a novel arousal promoting peptide transmitter. *Febs Journal*, *272*(22), 5689-5693.

Reinscheid, R. K., Xu, Y. L., Okamura, N., Zeng, J., Chung, S., Pai, R., ... & Civelli, O. (2005). Pharmacological characterization of human and murine neuropeptide s receptor variants. *Journal of Pharmacology and Experimental Therapeutics*, *315*(3), 1338-1345.

Resick, P. A., & Schnicke, M. K. (1992). Cognitive processing therapy for sexual assault victims. *Journal of consulting and clinical psychology*, *60*(5), 748.

Resnick, H. S., Yehuda, R., Pitman, R. K., & Foy, D. W. (1995). Effect of previous trauma on acute plasma cortisol level following rape. *The American journal of psychiatry*.

Reynolds, M., & Brewin, C. R. (1999). Intrusive memories in depression and posttraumatic stress disorder. *Behaviour research and therapy*, *37*(3), 201-215.

Richman, H.B., Frueh, C. (1997). Personality and PTSD II: Personality assessment of PTSD-diagnosed Vietnam veterans using the Cloninger Tridimensional Personality Questionnaire (TPQ). *Depression and Anxiety, 6, 2,* 70–77.

Riva, G., Mantovani, F., Capideville, C.S., Preziosa, A., Morganti, F., Villani, D., Gaggioli, A., Botella, C., & Alcaniz, M. (2007). Affective interactions using virtual reality: The link between presence and emotions. CyberPsychology & Behaviour, 10, 1, 45-56.

Rizzi, A., Vergura, R., Marzola, G., Ruzza, C., Guerrini, R., Salvadori, S., ... & Calo, G. (2009). Neuropeptide S is a stimulatory anxiolytic agent: a behavioural study in mice. *British journal of pharmacology*, *154*(2), 471-479.

Rizzo, A.A., Difede, J., Rothbaum, B.O., Johnston, S., McLay, R.N., Reger, G., Gahm, G., Parsons, T., Graap, K., & Pair, J. (2009). VR PTSD exposure therapy results with active duty OIF/OEF combatants. Studies in Health Technology & Informatics, 142, 277-282.

Rodriguez, S., Gaunt, T. R., & Day, I. N. (2009). Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies.*American journal of epidemiology*, *169*(4), 505-514.

Roediger, H. L. (1990). Implicit memory: Retention without remembering.*American psychologist*, *45*(9), 1043.

Roemer, L., Orsillo, S. M., Borkovec, T. D., & Litz, B. T. (1998). Emotional response at the time of a potentially traumatizing event and PTSD symptomatology: A preliminary retrospective analysis of the DSM-IV Criterion A-2. *Journal of Behavior Therapy and Experimental Psychiatry*, *29*(2), 123-130.

Rothbaum, B. O., Foa, E. B., Riggs, D. S., Murdock, T., & Walsh, W. (1992). A prospective examination of post-traumatic stress disorder in rape victims.*Journal of Traumatic stress*, *5*(3), 455-475.

Rothbaum, B. O., Kozak, M. J., Foa, E. B., & Whitaker, D. J. (2001). Posttraumatic stress disorder in rape victims: autonomic habituation to auditory stimuli. *Journal of traumatic stress*, *14*(2), 283-293.

Rothbaum, B.O., Hodges, L.F., Ready, D., Graap, K., & Renato, D. (2001). Virtual reality exposure therapy for Vietnam veterans with posttraumatic stress disorder. Journal of Clinical Psychiatry, 62, 617-622.

Ruiz-Padial, E., Sollers, J. J., Vila, J., & Thayer, J. F. (2003). The rhythm of the heart in the blink of an eye: Emotion-modulated startle magnitude covaries with heart rate variability. *Psychophysiology*, *40*(2), 306-313.

Rumball, F., & Karl, A. (2011). Virtual reality as a beneficial tool for experimental research into PTSD. *Traumatic Stress Points, September, 25*, 5.

Rutter, M., Caspi, A., & Moffitt, T. E. (2003). Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. *Journal of Child Psychology and Psychiatry*, *44*(8), 1092-1115.

Rybakowski, J. K. (2008). BDNF gene: functional Val66Met polymorphism in mood disorders and schizophrenia. *Pharmacogenomics*, *9*(11), 1589-1593.

Sakano, N., & Pickenhain, L. (1968). EVOKED RESPONSE AND STARTLE BLINK TO STRONG ACOUSTIC STIMULI OF DIEEERENT SIGNAL MEANING. *Psychophysiology*, *5*(1), 1-14.

Sánchez, M. B., Guerra, P., Muñoz, M. A., Mata, J. L., Bradley, M. M., Lang, P. J., & Vila, J. (2009). Communalities and differences in fear potentiation between cardiac defense and eyeblink startle. *Psychophysiology*, *46*(6), 1137-1140.

Schardt, D. M., Erk, S., Nüsser, C., Nöthen, M. M., Cichon, S., Rietschel, M., ... & Walter, H. (2010). Volition diminishes genetically mediated amygdala hyperreactivity. *Neuroimage*, *53*(3), 943-951.

Schelling, G., Roozendaal, B., Krauseneck, T., Schmoelz, M., De Quervain, D., & Briegel, J. (2006). Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. *Annals of the New York Academy of Sciences*, *1071*(1), 46-53.

Schipper, P., Nonkes, L. J., Karel, P., Kiliaan, A. J., & Homberg, J. R. (2011). Serotonin transporter genotype x construction stress interaction in rats.*Behavioural brain research*, *223*(1), 169-175.

Schmidt, N. B., Lerew, D. R., & Jackson, R. J. (1999). Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: replication and extension.*Journal of abnormal psychology*, *108*(3), 532.

Schooler, T. Y., Dougall, A. L., & Baum, A. (1999). Cues, frequency, and the disturbing nature of intrusive thoughts: Patterns seen in rescue workers after the crash of flight 427. *Journal of traumatic stress*, *12*(4), 571-585.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Birbaumer, N., & Lang, P. J. (1997). Probe P3 and blinks: Two measures of affective startle modulation.*Psychophysiology*, *34*(1), 1-6.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: the late positive potential is modulated by motivational relevance. *Psychophysiology*, *37*(2), 257-261.

Schupp, H. T., Flaisch, T., Stockburger, J., & Junghofer, M. (2006). Emotion and attention: event-related brain potential studies. *Progress in brain research*,*156*, 31-51.

Schupp, H. T., Lutzenberger, W., Rau, H., & Birbaumer, N. (1994). Positive shifts of event-related potentials: a state of cortical disfacilitation as reflected by the startle reflex probe. *Electroencephalography and Clinical Neurophysiology*,*90*(2), 135-144.

Schupp, H. T., Markus, J., Weike, A. I., & Hamm, A. O. (2003). Emotional facilitation of sensory processing in the visual cortex. *Psychological science*,*14*(1), 7-13.

Scott, M. J., Stradling, S. G. (1994). Post-traumatic stress disorder without the trauma. *British Journal of Clinical Psychology, 33,* 71 -74.

Scully, J. A., Tosi, H., & Banning, K. (2000). Life event checklists: Revisiting the social readjustment rating scale after 30 years. *Educational and psychological measurement*, *60*(6), 864-876.

Sen, S., Burmeister, M., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. American Journal of Medical Genetics: *Neuropsychiatric Genetics, 127B*, 1, 85-89.

Sen, S., Nesse, R.M., Stoltenberg, S.F, Li, S., Gleiberman, L., Chakravarti, A., Weber, A.B., Burmeister, M. (2003). A BDNF coding variant is association with the NEO personality inventory domain neuroticism, a risk factor for depression. *Neuropsychopharmacology, 28*, 397-401.

Shalev AY, Orr SP, Pitman RK. Psychophysiologic response during script-driven imagery as an outcome measure in posttraumatic stress disorder. J Clin Psychiatry. 1992;53:324–326.

Shalev, A. Y., Freedman, S., Peri, T., Brandes, D., Sahar, T., Orr, S. P., & Pitman, R. K. (1998). Prospective study of posttraumatic stress disorder and depression following trauma. *American Journal of Psychiatry*, *155*(5), 630-637.

Shalev, A. Y., Orr, S. P., Peri, T., Schreiber, S., & Pitman, R. K. (1992). Physiologic responses to loud tones in Israeli patients with posttraumatic stress disorder. *Archives of General Psychiatry*, *49*(11), 870-875.

Shalev, A. Y., Peri, T., Canetti, L., & Schreiber, S. (1996). Predictors of PTSD in injured trauma survivors: a prospective study. *American Journal of Psychiatry*, *153*(2), 219-225.

Shalev, A. Y., Peri, T., Orr, S. P., Bonne, O., & Pitman, R. K. (1997). Auditory startle responses in help-seeking trauma survivors. *Psychiatry research*,*69*(1), 1-7.

Shalev, A. Y., Sahar, T., Freedman, S., Peri, T., Glick, N., Brandes, D., ... & Pitman, R. K. (1998). A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder.*Archives of General Psychiatry*, *55*(6), 553.

Shalev, A.Y., Peri, T., Brandes, D., Freedman, S., Orr, S.P., Pitman, R.K. (2000). Auditory startle response in trauma survivors with posttraumatic stress disorder: A prospective study. *American Journal of Psychiatry, 157*, 255-261.

Sheehan, D., Janavs, J., Baker, R., Harnett-Sheehan, K., Knapp, E., Sheehan, M., Lecrubier, Y., Weiller, E., Hergueta, T., Amorim, P., Bonora, L.I., Lepine, J.P. Mini International Neuropsychiatric Interview: English version 5.0.0. http://www.nccpsychiatry.info/File/MINI500.pdf . (2006)

Sheehan, D.V, Lecrubier, Y, Harnett-Sheehan, K, Amorim, P, Janavs, J, Weiller, E, Hergueta, T, Baker, R, Dunbar, G (1998). The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. Journal of Clinical Psychiatry,59,(suppl 20), 22-33.

Sheehan, D.V, Lecrubier, Y, Harnett-Sheehan, K, Janavs, J, Weiller, E, Bonara, L.I, Keskiner, A, Schinka, J, Knapp, E, Sheehan, M.F, Dunbar, G.C. (1997). Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. European Psychiatry, 12, 232-241.

Sher, K. J. (1995). The Tridimensional Personality Questionnaire: Reliability and validity studies and derivation of a short form. *Psychological Assessment*, *7*(2), 195-208.

Shimizu, E., Hashimoto, K., & Iyo, M. (2004). Ethnic difference of the BDNF 196G/A (val66met) polymorphism frequencies: the possibility to explain ethnic mental traits. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *126*(1), 122-123.

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences*, *1071*(1), 67-79.

Shin, L. M., Whalen, P. J., Pitman, R. K., Bush, G., Macklin, M. L., Lasko, N. B., ... & Rauch, S. L. (2001). An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biological psychiatry*, *50*(12), 932-942.

Shipherd, J. C., & Beck, J. G. (2005). The role of thought suppression in posttraumatic stress disorder. *Behavior Therapy*, *36*(3), 277-287.

Shvil, E., Rusch, H. L., Sullivan, G. M., & Neria, Y. (2013). Neural, Psychophysiological, and Behavioral Markers of Fear Processing in PTSD: A Review of the Literature. *Current psychiatry reports*, *15*(5), 1-10.

Si, W., Aluisio, L., Okamura, N., Clark, S. D., Fraser, I., Sutton, S. W., ... & Reinscheid, R. K. (2010). Neuropeptide S stimulates dopaminergic neurotransmission in the medial prefrontal cortex. *Journal of neurochemistry*, *115*(2), 475-482.

Silver, R. C., Holman, E. A., McIntosh, D. N., Poulin, M., & Gil-Rivas, V. (2002). Nationwide longitudinal study of psychological responses to September 11. *JAMA: the journal of the American Medical Association*, *288*(10), 1235-1244.

Slater, M., Spanlang, B., Sanchez-Vives, M. V., & Blanke, O. (2010). First person experience of body transfer in virtual reality. *PloS one*, *5*(5), e10564.

Small, K. M., Brown, K. M., Forbes, S. L., & Liggett, S. B. (2001). Polymorphic deletion of three intracellular acidic residues of the α2B-adrenergic receptor decreases G protein-coupled receptor kinase-mediated phosphorylation and desensitization. *Journal of Biological Chemistry*, *276*(7), 4917-4922.

Smith, N.K., Cacioppo, J.T., Larsen, J.T., Chartrand, T.L. (2003). May I have your attention, please: electrocortical responses to positive and negative stimuli. *Neuropsychologia. 41(2),171-83.*

Sokolov, E. N. (1963). Higher nervous functions: The orienting reflex. *Annual review of physiology*, *25*(1), 545-580.

Solomon, Z., Mikulincer, M., Flum, H. (1988). Negative life events, coping responses, and combat-related psychopathology: A prospective study. *Journal of Abnormal Psychology, 97, 3*, 302-307.

Speisman, J. C., Lazarus, R. S., Mordkoff, A., & Davison, L. (1964). Experimental reduction of stress based on ego-defense theory. *The Journal of Abnormal and Social Psychology*, *68*(4), 367.

Spira, J.L., Johnston, S., McLay. R., Popovic, S., Russoniello, C., & Wood, D. (2010). Expert Panel: Future directions of technological advances in prevention, assessment, and treatment for militart deployment mental health. CyberPsychology & Behaviour, 13, 1, 109-117

Spitzer, R. L., First, M. B., & Wakefield, J. C. (2007). Saving PTSD from itself in DSM-V. *Journal of Anxiety Disorders*, *21*(2), 233-241.

Sprinkle, S. D., Lurie, D., Insko, S. L., Atkinson, G., Jones, G. L., Logan, A. R., & Bissada, N. N. (2002). Criterion validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a university counseling center sample. *Journal of counseling psychology*, *49*(3), 381.

Stam, R. (2007). PTSD and stress sensitisation: A tale of brain and body: Part 1: Human studies. *Neuroscience & Biobehavioral Reviews*, *31*(4), 530-557.

Stein, M. B., Schork, N. J., & Gelernter, J. (2008). Gene-by-environment (serotonin transporter and childhood maltreatment) interaction for anxiety sensitivity, an intermediate phenotype for anxiety disorders.*Neuropsychopharmacology*, *33*(2), 312-319.

Stein, M. B., Walker, J. R., & Forde, D. R. (2000). Gender differences in susceptibility to posttraumatic stress disorder. *Behaviour research and therapy*,*38*(6), 619-628.

Stokes, P.E., Sikes, C.R. (1987). Hypothalamic-pituitary-adrenal axis in affective disorders. In Meltzer H (ed), *Psychopharmacology: The Third Generation of Progress.* New York: Raven Press, pp 589-607.

Storch, E. A., Roberti, J. W., & Roth, D. A. (2004). Factor structure, concurrent validity, and internal consistency of the Beck Depression Inventory—Second Edition in a sample of college students. *Depression and anxiety*, *19*(3), 187-189.

Sugawara, M., Sadeghpour, M., De Traversay, J., & Ornitz, E. M. (1994). Prestimulation-induced modulation of the P300 component of event related potentials accompanying startle in children. *Electroencephalography and clinical neurophysiology*, *90*(3), 201-213.

Sukhodolsky, D.G., Scahill, L., Gadow, K.D., Arnold, L.E., Aman, M.G., McDougle, C.J., McCracken, J.T., Tierney, E., Williams, S., Lecavalier, L. (2008). Parent-rated anxiety symptoms in children with pervasive developmental disorders: Frequency and association with core autism symptoms and cognitive functioning. *Journal of Abnormal Child Psychology, 36*, 117-128.

Szekely, A., Ronai, Z., Nemoda, Z., Kolmann, G., Gervai, J., & Sasvari-Szekely, M. (2004). Human personality dimensions of persistence and harm avoidance associated with DRD4 and 5-HTTLPR polymorphisms. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *126*(1), 106-110.

Szeszko, P. R., Lipsky, R., Mentschel, C., Robinson, D., Gunduz-Bruce, H., Sevy, S., ... & Malhotra, A. K. (2005). Brain-derived neurotrophic factor val66met polymorphism and volume of the hippocampal formation. *Molecular psychiatry*, *10*(7), 631-636.

Tabachnick, B. G., & Fidell, L. S. (2001). Common Data Transformations. *Using Multivariate Statistics. 4th ed. Boston, Mass: Allyn & Bacon*, 80-82.

Tarrier, N., Pilgrim, H., Sommerfield, C., Faragher, B., Reynolds, M., Graham, E., & Barrowclough, C. (1999). A randomized trial of cognitive therapy and imaginal exposure in the treatment of chronic posttraumatic stress disorder.*Journal of consulting and clinical psychology*, *67*(1), 13.

Taylor, S., Kock, W.J., Crockett, D.J. (1991). Anxiety sensitivity, trait anxiety and the anxiety disorders. Journal of Anxiety Disorders, 5 (4), 293-311.

Terracciano, A., Tanake, T., Sutin, A.R., Deiana, B., Balaci, L., Sanna S., Olla, N., Maschio, A., Uda, M., Ferrucci, L., Schlessinger, D., & Costa, P.T. (2010). *Neuropsychopharmacology, 35, 5*, 1083-1089.

Tolin, D. F., & Foa, E. B. (2006). Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychological Bulletin*, *132*(6), 959.

Tortora, G.J, & Derrickson, B .(2006). Principles of anatomy and physiology. John Wiley & Sons, Inc: Danvers: MA.

Trickey, D., Siddaway, A. P., Meiser-Stedman, R., Serpell, L., & Field, A. P. (2012). A meta-analysis of risk factors for post-traumatic stress disorder in children and adolescents. *Clinical psychology review*, *32*(2), 122-138.

Tukey, J.W. 1962. The future of data analysis. *Annals of Mathematical Statistics* 33: 1-67.

Tull, M. T., Barrett, H. M., McMillan, E. S., & Roemer, L. (2007). A preliminary investigation of the relationship between emotion regulation difficulties and posttraumatic stress symptoms. *Behavior Therapy*, *38*(3), 303-313.

Turner, J. B., Turse, N. A., & Dohrenwend, B. P. (2007). Circumstances of service and gender differences in war-related PTSD: Findings from the National Vietnam Veteran Readjustment Study. *Journal of traumatic stress*,*20*(4), 643-649.

Turner, R. J., & Wheaton, B. (1995). Checklist measurement of stressful life events. *Measuring stress: A guide for health and social scientists*, 29-58. NY: Oxford University Press.

Turpin, G. (1986). Effects of stimulus intensity on autonomic responding: The problem of differentiating orienting and defense reflexes. *Psychophysiology*,*23*(1), 1-14.

Uddo, M ., Vasterling, J. J., Brailey, K., Sutker, P.B. (1993). Memory and attention in combat-related post-traumatic stress disorder (PTSD). *Journal of Psychopathology and Behavioral Assessment, 15, 1*, 43-52.

Ursano, R. J., Fullerton, C. S., Epstein, R. S., Crowley, B., Vance, K., Kao, T. C., & Baum, A. (1999). Peritraumatic dissociation and posttraumatic stress disorder following motor vehicle accidents. *American Journal of Psychiatry*,*156*(11), 1808-1810.

Vaidyanathan, U., Patrick, C. J., & Bernat, E. M. (2009). Startle reflex potentiation during aversive picture viewing as an indicator of trait fear.*Psychophysiology*, *46*(1), 75-85.

Valdez, C. E., & Lilly, M. M. (2012). Thought Control: Is It Ability, Strategies, or Both That Predicts Posttraumatic Symptomatology in Victims of Interpersonal Trauma?. *Journal of Psychopathology and Behavioral Assessment*, *34*(4), 531-541.

Valente, N. L. M., Vallada, H., Cordeiro, Q., Miguita, K., Bressan, R. A., Andreoli, S. B., ... & Mello, M. F. (2011). Candidate-gene approach in posttraumatic stress disorder after urban violence: association analysis of the genes encoding serotonin transporter, dopamine transporter, and BDNF.*Journal of Molecular Neuroscience*, *44*(1), 59-67.

Van Boxtel, A. V., Boelhouwer, A. J. W., & Bos, A. R. (1998). Optimal EMG signal bandwidth and interelectrode distance for the recording of acoustic, electrocutaneous, and photic blink reflexes. *Psychophysiology*, *35*(6), 690-697.

Van Loey, N. E. E., Maas, C. J. M., Faber, A. W., & Taal, L. A. (2003). Predictors of chronic posttraumatic stress symptoms following burn injury: results of a longitudinal study. *Journal of traumatic stress*, *16*(4), 361-369.

van Minnen, A., & Hagenaars, M. (2002). Fear activation and habituation patterns as early process predictors of response to prolonged exposure treatment in PTSD. *Journal of Traumatic Stress*, *15*(5), 359-367.

van Minnen, A., & Hagenaars, M. (2002). Fear activation and habituation patterns as early process predictors of response to prolonged exposure treatment in PTSD. *Journal of Traumatic Stress*, *15*(5), 359-367.

van Minnen, A., Wessel, I., Dijkstra, T., & Roelofs, K. (2002). Changes in PTSD patients' narratives during prolonged exposure therapy: A replication and extension. *Journal of Traumatic Stress*, *15*(3), 255-258.

vanOyen Witvliet, C., & Vrana, S. R. (2000). Emotional imagery, the visual startle, and covariation bias: An affective matching account. *Biological Psychology*, *52*(3), 187-204.

yes	platform+medline	author	author	

Vasterling, J. J., Brailey, K., Constans, J.I., Sutker, P.B. (1998). Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology, 12, 1,* 125-133.

Vasterling, J.J., Duke, L.M., Brailey, K., Constans, J.I., Allain, A.N., Stuker, P.B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology, 16, 1*, 5-14.

Vázquez, C., Hervás, G., & Pérez-Sales, P. (2008). Chronic thought suppression and posttraumatic symptoms: Data from the Madrid March 11, 2004 terrorist attack. *Journal of anxiety disorders*, *22*(8), 1326-1336.

Vermetten, E., & Bremner, J. D. (2002). Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder.*Depression and anxiety*, *16*(1), 14-38.

Viola, F. C., Debener, S., Thorne, J., & Schneider, T. R. (2010). Using ICA for the Analysis of Multi-Channel EEG Data. *Simultaneous EEG and fMRI: Recording, Analysis, and Application: Recording, Analysis, and Application*,121-133. NY: Oxford University Press.

Vogeley, K., May, M., Ritzl, A., Falkai, P., Zilles, K., & Fink, G. R. (2004). Neural correlates of first-person perspective as one constituent of human self-consciousness. *Journal of cognitive neuroscience*, *16*(5), 817-827.

Voisey, J., Swagell, C. D., Hughes, I. P., Morris, C. P., Van Daal, A., Noble, E. P., ... & Lawford, B. R. (2009). The DRD2 gene 957C> T polymorphism is associated with posttraumatic stress disorder in war veterans. *Depression and anxiety*, *26*(1), 28-33.

von dem Hagen, E. A., Passamonti, L., Nutland, S., Sambrook, J., & Calder, A. J. (2011). The serotonin transporter gene polymorphism and the effect of baseline on amygdala response to emotional faces. *Neuropsychologia*, *49*(4), 674-680.

Vrana, S. R. (1995). Emotional modulation of skin conductance and eyeblink responses to a startle probe. *Psychophysiology*, *32*(4), 351-357.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*, *59*(6), 1037-1050.

Walter, H., von Kalckreuth, A., Schardt, D., Stephan, A., Goschke, T., & Erk, S. (2009). The temporal dynamics of voluntary emotion regulation. *PLoS One*, *4*(8), e6726.

Wang, L., Ashley-Koch, A., Steffens, D. C., Krishnan, K. R. R., & Taylor, W. D. (2012). Impact of BDNF Val66Met and 5-HTTLPR polymorphism variants on neural substrates related to sadness and executive function. *Genes, Brain and Behavior*.

Weber, K., & Lavric, A. (2008). Syntactic anomaly elicits a lexico-semantic (N400) ERP effect in the second language but not the first. *Psychophysiology*, *45*(6), 920-925.

Wegner, D. M., & Zanakos, S. (1994). Chronic thought suppression. *Journal of personality*, *62*(4), 615-640.

Wegner, D. M., Quillian, F., & Houston, C. E. (1996). Memories out of order: Thought suppression and the disturbance of sequence memory. *Journal of Personality and Social Psychology*, *71*(4), 680.

Wegner, D. M., Schneider, D. J., Carter, S. R., & White, T. L. (1987). Paradoxical effects of thought suppression. *Journal of personality and social psychology*, *53*(1), 5.

Weidmann, A., Conradi, A., Gröger, K., Fehm, L., & Fydrich, T. (2009). Using stressful films to analyze risk factors for PTSD in analogue experimental studies–which film works best?. *Anxiety, Stress, & Coping*, *22*(5), 549-569.

Weisbrot, D.M., Gadow, K.D., DeVincent, C.J & Pomeroy, J. (2005). The presentation of anxiety in children with pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology, 15* (3), 477-496.Gillott, A., Furniss, F., & Walter, A. (2001). Anxiety and high functioning children with autism. *Autism, 5*, 277-286.

Weiss, D. S., Marmar, C. R., Metzler, T. J., & Ronfeldt, H. M. (1995). Predicting symptomatic distress in emergency services personnel. *Journal of Consulting and Clinical Psychology*, *63*(3), 361.

Wendland, J. R., Martin, B. J., Kruse, M. R., Lesch, K. P., & Murphy, D. L. (2006). Simultaneous genotyping of four functional loci of human SLC6A4, with a reappraisal of 5-HTTLPR and rs25531. *Molecular psychiatry*, *11*(3), 224-226.

Wessa, M., & Flor, H. (2007). Failure of extinction of fear responses in posttraumatic stress disorder: evidence from second-order conditioning.*American Journal of Psychiatry*, *164*(11), 1684-1692.

Wessa, M., & Flor, H. (2007). Failure of extinction of fear responses in posttraumatic stress disorder: evidence from second-order conditioning. *American Journal of Psychiatry*, *164*(11), 1684-1692.

West, S. G., Ryu, E., Kwok, O. M., & Cham, H. (2011). Multilevel modeling: Current and future applications in personality research. *Journal of personality*,*79*(1), 2-50.

Witteveen, A.B., Huizink, A.C., Slottje, P., Bramsen, I., Smid, T., & Ploeg, H.M. (2010). Associations of cortisol with posttraumatic stress symptoms and negative life events: A study of police officers and firefighters. *Psychoneuroendocrinology, 35*, 1113-1118.

Wood, D.P., Murphy, J., Center, K., McLay, R., Reeves, D., Pyne, J., Shilling, R., & Wiederhold, B.K. (2007). Combat-related posttraumatic stress disorder: a case report using virtual reality exposure therapy with physiological monitoring. CyberPsychology & Behaviour, 10, 309-315

Woud, M. L., Holmes, E. A., Postma, P., Dalgleish, T., & Mackintosh, B. (2012). Ameliorating intrusive memories of distressing experiences using computerized reappraisal training. *Emotion*, *12*(4), 778.

Wurtman, R. J. (2005). Genes, stress, and depression. *Metabolism-Clinical and Experimental*, *54*(1), 16-19.

Xu, Y. L., Reinscheid, R. K., Huitron-Resendiz, S., Clark, S. D., Wang, Z., Lin, S. H., ... & Civelli, O. (2004). Neuropeptide S: a neuropeptide promoting arousal and anxiolytic-like effects. *Neuron*, *43*(4), 487-497.

Yehuda, R, Teicher, M.T., Trestman, R.L., Levengood, R.A., & Siever, L.J. (1996). Cortisol regulation in Posttraumatic stress disorder and major depression: A chronobioogical analysis*. Biological Psychiatry, 40,* 79-88.

Yehuda, R. (2006). Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. *Ann NY Acad Sci, 1071*, 137–166.

Yehuda, R., & Bierer, L. M. (2009). The relevance of epigenetics to PTSD: Implications for the DSM-V. *Journal of traumatic stress*, *22*(5), 427-434.

Yehuda, R., & Flory, J. D. (2007). Differentiating biological correlates of risk, PTSD, and resilience following trauma exposure. *Journal of Traumatic Stress*, *20*(4), 435-447.

Yehuda, R., Giller, E. L., Southwick, S. M., Lowy, M. T., & Mason, J. W. (1991). Hypothalamic-pituitary-adrenal dysfunction in posttraumatic stress disorder. *Biological Psychiatry*, *30*(10), 1031-1048.

Yehuda, R., Kahana, B., Binder-Brynes, K., & Southwick, S. M. (1995). Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. *The American journal of psychiatry*.

Yehuda, R., Steiner, A., Kahana, B., Binder-Brynes, K., Southwick, S. M., Zemelman, S., & Giller, E. L. (1997). Alexithymia in Holocaust survivors with and without PTSD. *Journal of Traumatic Stress*, *10*(1), 93-100.

Yu H, Wang Y, Pattwell S, Jing D, Liu T, Zhang Y, Bath KG, Lee FS, Chen ZY. (2009). Variant BDNF Val66Met polymorphism affects extinction of conditioned aversive memory. Journal of Neuroscience, 29, 4056-4064.

Yu, H., Wang, D.D., Wang, Y., Llu, T., Lee, F.S., & Chen, Z.Y. (2012). Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants. Journal of Neuroscience, 32, 4092-4101.

Zhang, L., Hu, X. Z., Li, H., Li, X., Smerin, S., Benedek, D. M., & Ursano, R. (2011). Startle response related genes. *Medical Hypotheses*, *77*(4), 685-691.

Zoellner, L. A., Alvarez-Conrad, J., & Foa, E. B. (2002). Peritraumatic dissociative experiences, trauma narratives, and trauma pathology. *Journal of Traumatic Stress*, *15*(1), 49-57.