Outcome after Mild Traumatic Brain Injury: the Interplay of Concussion and Post-traumatic Stress Symptoms

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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 any other University.

(Signature) ……

Abstract

Background and aims

The provenance of post-concussion symptoms (PCS) and post-traumatic stress (PTSD) after mild traumatic brain injury (mTBI) is controversial. This thesis investigated factors influencing these two conditions separately, as well as the interplay between PCS and PTSD, in individuals with mTBI and a control sample without mTBI (orthopaedic injuries).

Method

Consecutive adult attendees of an Emergency Department with mTBI or orthopaedic injury were prospectively recruited and completed the Rivermead Post-concussion Questionnaire (RPQ) and Trauma Screening Questionnaire (TSQ) for PTSD at two weeks (T1) and three months (T2) post-injury. The sample at T1 consisted of 34 with complicated mTBI, 76 with uncomplicated mTBI and 47 with orthopaedic injury, and 18 with complicated mTBI, 43 with uncomplicated mTBI and 33 orthopaedic controls at T2.

Results

Although there were no differences in overall PCS symptomology between groups, a subset of PCS symptoms (headaches, dizziness and nausea) was found to be specific to mTBI at both time points. These symptoms are proposed to have a neurological basis, as opposed to a psychological basis. PTSD interacted with PCS, particularly in mTBI, such that PTSD was associated with

greater “neurogenic” and “psychogenic” symptomology in this group, but only a moderate increase in psychogenic symptoms for controls. A model of the influence of PTSD on PCS is presented. PTSD was influenced by poor memory quality for the traumatic event and attribution of blame to others, but not by mTBI.

Discussion and conclusions

Though mTBI may set the scene for at least neurogenic symptoms of PCS to occur, psychological mechanisms, particularly PTSD, have a significant role in the persistence of PCS. Our findings suggest the need for a clear story and sense of meaning for a traumatic event for good recovery from PTSD. Taken together, the results suggest that psychological interventions, particularly aimed at PTSD, may be most effective after mTBI.

For my wonderful wife, Ruthie.

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Integrated Overview and Discussion

OVERVIEW AND STRUCTURE OF THE THESIS

Mild traumatic brain injury (mTBI) is a common cause for attendance at emergency departments (EDs) and, despite being 'mild', is linked to significant morbidity. The high rate of mTBI worldwide makes investigating the causes of poor outcome following these 'mild' injuries an important research avenue. In particular, lingering post-concussion symptoms (PCS) and post-traumatic stress disorder (PTSD), arising from the injury event, are common causes of morbidity and disability in a significant minority of those incurring an mTBI. However, the development of both these conditions following mTBI has been the centre of a good deal of controversy in the literature over the last two decades. PCS has been found to occur frequently after injury in those without a head-injury and it has been asserted that PTSD and mTBI are mutually exclusive conditions. Research interest in outcome after mTBI has been especially fueled by military conflicts over the past twenty years, notably the wars in Iraq and Afghanistan, where combat-related mTBI resulted in significant morbidity due to both PCS and PTSD. These two conditions overlap in symptomology to some extent, which has hindered a clear investigation of outcome and, therefore, the development of suitable clinical interventions following mTBI.

The aim of this thesis was to investigate the provenance of PCS and PTSD symptomology following mTBI, compared to a control group with minor injuries not involving the head, as well

as study the interplay of PCS and PTSD. A longitudinal, prospective study of consecutive individuals who sought care at an ED was conducted, whereby outcome was assessed at the acute phase (two weeks) and three months post-injury, by which point symptomology for both PCS and PTSD is considered persistent. Analyses of these data are presented in this thesis, divided into three studies. Each study has been written in a format suitable for publication, though submitted versions would require revision to meet the specific limits and scope of the target journal. At the time of writing, the first study is under review by the Journal of Head Trauma Rehabilitation. The submitted version of this chapter can be found in Appendix 1.

First, this chapter will briefly review the literature that underpins this research, highlighting three particular areas where research is needed that this thesis contributes to. This review is furthered in each of the study chapters as appropriate. Then it will discuss the design of the longitudinal, prospective investigation (further details of this and the samples used are described in the three study chapters). The specific aims and results of the three studies will then be discussed in turn, with particular care taken to describe how these studies form a cohesive whole and contribute to the field. Finally, this chapter draws together the discussions and conclusions drawn from the three studies into an integrated whole and explains how they advance our knowledge of outcome after mTBI.

LITERATURE REVIEW

Definition of mTBI

There is no unified definition of mTBI. Indeed, there is debate over the usage of several terms to describe roughly the same injuries. The terms "mild/minor head injury", "mild traumatic brain injury" and "concussion" have been used interchangeably by parts of the literature; for some the terms are synonymous, whereas others argue for subtle differences between the conditions. Mild head injury is an antiquated term that refers to clinically evident injuries to the face, scalp and calvarium (the upper dome of the skull, excluding the lower jaw), for example lacerations, abrasions, contusions and fractures, which may or may not involve brain injury (Bruns & Hauser, 2003). Concussion is a term, predominantly applied in the literature on injury in sport, used to describe a transient and immediate disturbance in neurological function as a result of mechanical trauma (Kelly & Rosenberg, 1997), possibly including loss of consciousness (LOC). Traumatic brain injuries are a subset of head injuries in which brain damage is evident. They are associated with an alteration in brain function, as evidenced by LOC, confusion, neurological deficits and memory disturbances, and are caused by blunt or penetrating force to the head. When injuries are mild, it can be difficult to assess whether actual damage to the brain has been incurred; subtle behavioural and/or neuropsychological changes may be the only symptoms (Bruns & Hauser, 2003). Nevertheless, mTBI now appears to be the preferred term in the literature over mild head injury and concussion. This may be because there may be alteration in brain function that is transient indicated by immediate symptoms and/or there may be more permanent changes. Thus, the term mTBI will be used throughout this thesis.

Aetiology and epidemiology

There are a wide range of causes for mTBI. In adults, they most commonly result from road traffic accidents, assaults, falls and sports. In the United Kingdom, the annual incidence rate of hospital admission for TBI is 229/100,000 (Tennant, 2005) and in the US the rate is between 180-250/100,000 (Bruns & Hauser, 2003). Rates are likely to be much higher in non-western areas and are set to rise (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007). Around 80-90% of all TBIs are classified as 'mild' (Kraus, McArthur, Silverman, & Jayaraman, 1996; Thornhill, Teasdale, Murray, McEwen, Roy, & Penny, 2000; Yates, Williams, Harris, Round, & Jenkins, 2006). Incidence rates for mTBI vary considerably with age. A tri-modal relationship is typically revealed, with peak incidence rates in the very young, late adolescence/ young adulthood (17-25 years of age) and the elderly (Abelson-Mitchell, 2008; Bruns & Hauser, 2003; Tennant, 2005; Yates, et al., 2006). There is a male predominance of 2-4:1 across the ages, except perhaps in the very young, where the ratio is more equal (Abelson-Mitchell, 2008; Adelson & Kochanek, 1998; Bruns & Hauser, 2003). Low socio-economic status is also a risk factor (Hawley, Ward, Long, Owen, & Magnay, 2003; Tennant, 2005; Yates, et al., 2006).

These incidence studies are based on hospital admissions. Such figures are liable to underestimate the number of mTBIs that occur, as these often do not need prolonged medical attention and are usually discharged from emergency departments without admission (Vos, Battistin, Birbamer, Gerstenbrand, Potapov, Prevec, Stepan, Traubner, Twijnstra, Vecsei, & von Wild, 2002) or seen by the family doctor. It is also anticipated that reported rates are far below

actual incidence due to these injuries not being presented to health professionals at all (Adelson & Kochanek, 1998; House of Commons, 2001). A recent, prospective birth-cohort study of hospitalised and non-hospitalised mTBIs in 1265 individuals from 0-25 years of age demonstrates this discrepancy with a much higher annual incidence rate of 1.10-2.30 per 100, with an overall prevalence of 30% (McKinlay, Grace, Horwood, Fergusson, Ridder, & Macfarlane, 2008).

Diagnosis of mTBI

Severity of TBI is graded based on several clinical measures, for which diagnostic classifications provide criteria. These measures are the Glasgow Coma Scale (GCS) score, length of post-traumatic amnesia (PTA) and length of loss of consciousness (LOC). The Glasgow Coma Scale (Teasdale & Jennett, 1974) is a practical tool for recording the degree of consciousness of an individual who has suffered a TBI for initial and subsequent assessment. It has three domains; eye opening (score of 1-4), verbal responsiveness (score of 1-5) and motor responsiveness (score of 1-6), giving a total score of between 3 (indicating deep coma) and 15 (normal consciousness). A key limitation of GCS is that it is an "on-line" measure and cannot be accurately applied retrospectively, as scores may improve between the injury and being seen at an ED and GCS only provides an index of responsiveness at the time it is assessed (Ruff & Jurica, 1999). These assessments may occur at arbitrary times and GCS may not be properly recorded at all. Consequently, PTA and LOC are important measures to gauge severity as they can be assessed retrospectively. PTA may be defined as "a period of variable length following closed head trauma during which the patient is confused, disorientated, suffers from retrograde amnesia, and

seems to lack the capacity to store and retrieve new information" (Schacter & Crovitz, 1977, p. 151). It may be assessed by asking the individual to state what their first memory is after the incident and then asking "what happened next?" until a clear account can be given.

There are several classification systems for TBI that use these measures to guide diagnosis. The European Federation of Neurological Societies (EFNS) classify a TBI as mild if there is a GCS score of 13-15 on admission, LOC of less than 30 minutes and PTA of less than an hour (Vos, et al., 2002). The definition of mTBI by the American Congress for Rehabilitation Medicine is broadly the same, though PTA can be less than 24 hours (American Congress of Rehabilitation Medicine, 1993). Furthermore, some have suggested retrospectively diagnosing mTBI based from persistent post-concussion symptomology, such as in the Diagnostic and Statistical Manual 4th Edition (American Psychiatric Association, 1994). Difficulties associated with this suggestion are covered below.

The literature on mTBI, therefore, has several factors which may limit progress in the field. Firstly, different authors and fields use different terms, which may be synonymous or have other connotations. Secondly, there are different systems for the classification of mTBI, with no unified definition currently in universal usage. Thirdly, researchers do not necessarily use the established classification criteria, but rather there is a diverse range of definitions employed, such as classifying LOC of less than only 15 minutes as mild, with greater LOC being classified as moderate to severe. These discrepancies, in particular, make comparison of studies difficult, hence there is an inconsistent picture of what the phenomena under study actually is.

Is mTBI a homogenous population?

The above mentioned classification systems break mTBI down further into separate categories or grades of severity. Category 0 mTBI in the EFNS guidelines (Vos, et al., 2002) requires no LOC or PTA and a GCS of 15 (no change in consciousness); i.e. it only requires trauma to the head. Category 1 requires GCS of 15, but with LOC of less than 30 minutes and PTA less than an hour, whereas category 2 is essentially the same, but with the presence of risk factors (e.g. severe headache, vomiting, seizures and abnormal CT scan results). Finally, category 3 differs from category 2 in that the GCS score is 13-14 on admission. The American Congress for Rehabilitation Medicine system instead has five grades representing increasing length of retrograde amnesia and LOC, and thus increasing severity (American Congress of Rehabilitation Medicine, 1993).

Despite this heterogeneity in mTBI classification, the majority of the literature on outcome after mTBI has treated it as a homogenous population. However, there is growing awareness that this may not be prudent. For example, longer duration of PTA has been found to be associated with the development of both persistent PCS (Hessen, Anderson, & Nestvold, 2008) and persistent PTSD (Bryant, Creamer, O?Donnell, Silove, Clark, & McFarlane, 2009). Iverson (2006) compared those with "uncomplicated" mTBI to those with "complicated" mTBI, based on whether participants had a normal or abnormal CT scan respectively, on acute neuropsychological outcome. Visible structural brain damaged was related to increased risk for slow and/or incomplete recovery. However, the two groups could not be distinguished with logistic regression analysis, suggesting that the reasons for worse recovery remain poorly

understood. More research is therefore needed to explore whether mTBI needs to be treated as heterogeneous for the purposes of research into outcomes.

Morbidity

TBI is a leading cause of mortality and serious morbidity in developed countries (Paulson, 1988). According to the World Health Organisation, TBI will supersede many diseases as the major global cause of death and disability by the year 2020, with the resultant burden from medical care, rehabilitation and work-hours lost making it a pressing health concern (Hyder, et al., 2007). Such injuries have been pronounced a 'silent epidemic' (Langlois, Marr, Mitchko, & Johnson, 2005), because the subsequent neuropsychological and behavioural sequelae, which cause the most burden to the individual and their family (Fleminger & Ponsford, 2005; Ponsford, Olver, Ponsford, & Nelms, 2003), are not visible disabilities. There are three main, current foci for investigating outcome post mTBI: neurocognitive functions, PCS symptoms and PTSD. These will now be addressed in turn.

Neurocognitive functioning

One early, well-controlled study of 22 patients with mTBI compared to 19 matched controls indicated that a single "minor head injury" in those with no compromising prior conditions was related to mild, though probably clinically non-significant, neuro-cognitive difficulties 1 month post-injury (Dikmen, McLean, & Temkin, 1996). These difficulties were largely related to

concentration and new learning, but were not evident at 1 year post-injury, although disruption of everyday activities was extensive if "other system" injuries were also present. A meta-analytic review of studies from 1970-2004 of outcome in patients with mTBI across 9 cognitive domains (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005) found a moderate effect of mTBI on neuropsychological functioning. The effect of mTBI was greatest for delayed memory and fluency at 3 months post-injury. This was moderated by time since injury, patient characteristics and sampling methods, with samples selected from clinics or those involved in litigation having worse outcome than those prospectively recruited from EDs. However, in line with some of the discussion above, Pertab, James, and Bigler (2009) caution that meta-analyses finding non-significant clinical effects of mTBI at 3 months post-injury are considerably limited by combining mTBI samples that are heterogeneous due to sample differences in mechanism of injury, diagnostic criteria used, the assessment tools used and whether symptom groups were considered separately. This work has suggested that there may be a subset of those with mTBI that are at risk of poor outcome within the mTBI population as a whole

Post-concussion symptoms (PCS)

A constellation of post-concussion symptoms (PCS), such as headaches, dizziness, fatigue and cognitive difficulties, are common in the acute phase post-injury (Binder, 1986; Bohnen & Jolles, 1992), although these usually resolve by 1-3 months (Binder, 1986; Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, & Pepin, 2004; McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Yang, & Kelly, 2003; Ponsford, Willmott, Rothwell, Cameron, Kelly, Nelms, Curran, & Ng, 2000). However, a substantial subset of individuals may be left with persisting

PCS at 3 months (Meares, Shores, Taylor, Batchelor, Bryant, Baguley, Chapman, Gurka, Dawson, Capon, & Marosszeky, 2008) to over a year later (Dikmen, Machamer, Fann, & Temkin, 2010). Although such symptoms following head injury have been acknowledged for a long time (e.g. see Srauss & Sevitsky, 1934), it has been the recent wars in Afghanistan (Operation Enduring Freedom) and Iraq (Operation Iraqi Freedom) that have brought them to widespread interest (Hoge, McGurk, Thomas, Cox, Engel, & Castro, 2008; Lippa, Pastorek, Benge, & Thornton, 2010; Stein & McAllister, 2009).

Diagnosis of PCS

Currently, there are two main systems for diagnosing significant clinical levels of these symptoms; "post concussive syndrome" in the International Classification of Diseases 10th revision (ICD-10, World Health Organization, 1992) and "post concussive disorder" from the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV, American Psychiatric Association, 1994). The DSM-IV requires a) history of TBI involving significant cerebral concussion, b) cognitive deficits in memory and/or attention on formal testing, c) the persistence of three or more symptoms (sleep disturbance, fatigue, headache, dizziness, affective disturbance, irritability, personality change or apathy) for more than three months post-injury, d) new onset and/or worsening of symptoms, e) symptoms interfere with social functioning and f) exclusion of other disorders (e.g. dementia) that better account for symptomology. Criteria for (c) and (d) have a symptom threshold for onset, duration and discriminability from pre-existing disorders. Similarly, the ICD-10 criteria requires history of TBI and three or more symptoms (headache, dizziness, difficulty concentrating or with memory, fatigue, insomnia, irritability,

intolerance of stress, emotion or alcohol). However, the ICD-10 does not set a symptom threshold of onset or duration, require measurable cognitive deficit, clinical significance or discrimination from other disorders.

These two classification systems have good concordance between the symptoms involved (Boake, McCauley, Levin, Contant, Song, Brown, Goodman, Brundage, Diaz-Marchan, & Merritt, 2004), however, the added criteria of the DSM-IV over the ICD-10 can mean that vastly different rates of classifications are made between the two systems. Boake et al. (2004) assessed PCS three months post-injury in 178 participants with mild to moderate TBI and investigated the rates of classifications made between these two systems. Whereas 104 of these met criteria for post-concussive syndrome according to the ICD-10, only 19 were classified as having post-concussive disorder under DSM-IV criteria, with the difference being due to the cognitive deficit and clinical significance criteria imposed by this system. Thus, there is limited agreement between the two systems overall, with there being no clear evidence yet as to which is to be proffered (Boake, et al., 2004).

Furthermore, many researchers use alternative classifications developed for specific measures of symptoms associated with PCS based on frequency/severity/number of symptoms, or they use total scores to quantify severity of symptomology instead (Dikmen, et al., 2010; Hoge, et al., 2008; King, 1996; Meares, Shores, Taylor, Batchelor, Bryant, Baguley, Chapman, Gurka, & Marosszeky, in press; Meares, Shores, Batchelor, Baguley, Chapman, Gurka, & Marosszeky, 2006; Meares, et al., 2008; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009; Stulemeijer, van der Werf, Bleijenberg, Biert, Brauer, & E.Vos, 2006; Stulemeijer, van der Werf, Borm, &

Vos, 2008). For example, Stulemeijer et al. (2008) suggest a threshold of at least three symptoms out of 16 on the Rivermead Post-concussion Questionnaire (King, Crawford, Wenden, Moss, & Wade, 1995) rated as "severe" (being rated 3-5 on a 5-point Likert scale of severity, with 5 being most severe) as representing the presence of PCS. This lack of agreement of the diagnostic systems, and lack of consensus on how best to classify the disorder on measures, has led to confusion in the literature and probably, therefore, disparity in findings between studies and a lack of clarity on clincal implications of any such research.

Are these symptoms really "post-concussive"?

Work over the past decade has asserted that PCS may not be specific to mTBI (Iverson, Zasler, & Lange, 2007; Williams, Potter, & Ryland, 2010), but rather due to a number of factors (Carroll, et al., 2004; Ponsford, et al., 2000). Similar rates of classification of persistent PCS or symptom severity have been found after traumatic injuries not involving the head at both the acute stage (Meares, et al., 2008) and several months post-injury (McLean, Kirsch, Tan-Schriner, Sen, Frederiksen, Harris, Maixner, & Maio, 2009; Meares, et al., in press; Mickevičiene, Schrader, Obelieniene, Surkiene, Kunickas, Stovner, & Sand, 2004), as well as a high base-rate found in the normative population (Garden & Sullivan, 2010).

For example, Meares et al. (2008) found that 43.3% of those with an mTBI met criteria for PCS on a self report measure within the first 14 days of the injury, but so did 43.5% of controls with traumatic injuries not involving the head. Similarly, McLean et al (2009) followed up patients of an Emergency Department (ED) with either mTBI or other minor injuries at 1 month, 3 months

and 1 year post-injury to assess post-concussion symptomology via the Rivermead Post-concussion Questionnaire (King, et al., 1995). They found that diagnosis of PCS was not related to having a mTBI, but rather baseline mental and physical health. A follow up study of soldiers returning from Iraq with or without mTBI, Hoge et al (2008) showed that those with mTBI reported more PCS until the effect of post-traumatic stress was taken into account, at which point the difference disappeared.

Results such as these call into question whether TBI is a requisite for PCS, as is the case in the two diagnostic systems discussed above. Basing a diagnosis of mTBI from a PCS symptomology would thus seem imprudent. Indeed, calling this constellation of symptoms "post-concussive" may be erroneous if concussion is not the cause, as is the case for non-TBI samples. PCS has, therefore, been conceptualized as "neurogenic", i.e. resulting from neurological causes, but it seems that at least some of the symptoms are "psychogenic", i.e. resulting from psychological factors and mechanisms. Research is warranted to establish which symptoms are neurogenic and which are psychogenic, as it may be that TBI results in a different pattern of symptomology to other populations, and neurogenic symptoms may require different treatment and intervention than psychogenic symptoms.

In Study 1 we review which symptoms may be specific to mTBI. Furthermore, the influence of possible psychological factors in the genesis and maintenance of PCS should be investigated, as these are likely to be responsible for the symptomology in non-TBI populations and may be particularly amenable to amelioration with treatment compared to organic factors. One important psychological factor appears to be PTSD, another common issue after injury. Recent findings

suggest that PTSD symptomology may play a key role in the development and persistence of PCS symptomology (Belanger, Kretzmer, Vanderploeg, & French, 2010; Brenner, Ivins, Schwab, Warden, Nelson, Jaffee, & Terrio, 2010; Bryant, Marosszeky, Crooks, Baguley, & Gurka, 1999; Hoge, et al., 2008; Lippa, et al., 2010; Stein & McAllister, 2009). Study 2 provides a more in depth review of this work. We shall now, though, provide an overview to PTSD relevant to this thesis.

Post-traumatic stress disorder (PTSD)

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994), PTSD may develop after the experience of actual or threatened loss of life or serious injury to oneself or others, where this experience was accompanied by feelings of intense fear, helplessness and horror. Incidents that result in mTBI may well qualify as such antecedents (e.g. assaults, road traffic accidents). In order for PTSD to be diagnosed, symptoms across the three domains of re-experiencing (e.g. flashbacks, nightmares), avoidant behaviour/emotional numbing and hyper-arousal (e.g. difficulty sleeping, hyper-vigilance) must be present for longer than one month and must cause significant functional impairment.

The importance of memory quality in PTSD

The role of memory has been emphasised in recent accounts of the underlying mechanisms of PTSD. Ehlers and Clark (2000) have put forward a comprehensive cognitive model for persistent PTSD, based on previous theoretical and empirical work, which postulates that symptoms result from a sense of serious current threat. This persistent sense of current threat is argued to result from three main cognitive mechanisms; poor quality of memory for the trauma, excessively negative appraisals of the trauma and its consequences, and coping strategies that prevent change in the nature of the traumatic memories and appraisals. Data-driven processing during the trauma, characterised by overwhelming sensory impressions, is proposed to result in memories for the traumatic event that are poorly elaborated and integrated with other autobiographical memories, such that they are not contextualised within their correct place in the past and therefore feel current. Memories of this nature are thought to be predominantly sensory based (seeing, hearing or smelling aspects of the event during recall) and harder to verbalise into a narrative, being fragmented and poorly organized (the temporal order of events is confused). Traumatic memories are often difficult to intentionally recall, but there is a high frequency of intrusive, involuntarily triggered memories. These memories are often characterized by consisting of sensory impression more than thoughts and are predominantly visual, though can involve all modalities (for a review of the evidence base, see Ehlers & Clark, 2000). These characteristics make memories more likely to be intrusive. Additionally, they propose the presence of strong stimulus-response and stimulus-stimulus associations, such that reminders of the event (e.g. hearing a car horn, as they may have experienced prior to a road traffic accident) trigger traumatic re-experiencing.

Similarly, but taking a neuroscientific approach, Brewin and colleagues (Brewin, 2001; Brewin, Dalgleish, & Joseph, 1996) have proposed that separable brain regions may be involved in two distinct memory systems for supporting recall; one for verbally accessible memories (VAMs) and a second for situationally accessible memories (SAMs). Whereas VAMs are easily accessible by conscious though and readily verbalised, as is normal for autobiographical memories, SAMs encode different sensory and physiological aspects of events and are not readily accessible for conscious amendment and editing, leading to the characteristic re-experiencing central to PTSD. These assertions that the *characteristics* of traumatic memories play a key role in the genesis and maintenance of PTSD symptomology, not just the presence of such memories, has received some support from recent experimental work (see Study 3, this thesis, for a detailed review).

Are mTBI and PTSD mutually exclusive?

Initial empirical studies seemed to suggest that PTSD did not occur after mTBI (Mayou, Bryant, & Duthie, 1993). It was then proposed that PTSD and injury to the head causing loss of consciousness were mutually exclusive diagnoses (Spordone & Liter, 1995), because "patients who sustain PTSD simply cannot 'forget' the traumatic event, whereas patients who sustain mTBI (e.g. cerebral concussion) have no recollection of the event" (p.406). However, recent research has shown that sustaining an mTBI results in a similar prevalence of PTSD to those with other injuries not involving the head (Glaesser, Neuner, Lutgehetmann, Schmidt, & Elbert, 2004; Jones, Harvey, & Brewin, 2005; Mayou, Black, & Bryant, 2000). Indeed, using a sample of 1148 adult admissions after road traffic accidents, Mayou et al (2000) found that a brief period of unconsciousness, as incurred due to mTBI, significantly increased PTSD symptomology relative

to those without a period of unconsciousness, or even injury to the head, marking a complete contrast to their previous study (Mayou et al., 1993). There is, then, an apparent paradox, with the nature of memory for the event at the centre of the controversy (see Study 3 for a review of possible resolutions to this paradox). Given the importance of memory quality in recent theories, and the disturbance in awareness (GCS), consciousness (LOC) and memory encoding/retrieval (PTA) associated with mTBI (as discussed above), investigating the role of memory quality in the genesis and maintenance of PTSD symptomology following mTBI would be a valuable avenue of enquiry into this controversy.

Gender differences in PCS and PTSD

Female gender is often found as a risk factor for developing persisting PCS. For example, Bazarian and colleagues (Bazarian, Wong, Harris, Leahey, Mookerjee and Dombovy, 1999) found that women were 7.8 times more likely than men to receive a classification of PCD, according to the DSM IV (APA, 1994), and was the main explanatory factor in the investigation, as is in line with other prognostic models (Meares et al, 2008). Similarly, women have been shown to be at greater risk of developing post-traumatic stress (for a review, see McMillan, Williams and Bryant, 2003). However, there does not appear to be an interaction between the factors of gender and mTBI for risk of developing either of these disorders; the differences found between men and women appear consistent, regardless of whether there is injury to the head, for both PCS (Dikmen et al., 2010) and PTSD (McMillan, Williams and Bryant, 2003). Thus, the evidence suggests that gender is an additive risk factor for these conditions. As such, gender

differences are not a main focus of this thesis, though they are explored to investigate further whether or not they interact with mTBI in the post-injury interplay of PCS and PTSD.

SUMMARY OF KEY AREAS FOR FURTHER INVESTIGATION

Three key areas for further investigation into outcome after mTBI have been highlighted by the brief literature review above. Firstly, the nature of PCS needs to be better understood. Although TBI is required by the two classification systems for this condition, it appears that PCS is not specific to TBI. Therefore, work is needed to explore whether there is a subset of symptoms which are specific to mTBI and, hence, are really "post-concussive", as opposed to those that are observed after other minor injuries not involving the head, which would be better termed "post-traumatic complaints" (here, "trauma" would refer to physical trauma, as is the term used in the emergency medicine literature, as opposed to psychological trauma). Knowing which symptoms are specific to mTBI will help identify those with mTBI from their PCS symptomology, which is currently flawed due to apparent non-specificity of PCS classifications. Furthermore, those symptoms that are only common in an mTBI sample are likely to be neurogenic rather than psychogenic, as they related to injury to the head. Such neurogenic symptoms may require different forms of intervention and treatment to those which are psychological in nature.

Secondly, the influence of PTSD symptomology on the provenance of persistent PCS symptomology warrants further investigation, particularly in civilian samples, as most prior

studies in this vein of research have used military samples exposed to conflict. PTSD is also commonly experienced following the kind of events that are frequent causes of mTBI. Research suggests that PTSD may be a key psychological factor in the development and persistence of PCS. However, the way in which PTSD interacts with PCS in those with mTBI compared to other populations is still not well understood. It has been proposed that depletion in coping resources due to PTSD may particularly exacerbate PCS symptomology in those with mTBI relative to controls (Bryant & Harvey, 1999), though it is not clear how PTSD may interfere with neurogenic PCS symptoms, compared to psychogenic symptomology. Also, due to overlapping symptomology between PCS and PTSD, which other studies have not carefully controlled for, the unique influence of PTSD should be investigated on the development of persistent PCS symptoms, over that of acute PCS symptoms.

Thirdly, more work is needed to shed light on the controversy of PTSD occurring following mTBI, particularly testing proposals of recent cognitive theories. There is some evidence that mTBI is a protective factor in the development of PTSD due to lack of declarative memory for the traumatic event. However, recent studies have found PTSD in mTBI samples, sometimes at similar to greater levels than in individuals without mTBI. Possible reasons for this are 1) that mTBI is associated with a different constellation of symptoms, specifically less re-experiencing, but greater avoidance and hyper-arousal symptomology, and 2) that mTBI results in a poorer quality of memory for the event. Poor quality of memory, characterized by being hard to put into words, being highly sensory and poorly contextualized in an individual's temporal, autobiographical account, has been asserted to be a key factor in the persistence of PTSD symptomology (Brewin, et al., 1996; Ehlers & Clark, 2000). The effect of mTBI, with the associated loss of awareness immediately following injury, possible loss of consciousness and

post-traumatic amnesia (a disturbance of memory formation and retrieval), on memory quality, and the resulting impact on development of PTSD symptomology, has not yet been thoroughly explored.

Additionally to these three key areas for further investigation, the literature suggests that treating mTBI as a homogenous sample may not be prudent. Thus, explorations of these areas may benefit from an examination of differences between those with very mild TBI, where no damage to the brain may in fact be indicated, to those with more complicated mTBI; for example, where there has been LOC, PTA or lowered awareness on presentation. A meaningful discrepancy between "uncomplicated" and "complicated" mTBIs may be responsible for the wide range of findings in the literature, and the resultant lack of clarity in outcome following mTBI.

A PROSPECTIVE, LONGITUDINAL INVESTIGATION

In order to investigate outcome after mTBI, specifically addressing the key issues highlighted above, a longitudinal study was conducted. Participants were prospectively recruited from consecutive admissions to the ED of the Royal Devon and Exeter Hospital between November 2008 and October 2009 with either mTBI or orthopaedic injury. Recruiting participants prospectively from the ED allows a more thorough investigation, as artifacts from sample biases

due to cross-sectional designs and recruiting individuals from clinics (where those who attend do so due to high symptomology), or those involved in litigation, are avoided. Participants were approached for recruitment at two weeks post-injury (time 1, T1) and were contacted for a follow-up assessment at three months post-injury (time 2, T2), as well as one year post-injury (Time 3), though analyses of this time point are not included in this thesis due to the drop-out rate making the participant numbers too low to make analyses feasible. Informed written consent was obtained prior to participation. Data collection for Time 3 finished in October 2010.

The study was approved by the regional National Health Service Research Ethics Committee. Patients were eligible for participation if they were aged between 18-65 years and had received a diagnosis of either mTBI or an upper limb fracture, which served as our comparison group (see below for reasons for this choice). Exclusion criteria were attendance as a result of domestic violence or sexual assault, previous attendances within the past 5 years for similar injuries (as an indicator of domestic violence), attendances for urgent care for a pre-existing medical condition, significant history of mental health problems or learning disabilities and inability to complete questionnaires due to non-fluency in English. These exclusion criteria were set to avoid possible biases, as indicated in the literature.

Participants completed the same questionnaire at all time points. This questionnaire included questions about demographic information (age, gender, highest educational attainment), pre-injury functioning (previous stress/trauma, need for mental health support, hospitalization for mTBI), attributions surrounding the event (e.g. fear of death, perceived severity of the event, attributions of blame), the Rivermead Post-concussion Questionnaire (RPQ, measuring PCS,

King, et al., 1995), the Trauma Screening Questionnaire (TSQ, measuring PTSD sympotmology, Brewin, Rose, Andrews, Green, Tata, McEvedy, Turner, & Foa, 2002) and the Trauma Memory Quality Questionnaire (TMQQ, measuring memory quality of the injury event, Meiser-Stedman, Smith, Yule, & Dalgleish, 2007), as well as measures of group memberships and social support felt before and after the injury (analyses of these measures are not included in this thesis). Additionally, participants gave permission for their medical records to be accessed, which allowed us to have information for the mTBI group on their GCS, whether or not they had been unconscious and whether they had PTA. This information was used to determine whether the mTBI could be considered "uncomplicated" (with no LOC, PTA or GCS below 15) or "complicated" (having any of the following in any combination: GCS between 13-14, LOC and/or PTA). Thus, individuals with uncomplicated mTBI (by our definition) only had trauma to the head as the diagnostic basis for mTBI and as such is the same as Category 0 of the EFNS guidelines (Vos, et al., 2002).

More details about the procedure used, measures employed and the samples obtained are given in the three studies where relevant. The study questionnaire can be found in Appendix 2. Lastly, the original protocol submitted to the National Health Service Research Ethics Committee is in Appendix 3.

Reasons for our choice of comparison group

Upper limb (e.g. wrist) fractures were deemed by the head clinician of the ED to be a suitable comparison group in terms of injury severity and functional impairment post-injury. These orthopaedic injuries and mTBIs are both common consequences of traumas such as road traffic

accidents (RTAs), assaults and falls. Although similar in frequency, severity and aetiology, they differ in important respects. As the name implies, mTBI involves trauma sustained to the head (brain, scalp, skull) and is associated with altered consciousness (GCS, LOC) and a disturbance in memory formation and retrieval (PTA). Orthopaedic injury, however, pertains to trauma sustained to the musculoskeletal system (typically arms and/or legs), including but not limited to, fracture breaks or torn ligaments, and does not involve disturbance of consciousness or memory. The short-lived cognitive problems and patchy, incomplete memory likely after mTBI may lead to them being unable to construct a complete "story" of what happened to them, which may hamper recovery and put them at greater risk of PTSD symptomology (see McMillan, Williams, & Bryant, 2003). PCS are also meant to be specific to mTBI, according to the classification systems for this symptomology, though recent work suggests this is controversial. Thus, patients with minor orthopaedic injuries are a suitable comparison group for those with mTBIs because the effect of injury to the head can be examined whilst controlling for aetiological factors and any biases due to hospital treatment.

THREE STUDIES

In line with the three key areas for further research highlighted from the literature above, three studies were made of the data collected through the prospective, longitudinal investigation. An overview of the main aims and findings of these is given below.

Study One: Aims

Study One is titled "Neurogenic and Psychogenic Acute Post-concussion Symptoms following mTBI". This study had three aims; 1) the primary focus was to identify which PCS symptoms are specific to mTBI and therefore likely to be neurogenic. Specifically, the symptoms of headaches, dizziness and nausea were thought to be neurogenic, as these are common symptoms of mTBI on presentation to EDs and have been found to be separable from other PCS symptoms by factor analysis (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005). We predicted that individuals with complicated mTBI (those with evidence in medical notes at admission of altered consciousness (GCS, LOC) and/or disturbance in memory (PTA)) would experience worse symptomology on these items compared to those with orthopaedic controls, but similar severity of symptoms on the other symptoms. 2) We wanted to assess whether it was prudent to split mTBI samples into "complicated" and "uncomplicated" groups, by examining differences between these group and comparing them to orthopaedic controls. Finally, we report the rates of clinically meaningful PCS symptoms across the groups, using established criteria for our measure. These analyses were made with the data from the first time point, at two weeks post-injury, as understanding differences in acute symptomology may help explain differences at three months and be particularly useful for informing interventions and treatments.

Study One: Main findings

Neurogenic PCS symptoms were identified in the acute phase after injury. As expected, patients with complicated mTBI reported greater severity of headaches, dizziness and nausea, as well as concentration difficulties, than orthopaedic controls. However, the severity of other symptomology measured on the RPQ was not significantly different between these groups. Differences were evident between the two mTBI samples on the items of dizziness, nausea, fatigue, sleep disturbance and concentration difficulties. The uncomplicated mTBI sample tended to have the lowest symptoms severity of any group. These findings suggest that complicated mTBI can be identified by a subset of PCS symptoms, with headaches, dizziness, nausea and concentration difficulties appearing to be neurogenic, rather than due to psychological factors, which would be common for all groups. Furthermore, mTBI was found to be heterogeneous and care should be taken in future work when making conclusions about PCS after mTBI where this has not been accounted for.

Study Two: Aims

Study Two is titled "The Prospective Course of Persistent Post-Concussion Symptomology and Its Influences: The Role of Post-Traumatic Stress". This study followed on from Study One and had two main aims; 1) to assess change in PCS symptomology between two weeks post-injury and three months post-injury across complicated and uncomplicated mTBI groups, as well as orthopaedic controls. Importantly, we also classified participants as having likely PTSD or not, based on criteria developed for the TSQ, and examined the impact of having such a classification

on PCS over time and across the three diagnostic groups. Thus the primary aim of this study was to examine the interplay between PCS and PTSD. 2) In order to understand the influences on persistent PCS symptomology, we established a predictive model using demographic, pre-injury, injury-related and post-injury factors. Specifically, the individual contribution of acute and persistent PTSD symptomology on persistent PCS was examined by using a hierarchical linear regression analysis to form this model.

Study Two: Main findings

Very little change over time was found in both mean PCS symptom scores and rates of those with three or more severe PCS symptoms between individuals with complicated mTBI and orthopaedic controls. There was, though, some evidence for improvement of symptomology in the uncomplicated mTBI sample. Those with likely PTSD tended to have worsening PCS symptomology over time, whereas those without tended to have better recovery. Indeed, elevated levels of PCS symptomology were only found in those with likely PTSD. PTSD exacerbated both neurogenic (headaches, dizziness and nausea) and psychogenic PCS symptoms in the complicated mTBI group, but only psychogenic symptoms in orthopaedic controls. A hierarchical linear regression, controlling for demographic, pre-injury and injury related variables, found that acute PCS symptomology was most predictive of persistent PCS symptomology, but persistent PTSD symptomology was also highly related. A path analysis suggested acute PTSD symptomology had an indirect role in the maintenance of PCS and a model is proposed.

Study Three: Aims

Study Three is titled "Post-Traumatic Stress after Mild Traumatic Brain Injury: The Influence of Memory Quality". In this study, we assessed change over time in PTSD symptomology in those with mTBI compared to orthopaedic controls, between two weeks and three months post-injury. We also investigated differences in memory quality, expecting individuals with mTBI to have poorer quality of memory, characterized by being hard to put into words, highly sensory and fragmented, than controls due to the potential lessened awareness, loss of consciousness and disturbance in memory associated with mTBI. We also used a stepwise linear regression to select the most influential predictors of persistent PTSD symptomology out of various demographic, pre-injury, injury-related and post-injury factors. We expected individuals with mTBIs to have similar levels of PTSD to orthopaedic injury controls and that memory quality would be an influential predictor of persistent PTSD symptomology.

Study Three: Main findings

No differences were found between the mTBI group and controls in overall symptomology, distribution of symptoms across the clusters of PTSD (re-experiencing and hyper-arousal), change of symptomology over time, or, contrary to our expectation, in characteristics of trauma memory. Poorer memory quality was highly correlated with worse PTSD symptoms on total PTSD symptomology, as well as symptomology on both the re-experiencing and hyper-arousal cluster subscales, at both time points. Memory quality and attributions of blame to others were

the only variables selected by the stepwise regression procedure as predictors of persistent PTSD symptoms.

INTEGRATED DISCUSSION OF FINDINGS

Post-concussion symptomology after mTBI

There has been a great deal of controversy in the literature regarding post-concussion symptomology following mTBI. In particular, recent work suggests that calling the symptomology "post-concussive" may not be accurate, but rather misleading, as this symptomology has appeared to not be specific to mTBI, but also occurs to a similar extent in those with minor injuries not involving the head (e.g. McLean, et al., 2009; Meares, et al., 2008). We believe that our work has helped to bring greater clarity to this controversy. We utilized a popular self-report measure of PCS (the RPQ) for both analysis of continuous, symptom severity scores and using presence of three or more "severe" symptoms as criteria for having a PCS classification. In terms of overall symptomology, in both continuous and categorical analyses, individuals with "complicated" mTBI (having any of the following: GCS of 13-14, any LOC and any PTA) were not found to differ to those in our orthopaedic control group. This was the case at both two weeks post-injury (Study One) and three months post-injury (Study Two), by which time the symptomology could be considered persistent. Furthermore, in Study Two we found that PCS did not decrease significantly over time in either mean symptom severity or rate of

classification of PCS, and that there were no differences between the complicated mTBI group and orthopaedic controls in change over time in symptomology, though there was evidence of recovery in the uncomplicated mTBI group (who only had trauma to the head with no complicating factors). Indeed, the complicated mTBI group and orthopaedic controls were very similar in the rate of new cases of PCS classifications between Time 1 and Time 2 and around 80% of those with a PCS classification in these groups at Time 1 continued to have a classification at Time 2.

However, looking only at *overall* symptom severity and rate of classification of PCS on this measure (and this measure is typical of PCS measures) masks an important difference between the symptom profiles of those with complicated mTBI compared to controls. At both the acute phase post-injury (Study One) and when symptoms were persistent (Study Two) a subset of symptoms was identified that were specific to at least those with complicated mTBI, though less so for the uncomplicated mTBI group. The cardinal symptoms of mTBI were headaches, dizziness and nausea/vomiting. These three symptoms are commonly seen in individuals who present to Emergency Departments with mTBI (McCrory, Johnston, Meeuwisse, Aubry, Cantu, Dvorak, Graf-Baumann, Kelly, Lovell, & Schamasch, 2004) and have previously been shown to predict later PCS (de Kruijk, Leffers, Menheere, Meerhoff, Rutten, & Twijnstra, 2002; Stulemeijer, et al., 2008). Factor analysis of the RPQ also found them to measure a different construct to the other 13 symptoms of the measure (Eyres, et al., 2005), hence these symptoms were treated as a subscale in our analyses.

Finding this subset of symptomology unique to mTBI has several implications. Firstly, it indicates that (complicated) mTBI can be identified retrospectively by assessing PCS (as discussed above), as long as this is based off a small subset of symptoms (particularly headaches, dizziness and nausea). Identifying mTBI in this way is only suggested if other factors are not known, namely level of responsiveness immediately after the injury (GCS, which cannot be assessed retrospectively), length of loss of consciousness and post-traumatic amnesia. Secondly, since these symptoms represent only a small portion of the proposed symptomology of post-concussive syndrome (for example, 3 items out of 16 on the RPQ), the criteria of PCS needs to be refined. Currently, both classification systems for persistent PCS require TBI (American Psychiatric Association, 1994; World Health Organization, 1992), yet are not specific to TBI. If a classification of PCS is to be useful, it either needs to become specific to TBI in the symptoms required, or not require TBI for a diagnosis and be re-defined into a more general post-trauma condition. For example, the term "post-traumatic complaints" has already been coined (de Kruijk, et al., 2002) to avoid the misleading "post-concussion" terminology. The lack of agreement between these two systems in rates of classifications is also cause for a re-shape of diagnostic criteria (Boake, et al., 2004).

Finally, those symptoms specific to mTBI are indicated to be neurogenic, being caused by neurological factors, whereas symptoms that are experienced regardless of whether trauma to the head was sustained are indicated to be psychogenic, resulting from psychological factors. The fact that headaches, dizziness and nausea are common on presentation to EDs following mTBI (and are indicators of TBI) adds weight to this assertion. There are two further implications from this. Firstly, neurogenic symptoms may require different intervention and treatment to psychogenic symptoms, as the root cause of the symptoms are different. However, psychological

factors may well be responsible for the maintenance of such symptoms due to lessening of coping and cognitive resources. Secondly, psychological factors are implicated in the genesis and maintenance of a wide range of symptoms (cognitive, somatic and affective) across a wide range of populations following minor injuries. Study Two shed further light onto these two implications by examining the interplay of post-traumatic stress and post-concussion symptomology, which is discussed below.

Post-traumatic stress after mTBI

PTSD symptomology is a common response to events that evoke feelings of fear, helplessness and horror, such as road traffic accidents and assaults, which are also common causes of mTBI. However, there has been controversy over the development of persistent PTSD following mTBI, because PTSD is thought to be based on declarative memory of the traumatic event, whereas mTBI is associated with loss of consciousness, amnesia and disturbance in memory, which has been proposed to make the two conditions mutually exclusive (Sbordone & Liter, 1995). On the other hand, studies have since found that PTSD can develop after mTBI (e.g. Mayou, et al., 2000). Indeed, our examination of levels of PTSD symptomology, based on the number of symptoms reported on a 10 item screening measure, rather than an established PTSD diagnosis, found no differences between individuals with mTBI compared to orthopaedic controls without injury to the head. Furthermore, our mTBI sample did not differ from controls on the rate of recovery of PTSD symptomology over time, with similar rates of acute stress symptomology at two weeks post-injury as to persistent symptomology at three months. Previous work has found that re-experiencing symptomology may be reduced in those with mTBI (Gil, Caspi, Zilberman

Ben-Ari, Koren, & Klein, 2005; Jones, et al., 2005). We found no differences between individuals with mTBI and controls on the distribution of symptoms across the re-experiencing and hyper-arousal clusters (the avoidance cluster was not assessed) across time points. We therefore did not find evidence that mTBI is a protective factor for the development of PTSD. These disparate findings in the literature may be due to variability in methods, samples and measures used across studies.

Our findings in Study Three support cognitive theories that posit that characteristics of trauma memory play a key role in the genesis and maintenance of PTSD (Brewin, et al., 1996; Ehlers & Clark, 2000). We found that poorer memory quality, indicated by memories being harder to put into words, highly sensory and fragmented (being more like a slideshow than a continuous film, as is normal in autobiographical memory), was highly correlated with PTSD symptomology on both re-experiencing and hyper-arousal clusters at both the acute phase and three months post-injury. Measures of memory quality were selected by a stepwise regression procedure, with attribution of blame for the event to someone else being the only other variable selected, for a model of persistent PTSD symptomology. Memory quality was not affected by mTBI and did not tend to change over time.

Our finding that less clear and detailed memories, as well as personal attributions associated to it, led to greater PTSD symptomology, regardless of injury type, suggests a need for meaning in explaining the trauma, a clear story of what happened. Similarly, attributions of blame have previously been found to be related to greater PTSD symptomology (Williams, Evans, Needham, & Wilson, 2002) and worse recovery (Janoff Bulman & Wortman, 1977) after traumatic injury.

Supporting this idea is the finding that the most effective treatment for PTSD, according to a recent meta-analysis of 38 randomised control trials of various psychological therapies (Bisson, Ehlers, Matthews, Pilling, Richards, & Turner, 2007), is trauma-focused cognitive behavioural therapy (TF-CBT). TF-CBT specifically addresses individuals' troubling memories of the traumatic event and their personal meanings of the event and its consequences. Our findings therefore suggest that TF-CBT should be beneficial for mTBI patients suffering from PTSD, as well as those without TBI.

The interplay of concussion and traumatic stress symptoms

Thus far, post-concussion symptomology and post-traumatic stress symptomology have been discussed individually. Aside from a small subset of symptoms, individuals with mTBI were not distinguishable from orthopaedic controls in PCS, nor were there any differences in PTSD between these groups. A key focus of this thesis, however, is the interaction of these two symptomologies after mTBI, which was addressed by Study Two; specifically, it investigated the influence of PTSD on the provenance of persistent PCS. PTSD was found to have a sizeable impact on the severity of PCS. We classified those who reported the presence of just three or more PTSD symptoms out of the ten items on the TSQ as having likely PTSD. Those meeting this criterion had considerably more severe PCS than those who did not, and showed a trend for worsening PCS over time in comparison to the trend for recovery found in those not meeting the criterion. Further partitioning of this effect revealed an interesting interaction between PTSD and mTBI, such that individuals with complicated mTBI with co-morbid PTSD experienced greater

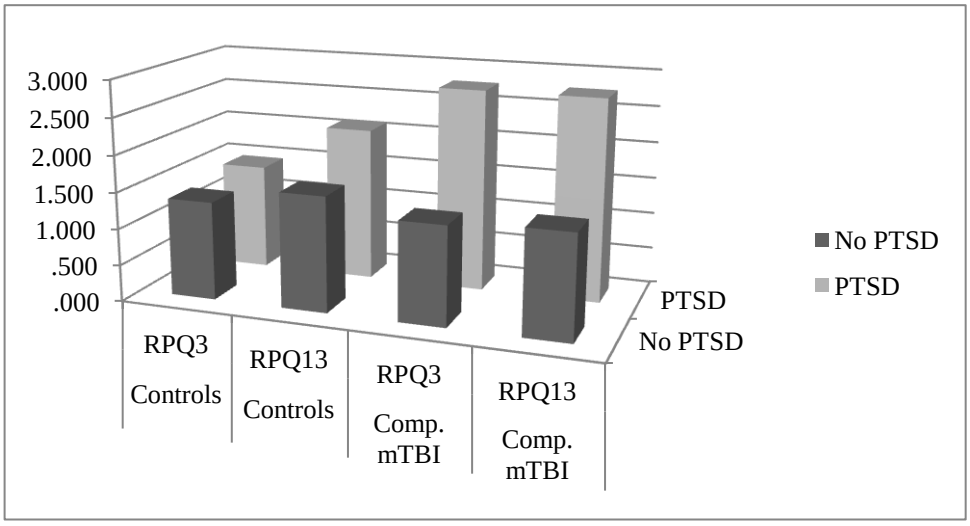
PCS symptomology than those without PTSD, and than orthopaedic controls regardless of PTSD classification.

This interaction is consistent with work reported in the literature. Bryant and Harvey (1999) found that, in a sample of road accident survivors, 46 of whom had mTBI and 59 who did not, PCS was more evident in mTBI patients with PTSD than those without, and in mTBI patients than in controls. They concluded that PCS is mediated by neurological and psychological factors, as is supported by our work as a whole. Hoge et al (2008) investigated physical outcome, including post-concussive symptoms, in a large sample of 2,525 soldiers; 124 with injuries involving loss of consciousness, 260 with injuries involving altered mental status and 435 with other minor injuries. Soldiers experiencing a loss of consciousness were at far greater risk of PTSD, and had significantly worse physical outcomes and PCS than those with other minor injuries. However, when the effects of post-traumatic stress and depression were controlled for, mTBIs were only uniquely associated with persistent headaches, but no other physical outcomes differentiated them from other groups. Similarly, Lippa et al (2010) found that post-traumatic stress accounted for a substantial portion of the variance of PCS severity in veteran outpatients with a history of mTBI.

Our findings extend this literature, as we partitioned the effect further still and found a triple interaction between PTSD, mTBI and type of PCS (neurogenic or psychogenic). In Figure 1 below, we reproduce the graph of these results (Study Two, Figure 8). The scale of this graph is mean PCS symptom severity, which is between 1 (no problem) and 5 (severe problem), where 3 can be considered a clinically meaningful symptom severity (see Stulemeijer, et al., 2008). This

graph shows that very little difference was evident between individuals with mTBI and orthopaedic controls without PTSD, even on the neurogenic PCS symptoms (headaches, dizziness and nausea, as measured by a subscale of the RPQ, here termed the RPQ3). In fact, the means for these groups are very close to 1 (no problem). In contrast, it can be seen that PTSD is associated with greatly elevated levels of PCS in complicated mTBI patients for both the neurogenic symptoms and the psychogenic symptoms (termed the RPQ13, measuring the remainder of the symptoms). Indeed, the mean scores for both these scales are similar and are both close to 3, the criteria for being clinically meaningful, indicating that complicated mTBI with co-morbid PTSD symptomology produces substantial PCS. For orthopaedic controls, PTSD is only associated with a moderate increase in psychogenic symptoms.

Figure 1 The interaction between condition, PTSD at T2 and RPQ scale (the RPQ3 measures headaches, dizziness and nausea/vomiting).



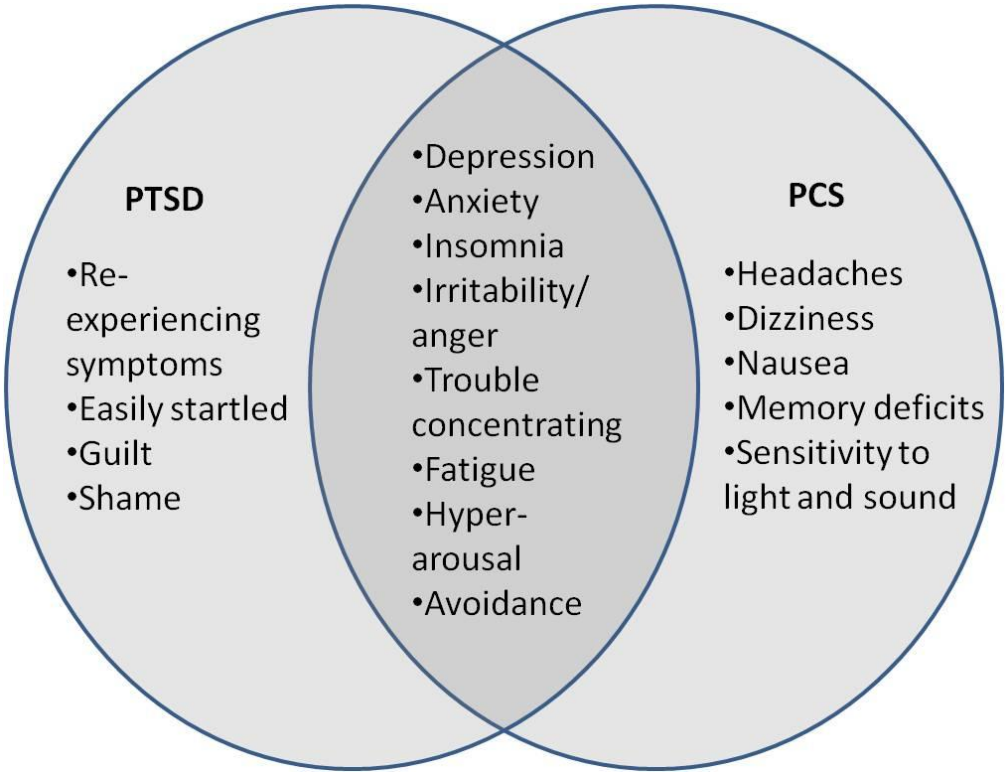
As discussed above, the symptoms of headaches, dizziness and nausea were found to be likely to have a neurological basis (Study One and Study Two), yet the provenance of these symptoms appears to be mediated almost entirely by post-traumatic stress symptomology. The exact reason for this is not clear, but it seems plausible that PTSD symptomology hampers the resolution of these symptoms by increasing cognitive demand and lessoning coping resources in the same way as is proposed for the exacerbation of psychogenic symptoms. An important implication of this finding is that neurogenic PCS symptoms may be treatable – to some degree - in the same way as psychogenic symptoms. Specifically, treating PTSD symptomology may reduce both neurogenic and psychogenic PCS symptomology, as well as co-morbid PTSD symptoms.

We established a model of the influence of PTSD on persistent PCS symptomology by investigating the associations between acute and persistent PTSD and PCS classification and through a hierarchical linear regression (HLR) in our total sample (mTBI and orthopaedic groups together). Acute PTSD classification was highly associated to both acute and persistent PTSD, as was persistent PTSD classification. However, these tests did not allow us to control for a number of possible extraneous factors, such as demographics, pre-injury mental health status and injury-related factors. Additionally, the overlap between PTSD symptomology and PCS symptomology, as shown in Figure 2 below (reproduced from Study Two, Figure 1), was likely to be a significant confounding factor in the examination of the interaction of these two conditions. To avoid this, three symptoms that were nearly identical between the RPQ and TSQ were removed from the TSQ before being entered into the HLR, leaving five re-experiencing symptoms and two hyper-arousal symptoms relating to hyper-vigilance. Controlling for the other possible extraneous variables listed above, the HLR found that only PCS symptoms at two weeks post-injury and PTSD symptoms at three months post-injury were significantly associated to

persistent PCS symptomology. Together, these two variables accounted for over two thirds of the variance in symptom severity scores for PCS at three months, with acute PCS accounting for 37.3% of the variance and persistent PTSD accounting for just 3.7%.

As can be seen in Figure 2 below, problems with concentration is a common symptom of both PCS and PTSD. In PCS, this is most likely due to the effect of trauma on cognitive processing and the resultant extra cognitive load meaning that there is less capacity or cognitive resources for concentrating, whereas such problems in PTSD may be due to re-experiencing symptoms, unpredictable flashbacks and/or being hyper-vigilant and easily startled, as well as extra cognitive load again being a factor. Study One found that those with complicated mTBI had greater difficulties with concentration than the other two groups in the acute phase post-injury. Results from Study Three reveal that this is not due to PTSD differences between the groups. It appears from these results, then, that concentration difficulties were likely to have a more neurological basis in our sample, though Study Two did not specifically look at this symptom, so it cannot be said if this was due to those specifically reporting concentration as a problem also having greater PTSD symptomology, which was found to mediate PCS as discussed above.

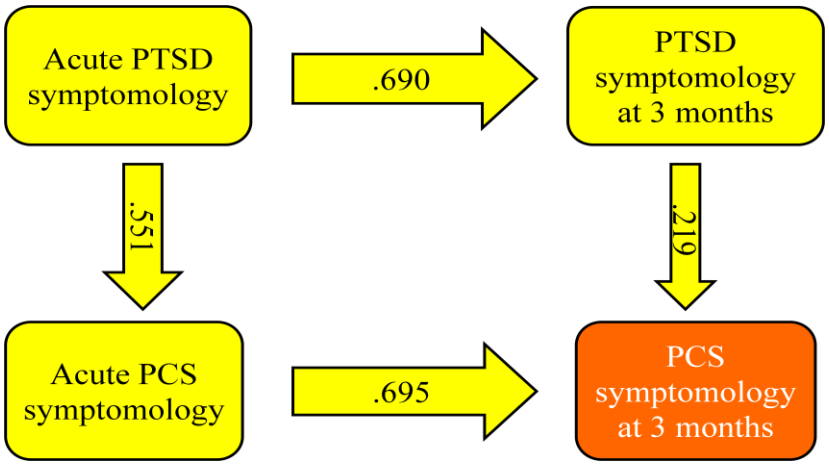
Figure 2 Overlapping symptomology between PCS and PTSD



As stated above, acute PTSD classification appeared to be highly related to PCS classification at both time points, but, in the presence of other variables, acute PTSD symptomology did not predict PCS scores at three months post-injury. Therefore we postulated an indirect effect of acute PTSD symptomology on persistent PCS by influencing both persistent PTSD and acute PCS symptomology. A path analysis was performed on the model displayed below in Figure 3 (reproduced from Study Two, Figure 13). The size of the arrows and the standardized Beta weights reported within them represent the strength of the relevant associations. This model supports the suggestion of an indirect effect of acute PTSD on persistent PCS, which is also supported by recent work finding that the strength of association between PTSD and PCS increases over time (Meares, et al., in press). This model indicates that treatment of PTSD (to reduce both PTSD and PCS, as discussed above) should be carried out in the acute phase after

injury, as doing so may prevent both PTSD and PCS symptoms becoming persistent. Although persistent PTSD was found to be significantly associated to persistent PCS, the strength of this association was relatively low and the amount of additional variance explained by persistent PTSD was small in the HLR. This finding indicates that, although there is considerable interplay between PTSD and PCS, the two conditions are distinct.

Figure 3 Proposed model of influence of PTSD on persistent PCS symptomology.



The numbers in the path arrows are standardized Beta weights and represent the strength of the relevant association.

Heterogeneity of mTBI

Study One and Two separated those with uncomplicated mTBI from those with more complicated mTBI. Those with uncomplicated mTBI had very minor injuries, having not suffered reduction in awareness, any loss of consciousness or post-traumatic amnesia, whereas our complicated group was very broad, consisting of those with any indication of the above signs

of greater severity of injury. Complicated mTBI usually refers to those with established abnormalities on CT scans, though this information was not available to us. Despite the broad nature of our complicated mTBI group, a differing profile of PCS was observed at both the acute phase and at three months post-injury, though the magnitude of differences was rarely large. These results do suggest that those with very minor mTBI can expect a good recovery in terms of PCS. They also suggest that caution should be taken when assessing outcome after mTBI, as those with more complicated injuries are likely to have worse prognoses.

Future research directions

Research in this area is currently hampered by a lack of agreement on some key issues, which should be addressed in order to enable better quality work that can bring further light to the true nature of outcome after mTBI. Firstly, greater consensus over the criteria for diagnosing an mTBI would enable easier comparison of studies, which currently have great variability in, for example, the length of loss of consciousness and post-traumatic amnesia used as a criterion for mTBI. Secondly, the classification systems of PCS have been shown to be inadequate, both in their agreement to each other, and in the utility of their criteria, given that they require mTBI, but are not specific to mTBI, and as such are not optimal either for diagnosing "post-concussive" symptoms or general post-trauma symptoms.

The findings from this thesis suggest that treatment of PTSD in the acute phase after injury, especially using TF-CBT (as indicated by the role of memory quality and attributions), could be a successful intervention for both PCS and PTSD in both individuals with mTBI and those with

other minor injuries. For those with mTBI, our findings suggest that TF-CBT could reduce both neurogenic and psychogenic PCS symptoms. This assertion warrants proper investigation through randomised control trials (RCTs). Intervention for PCS typically involves providing individuals with information about PCS symptomology being a common, but transient phenomenon after mTBI. A meta-analysis of five studies up to 1997 found a modest, positive effect size for this kind of treatment in reduction of persistent PCS (Mittenberg, Canyock, Condit, & Patton, 2001). Thus, this form of treatment may form a useful control for TF-CBT in an RCT. A small number of studies have found cognitive behavioural therapy to be effective in reducing some PCS symptomology (for a review, see Williams, et al., 2010), though, to our knowledge, the efficacy of trauma-focused cognitive behaviour therapy at reducing PCS symptomology as a whole has not been ascertained.

Future work should also investigate further the influence of various psychological factors in the genesis and maintenance of persistent PCS. For example, there seems to be at least two routes by which post-traumatic stress symptomology could influence recovery; by contributing to a neurogenic process by lessening coping skills and cognitive resources, and/or by the negative appraisals of the trauma and its consequences leading to expectation as aetiology (see Whittaker, Kemp, & House, 2007). A more thorough examination of the psychological mechanisms involved in PCS development would thus be useful, especially if controlling for somatic factors, such as post-injury pain (e.g. Bryant, et al., 1999).

OVERALL CONCLUSIONS FROM THIS THESIS

The studies from this thesis provide clarification to some key areas of confusion in the literature. A subset of PCS symptoms (headaches, dizziness and nausea) is detectable at the acute phase after injury (within two weeks) that is specific to those with (more complicated) mTBI, meaning that mTBI can be identified retrospectively from these symptoms and that these symptoms are likely to be neurogenic. We found no evidence for mTBI to be a protective factor in the development of persistent PTSD, but found that the poor quality of traumatic memories, being hard to verbalise, highly sensory and fragmented, as well as attribution of blame for others, play a significant role in this, regardless of injury type, in line with cognitive theories. This suggests the need for a clear story and sense of meaning for a traumatic event, supporting the efficacy of TF-CBT. Furthermore, we found that PTSD interacts with PCS, particularly in mTBI, such that PTSD was associated with much greater neurogenic and psychogenic symptomology in this group, but only a moderate increase in psychogenic symptoms for orthopaedic controls. Thus, though mTBI may set the scene for at least neurogenic symptoms of PCS to occur, psychological mechanisms, particularly PTSD, have a significant role in the persistence of PCS. Specifically, our model suggests that acute PTSD has an indirect impact on persisting PCS by exacerbating acute PCS symptomology and leading to persistent PTSD, which both have a direct influence on persistent PCS. Taken together, these findings indicate that TF-CBT in the acute phase post-injury should not only reduce PTSD symptomology, as it was established for, but also all PCS symptomology in both individuals with mTBI and other minor injuries.

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Study One - Neurogenic and Psychogenic Acute Post-Concussive Symptoms Following MTBI

ABSTRACT

Background

The provenance of post-concussion symptoms (PCS) after mild traumatic brain injury (mTBI) is controversial, as similar rates have been found in other populations. This study aims to indentify which PCS are specific to mTBI, as opposed to those with injuries not involving the head. We also investigated differences between complicated and uncomplicated mTBI. Symptoms of headaches, dizziness and nausea were predicted to be more severe in the complicated mTBI group compared to orthopaedic controls.

Methods

Consecutive Emergency Department attendees were asked to complete the Rivermead Post-concussion symptom Questionnaire (RPQ) at two weeks post-injury. The sample consisted of 34 with complicated mTBI, 76 with uncomplicated mTBI and 47 with orthopaedic injury. Pre-injury factors were also measured and used as covariates in the analyses.

Results

Patients with complicated mTBI reported greater severity of headaches, dizziness and nausea, as well as concentration difficulties, than orthopaedic controls. However, the severity of other symptomology measured on the RPQ was not significantly different between these groups. Differences were evident between the two mTBI samples on the items of dizziness, nausea, fatigue, sleep disturbance and concentration difficulties. The uncomplicated mTBI sample tended to have the lowest symptoms severity of any group.

Discussion and conclusion

Neurogenic and psychogenic PCS were identified at the acute phase post-injury. Preliminary findings suggest that treating individuals with mTBI as a homogenous sample may not be prudent. Knowledge of this should inform prognostic models and the kinds of follow up support offered after leaving the Emergency Department.

INTRODUCTION

Mild Traumatic Brain Injury (mTBI) is a major public health issue and the term is often used synonymously with concussion. Around 90% of all TBIs are classified as 'mild' (Kraus, McArthur, Silverman, & al., 1996; Thornhill, Teasdale, Murray, McEwen, Roy, & Penny, 2000; Yates, Williams, Harris, Round, & Jenkins, 2006). Despite much research having been carried out into outcome following mTBI, there is still considerable confusion in the literature as to why

some are left with persistent concussion symptoms (for a review, see Williams, Potter, & Ryland, 2010). A more accurate diagnosis is crucial for appropriate management of symptoms at various points post-injury. An understanding of symptomology in the acute phase may prove particularly useful as this may have an immediate impact on recovery from the injury. Additionally, the aetiology of symptomology at the acute stage may precipitate a better grasp of how symptoms become persistent and thus aid identification of those at risk.

A mTBI is typically diagnosed (see Vos, Battistin, Birbamer, Gerstenbrand, Potapov, Prevec, Stepan, Traubner, Twijnstra, Vecsei, & von Wild, 2002) if there is trauma to the head with or without loss of consciousness (LOC) of up to half an hour, a Glasgow Coma Scale (GCS) score of 13-15 on admission (this is a measure of peri-injury responsiveness in which lower scores represent less responsiveness) and with or without post-traumatic amnesia (PTA). Immediate symptoms of acute mTBI include headaches, dizziness and nausea as well as physical signs, which may include unsteady gait, slurred speech, poor concentration and slowness when answering questions (McCrory, Johnston, Meeuwisse, Aubry, Cantu, Dvorak, Graf-Baumann, Kelly, Lovell, & Schamasch, 2004b).

For most people injured, acute symptoms ameliorate within hours, and then, typically, a person may be symptom free by around 10 days (McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Yang, & Kelly, 2003), hence the injury being described as "reversible" (Iverson, 2006; Ommaya & Gennarelli, 1974). Yet between 10 and 20% of those injured may be expected to have some ongoing problems, termed persistent Post Concussion Syndrome (PCS), weeks or months later (Kraus & Chu, 2005; Ruff & Weyer Jamora, 2009) and have been dubbed the

"miserable minority" (Ruff, Camenzuli, & Mueller, 1996). Criteria for diagnosing PCS can be found in the International Classification of Diseases 10 (ICD-10) section F07.2 and The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) research classification (e.g. Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, & Pepin, 2004). There is significant agreement between the two sets of criteria for general symptoms (Boake, McCauley, Levin, Contant, Song, Brown, Goodman, Brundage, Diaz-Marchan, & Merritt, 2004). However, in the DSM-IV objective cognitive impairment and disturbance in social or occupational functioning is required (McCauley, Boake, Pedroza, Brown, Levin, Goodman, & Merritt, 2008). Furthermore, within the ICD-10 criteria there is no point at which symptoms can be regarded as persistent whilst DSM-IV specifies 3 months. These symptoms typically fall into the cognitive (e.g. poor concentration and memory), affective (e.g. depression, irritability) and somatic (e.g. headaches, dizziness and nausea) domain clusters.

The provenance of such ongoing problems remains controversial. There is a lack of clarity as to whether certain signs, symptoms and cognitive functions are reliable post-concussion sequelae (Williams, et al., 2010). This is in part due to PCS apparently not being specific to mTBI, but also occurring in other conditions, such as depression, post-traumatic stress and other traumatic injuries (Bazarian, Wong, Harris, Leahey, Mookerjee, & Dombovy, 1999; Garden & Sullivan, 2010; Hoge, McGurk, Thomas, Cox, Engel, & Castro, 2008; McLean, Kirsch, Tan-Schriner, Sen, Frederiksen, Harris, Maixner, & Maio, 2009; Meares, Shores, Taylor, Batchelor, Bryant, Baguley, Chapman, Gurka, Dawson, Capon, & Marosszeky, 2008; Mickevičiene, Schrader, Obelieniene, Surkiene, Kunickas, Stovner, & Sand, 2004). For example, Meares et al.. (2008) found that 43.3% of those with an mTBI met criteria for PCS on a self report measure within the first 14 days of the injury, but so did 43.5% of controls with traumatic injuries not involving the

head. Similarly, McLean et al. (2009) followed up patients of an Emergency Department (ED) with either mTBI or other minor injuries at 1 month, 3 months and 1 year post-injury to assess post-concussion symptomology via the Rivermead Post-concussion Questionnaire (RPQ, King, Crawford, Wenden, Moss, & Wade, 1995). They found that diagnosis of PCS was not related to having a mTBI, but rather baseline mental and physical health. Following up soldiers returning from Iraq with or without mTBI, Hoge et al. (2008) found that those with mTBI reported more PCS until the effect of post-traumatic stress was taken into account, at which point the difference disappeared. Such findings raise questions as to the supposed neurological genesis of PCS. That is, it is not clear whether PCS are "neurogenic" and a result of trauma to the head, or whether they are "psychogenic", being caused by psychological factors.

One explanation for similar rates in diagnoses may be that the current criteria of PCS include generic post-traumatic symptomology, as well as post-concussive symptoms. Many studies have attempted to predict whether or not a patient has a diagnosis of PCS based on symptomology passing a set criterion, i.e. using cut-off values. Diagnoses by these means for non-head-injured populations might result from a different pattern of PCS symptomology than those with mTBI. This could mask persistent symptoms that have a genuine neurological basis, as opposed to a psychological basis. For example, Meares et al. (2008) classified participants as having PCS if 3 or more symptoms on a measure of 13 symptoms were rated as 3-5 on a 5 point scale of severity (5 being most severe). It is possible that the similar rates they found between mTBI patients and controls, discussed above, resulted from different clusters of symptoms being endorsed between the two groups.

More work is needed, therefore, to clarify which symptoms are a direct result of concussion, and, as such, can be correctly termed "post-concussive", by examining the symptom profiles of those with mTBI compared to controls. Research suggests at least three symptoms may be neurogenic: Headaches, dizziness and nausea/vomiting are all symptoms of PCS that are also commonly seen in the Emergency Department (ED) immediately after mTBI (McCrory, Johnston, Meeuwisse, Aubry, Cantu, Dvorak, Graf-Baumann, Kelly, Lovell, & Schamasch, 2004a), which have also been found to be highly predictive of PCS (de Kruijk, Leffers, Menheere, Meerhoff, Rutten, & Twijnstra, 2002; Stulemeijer, van der Werf, Bleijenberg, Biert, Brauer, & E.Vos, 2006; Stulemeijer, van der Werf, Borm, & Vos, 2008a).

These three symptoms have also been found to be separable from other post-concussive symptoms. The RPQ is one of the most widely-used, validated measures of PCS, but has been found to possess poor psychometric qualities if analysed as a uni-dimensional construct (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005). Having performed an exploratory factor analysis, Eyres et al. (2005) suggest that the RPQ should be analysed as two separate scales; one comprising of the items measuring headaches, dizziness and nausea/vomiting (henceforth referred to as the RPQ3), and the second containing the remaining items (the RPQ13). By splitting the measure in such a way, both subscales have acceptable reliability and validity. This appears to reinforce the assertion that these three symptoms measured by the RPQ3 specifically have a neurological vector.

A second reason for the comparable rates of PCS in mTBI patients and other populations may be that most studies have treated mTBIs as a homogenous group. There has been a growing

awareness in the literature that mTBIs can be fairly heterogeneous and that injuries can be individualised and graded by severity (Iverson, 2006). For example, the European Federation of Neurological Societies (EFNS) guidelines split mTBIs into categories 0-3 representing increasing severity or complication of the injury (Vos, et al., 2002). Category 0 requires no LOC or PTA or signs of TBI or other complicating factors and with a GCS of 15, whereas category 3 includes those with LOC, PTA, GCS of 13-14 and with or without risk factors (e.g. risk of haemorrhaging). However, despite decades of research into recovery after mTBI, little research has investigated the differences between category 0, "uncomplicated" mTBIs and those with more complex injuries, though there is evidence that indicators of complicated injury, such as longer PTA, are associated with persistent PCS (Hessen, Anderson, & Nestvold, 2008). Not treating mTBIs as heterogeneous may therefore fail to accurately capture the risk of persistent PCS of those with more 'severe' mTBIs.

A more accurate diagnosis is crucial for appropriate management of symptoms at various points post-injury. An understanding of symptomology in the acute phase may prove particularly useful as this may have an immediate impact on recovery from the injury. Additionally, understanding the aetiology of symptomology at the acute stage may provide insight into the processes by which symptoms become persistent and thus aid identification of those at risk. Those at risk may then be followed up and provided with information, for example, for self-monitoring, to ensure that their recovery is maximised.

The identification of early symptoms of persistent PCS using an established self-report measure is therefore critical. It is also important to include a control sample who have suffered an injury

not involving the head in order to distinguish between symptoms which are truly "post-concussive", i.e. have a neurological root, and those which are "general trauma" symptoms that may be experienced after any injury. More than this, research needs to investigate whether differences develop in acute outcome between those with complicated mTBI compared to uncomplicated mTBI.

In the present study we followed up ED attendees with mTBI or orthopaedic injuries at two weeks post-injury and assessed PCS using the RPQ. The mTBI sample was then divided into uncomplicated or complicated mTBIs based on neurological functioning on arrival. We intend to a) report the rates of clinically meaningful PCS for our three diagnostic groups, b) explore whether, on the basis of reported PCS, it is prudent to split mTBI samples into complicated or uncomplicated injuries and c) determine which symptoms on the RPQ are specific to mTBI and which are general trauma symptoms. Due to the co-morbidity of PCS with affective disorders such as depression and PTSD, we collected information on pre-injury experiences, as well as previous hospitalisation for head-injury, in order to control for these extraneous effects.

We predict that complicated mTBIs will report higher mean RPQ scores than uncomplicated mTBIs. However, we expect that complicated mTBIs will have comparable scores to orthopaedic controls on the RPQ13, though not on the RPQ3, which measures headaches, dizziness and nausea, as we believe these to be the symptoms most likely to be neurogenic, and therefore we would expect the complicated mTBIs to report higher mean scores on this subscale. We would therefore also predict that the complicated mTBI group would have a higher rate of clinically meaningful headaches, dizziness and nausea than the orthopaedic controls. Based on

many previous studies, we would also expect females to report more severe symptomology than males (Bazarian, et al., 1999; Meares, et al., 2008), but this difference should be stable across diagnostic groups.

METHOD

Adults with mTBI or orthopaedic injuries were prospectively recruited from consecutive ED attendances between November 2008 and October 2009. They were approached to participate via post at two weeks post-injury. The study was approved by the regional National Health Service Research Ethics Committee and informed, written consent was obtained from the participants. Inclusion criteria were age between 18-65 and diagnosis of either mTBI or an upper limb fracture. Exclusion criteria were attendance as a result of domestic violence or sexual assault, previous attendances within the past 5 years for similar injuries (as an indicator of domestic violence), attendances for urgent care for a pre-existing medical condition, significant history of mental health problems or learning disabilities and inability to complete questionnaires due to non-fluency in English.

Participants

A total of 157 attendees accepted the invitation to participate, 110 with mTBI and 47 with orthopaedic injury. The recruitment rate was a little higher for the orthopaedic group than for the combined mTBI sample (21.9% vs. 16.1% respectively), though this difference was not significant ($\chi^2 = 3.681$, df = 1, ns), and was 17.5% overall. The mTBI group was split into two subgroups; those with uncomplicated mTBI and those deemed to have complicated mTBI based on a GCS of 13-14 and/or reported LOC or amnesia in their medical notes. Thus, for the purposes of this study, uncomplicated mTBI is equivalent to "category 0" of the EFNS guidelines for mTBI, having just traumatic injury to the head with no LOC, amnesia or lowered GCS, and those with complicated mTBI would fall in categories 1-3, including any implication of complication.(Vos, et al., 2002) The final sample consisted of 47 orthopaedic controls, 76 with uncomplicated mTBI and 34 with complicated mTBI. See Figure 1 for a flowchart of recruitment into the study. As can be seen in Table 1, the groups did not differ significantly in terms of the ratio of men to women ($\chi^2 = 3.365$, df = 2, ns), or highest educational attainment ($\chi^2 = 1.920$, df = 4, ns), but reliable differences were evident in age ($F_{2,144} = 4.833$, p=0.009), with the complicated group tending to be younger than the other two diagnostic groups. Chi-square tests did not reveal any significant differences between the diagnostic groups in rates of those who had experienced three pre-trauma factors; previous stress/ trauma ($\chi^2 = .551$, df = 2, ns), previous need for mental health support ($\chi^2 = 2.914$, df = 2, ns) and previous admission for a head injury ($\chi^2 = .298$, df = 2, ns).

Non-responders with mTBI could not be divided into complicated and uncomplicated subgroups, as permission was not obtained to access their medical records (see below for the study procedure), so comparisons between our sample and non-responders use a combined mTBI group. The only data available for non-responders, other than injury type, was their age and gender. Chi-square tests found that responders were more likely to be women in both the orthopaedic control group (χ^2 = 7.519, df = 1, p=.006) and the combined mTBI group (χ^2 = 11.595, df = 1, p=.001). Independent samples t-tests also found that responders were significantly older for the orthopaedic sample (t_{213}=3.599, p<.001), as well as the mTBI group (t_{673}=5.676, p<.001). See Table 1 for descriptive data.

Figure 4 Flowchart describing the recruitment of participants and the final samples.

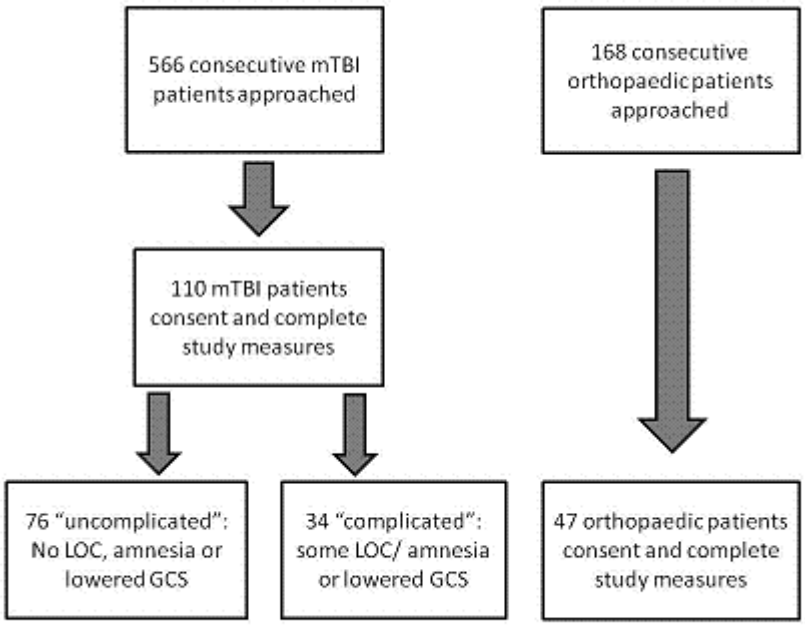


Table 1 Demographic and pre-injury characteristics of the samples.

Responders **n=157**		Orthopaedic injury n=47	uncomplicated mTBI n=76	complicated mTBI n=34
	Mean age (SD)	47.80 (13.42)	45.18 (14.09)	38.12 (14.68)
	Males (%)	15 (33.9)	37 (48.7)	14 (41.2)
Highest level of education (%):	Secondary school	12 (27.3)	25 (35.2)	8 (23.5)
	College	18 (40.9)	27 (38.0)	16 (47.1)
	University	14 (31.8)	19 (26.8)	10 (29.4)
Suffered major stresses / trauma prior to injury		9 (20.5)	11 (15.9)	7 (20.6)
Previous need for mental health support		3 (7.0)	6 (8.7)	6 (18.2)
Previous mTBI		5 (11.4)	10 (14.7)	4 (12.1)
Non-responders **n=734**		Orthopaedic injury n=168	Combined mTBI n=566	
	Mean age (SD)	39.36 (14.77)	34.36 (13.53)	
	Males (%)	88 (52.4)	363 (64.1)	

The number of participants involved in the above analyses occasionally differed from the overall sample n due to lack of responses for certain items.

Assessment procedure

Trained research assistants working at the hospital identified those who met the study's inclusion/exclusion criteria from the medical records of patients of the ED. A study information pack was sent via post to those identified as eligible for participation, explaining the nature and aims of the research and inviting them to take part, as well as including a consent form and the study questionnaire. The consent form also asked for permission for the researchers to access their medical records. Those that wished to participate completed the questionnaire and signed the consent form, then returned these to the researchers by post. Non-responders were therefore those that did not wish to take part in the research.

Participants were asked to complete the Rivermead Post-concussion Questionnaire.(King, et al., 1995) The RPQ consists of 16 items assessing the presence and severity of symptoms common in persistent post-concussion syndrome, such as headaches, dizziness and concentration problems, on a 5-point scale ranging from "1 - no problem" to "5 - severe problem". In addition to the RPQ participants reported their age and gender, and answered three questions relating to their pre-injury status, all of which required yes/no responses. These were "had you suffered a previous stress or trauma prior to this incident?", "had you needed any mental health support?" and "had you ever had a head injury that needed hospitalisation?". We also asked participants to report their highest education level completed, with options of "Secondary school", "College" and "University". In the UK, pupils sit exams at age 16 called "General Certificate in Secondary Education" (GCSEs), which are compulsory. They can then choose to go on to study Advanced Level courses (A-Levels), or equivalents, at college, which are 2-year courses that are required

for entrance to most university courses. Universities are separate from colleges in the UK; they provide higher education Bachelors degree courses, typically lasting 3 years, which can be taken after completing college (in most instances).

Access to participants' medical records was required in order to provide detailed information on the nature of their state on attendance at the ED, such as GCS, LOC and presence of amnesia for the mTBI group, which was used to determine whether the participant had a complicated mTBI, as outlined above. Participants gave their consent for this access on their study consent form.

Data analysis

This exploratory work required a number of comparisons. Due to the main effects of our treatment variables being significant, the follow up pair-wise comparisons between groups were protected from inflated Type 1 error rates, according to Fisher's Least Significant Difference theory. Where repeated measures are reported in the following ANOVAs and ANCOVAs, the Huyh-Feldt correction for sphericity will be used, and therefore degrees of freedom and *p*-values will be reported at the Huynh-Feldt criterion. All analyses were performed on Statistical Package for the Social Sciences (SPSS) version 18.0.

ANOVAs and ANCOVAs

There are a number of ways that the RPQ can be analysed. King et al.. (1995) designed the instrument to be used as a single measure of PCS and the mean scores of the 16 item scale

(RPQ16). However, Eyres et al.. (2006) caution against this as they did not find the RPQ to possess unidimensionality. In accordance with their suggestions, the items measuring headaches, dizziness and nausea/vomiting were used as a separate scale from the remaining 13 items; forming the RPQ3 and the RPQ13 respectively. The items of each scale were entered as levels of a single repeated measure for the scale in an ANOVA, with condition (orthopaedic controls, uncomplicated mTBI, complicated mTBI) and gender as between-subjects fixed factors. The main effect of condition and gender thus indicates whether there were differences between levels of these factors on overall symptomology for the scale, whereas the main effect of the scale (the repeated measure) indicates whether some symptoms were rated consistently more severe than others. Of interest, the interaction between the repeated measure of scale and condition examines whether different patterns of symptomology are evident between the diagnostic groups. For example, complicated mTBI participants may consistently report different symptoms as more severe than those reported by orthopaedic controls. Using repeated measures is appropriate as the same variable of "symptom severity" is being measured over various "conditions" (i.e. the symptoms) for the same participant. This procedure also allows the above examination of differing symptom profiles across groups. Inter-group differences on the individual symptoms were also examined by performing ANOVAs on each symptom separately.

Additionally, pre-injury factors were controlled for by entering them as covariates. Linear regressions indicated that having had a major stress/trauma prior to the injury was the only predictor significantly associated with the total score of the RPQ13 and that previous use of mental health support was the only predictor significantly associated with the RPQ3. Accordingly, only the variable that was a significant correlate of the total score was entered as a covariate in Analysis of Covariance (ANCOVA) of the respective scale. Due to the significant

age differences between the three diagnostic groups, the effect of age was also included as a covariate. Running the regression analyses detailed above with participants' age included revealed that age was significantly associated with both scales, even in the presence of the other predictors.

Exploring the presence of clinically significant symptomology

Exploring differences in mean scores in this way may not be very clinically meaningful, however, as there is no clear distinction between a mild or severe problem caused by a symptom; a statistically significant difference does not necessitate a difference of clinical significance. For this reason, in line with Stulemeijer et al. (2008b), scores for each of the RPQ items were transformed into dichotomies representing a mild (score of 1-3) or severe problem (score of 4-5), and a further dichotomy of absence or presence of three or more severe problems out of the RPQ16 was created for each participant, indicating a diagnosis of post-concussion syndrome. The differences in the proportions of these dichotomies across the diagnostic groups were then explored using chi-square tests.

RESULTS

Group differences on continuous scores

RPQ13

An ANOVA on the RPQ13, with all 13 items entered as separate levels of a single repeated measures factor, and gender (discussed separately below) and condition as between subjects factors, found the main effect of condition to be non significant, $F_{2,138} = 1.85$, ns, meaning that no reliable differences were found between the groups on overall mean symptom severity for this scale. However, the interaction between condition and the RPQ13 was significant, $F_{15.24,1051.21} = 2.10$, p=0.008, indicating that the diagnostic groups had reliably different patterns of symptom severity (see Figure 1 below), although overall symptom severity was not different (i.e. the non significant main effect). In other words, different symptoms on the RPQ13 were consistently rated as more severe in some groups than in others. See below for analyses on individual symptoms.

Planned contrasts investigated our hypotheses that i) the complicated mTBI group would not differ significantly from orthopaedic controls, but ii) they would have greater symptomology than the uncomplicated mTBI group. The first hypothesis was confirmed, $F_{1,138} = 2.30$, ns, as no reliable difference was found between the complicated mTBIs and controls, and marginal support was found for our second hypothesis as the difference between the uncomplicated mTBI group and the complicated mTBI group approached significance, $F_{1,138} = 3.20$, p=.076. See Table 3 for

means. Adding in the covariates of previous stress/trauma and age did not qualitatively alter these results.

Investigating differences on individual items, the main effect of condition was significant for just two of the thirteen items; sleep disturbance ($F_{2,145} = 3.64$, p=.029) and fatigue ($F_{2,144} = 3.40$, p=.024), indicating that reliable differences exist between the diagnostic groups scores for these symptoms. The condition main effect was also marginally significant for concentration difficulties ($F_{2,145} = 2.48$, p=.087). The nature of these differences was further explored by means of post-hoc comparisons. These indicated that sleep disturbance was greater for the complicated mTBI group compared to the uncomplicated mTBI group ($F_{1,145} = 5.47$, p=.021). The complicated mTBI group also experienced more fatigue ($F_{1,144} = 6.11$, p=.015) and poorer concentration ($F_{1,145} = 3.94$, p=.049) than the uncomplicated group, as well as poorer concentration than the orthopaedic group ($F_{1,145} = 4.03$, p=.048). Descriptive data are presented in Figure 2 and Table 2. Due to the lack of qualitative changes between the ANOVAs and ANCOVAs performed for the overall scale, and due to low observed power on adding in the covariates, ANCOVAs were not run on the individual items.

Figure 5 Mean scores on the RPQ13 items across the diagnostic groups

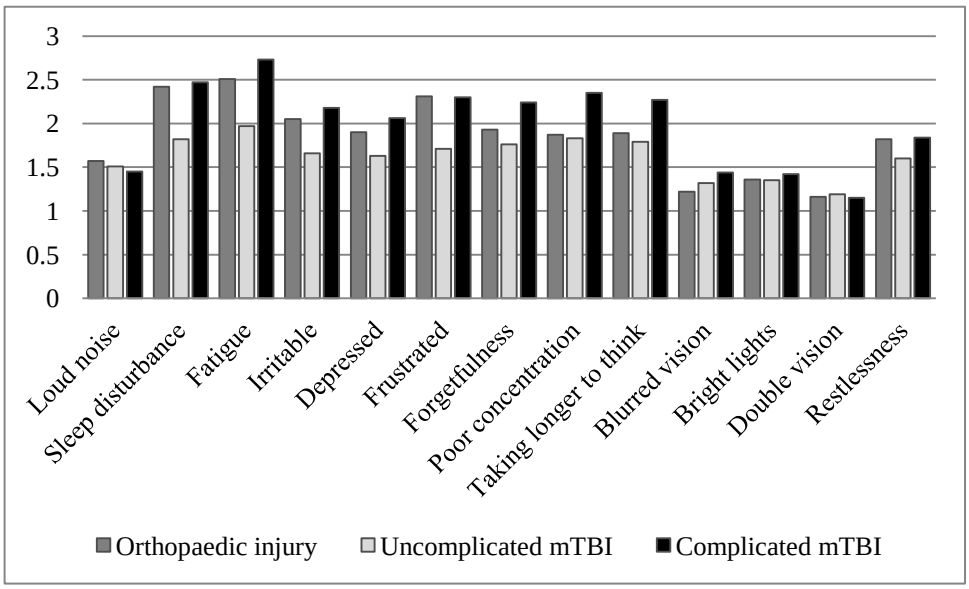


Table 2 Means and standard deviations of the RPQ scale and item scores across the diagnostic groups.

	Orthopaedic Injury			Uncomplicated mTBI			Complicated mTBI		
RPQ scale/ item	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*
Total RPQ13	41	23.17	(10.74)	70	21.23	(10.77)	33	25.76	(10.79)
Upset by loud noise	45	1.57	(0.95)	72	1.51	(1.06)	34	1.45	(0.83)
Sleep disturbance [U]	45	2.42	(1.42)	72	1.82	(1.20)	34	2.47	(1.26)
Fatigue [U]	45	2.51	(1.38)	72	1.97	(1.22)	33	2.73	(1.42)
Irritable	44	2.05	(1.20)	70	1.66	(1.06)	33	2.18	(1.31)
Depressed	42	1.90	(1.14)	71	1.63	(1.09)	34	2.06	(1.13)
Frustrated	45	2.31	(1.26)	72	1.71	(1.11)	33	2.30	(1.49)
Forgetfulness	45	1.93	(1.23)	72	1.76	(1.13)	34	2.24	(1.23)
Poor concentration [U, C]	45	1.87	(1.14)	72	1.83	(1.16)	34	2.35	(1.39)
Taking longer to think	45	1.89	(1.17)	72	1.79	(1.11)	33	2.27	(1.23)
Blurred vision	45	1.22	(0.70)	72	1.32	(0.71)	34	1.44	(0.75)
Upset by bright lights	45	1.36	(0.93)	72	1.35	(0.82)	33	1.42	(0.90)
Double vision	45	1.16	(0.56)	72	1.19	(0.57)	33	1.15	(0.44)
Restlessness	45	1.82	(1.23)	72	1.60	(1.00)	33	1.84	(1.03)
Total RPQ3	45	4.49	(1.79)	72	4.86	(2.40)	33	5.91	(3.25)
Headaches [C]	45	1.76	(1.00)	72	2.04	(1.22)	33	2.27	(1.18)
Dizziness [U, C]	45	1.51	(0.79)	72	1.54	(0.90)	34	2.15	(1.40)
Nausea/vomiting [U, C]	45	1.22	(0.52)	72	1.28	(0.63)	33	1.61	(1.00)

[U] Means for the complicated and uncomplicated mTBI groups differ significantly

[C] Means for the complicated mTBI and orthopaedic control groups differ significantly

RPQ3

A different pattern of results was found when looking at the RPQ3, containing just the items measuring headaches, dizziness and nausea. The main effect of condition on the RPQ3 was significant, $F_{2,144} = 3.65$, p=.026, revealing that the mean scores for the scale varied between the diagnostic groups, though this time the pattern of differences did not differ between the groups, as the interaction was not significant. Once again, planned contrasts tested our hypotheses that the complicated mTBI group would have greater severity of symptoms on the RPQ3 than both other groups. Robust differences in the mean scores were found between orthopaedic controls and complicated mTBIs, $F_{1,144} = 7.20$, p=.008, and marginal differences were again evident between the mTBI groups, $F_{1,144} = 3.65$, p=.056, with those with complicated injuries experiencing more severe symptoms in both instances. See Table 2 for means and standard deviations. There were no qualitative differences in the ANCOVAs.

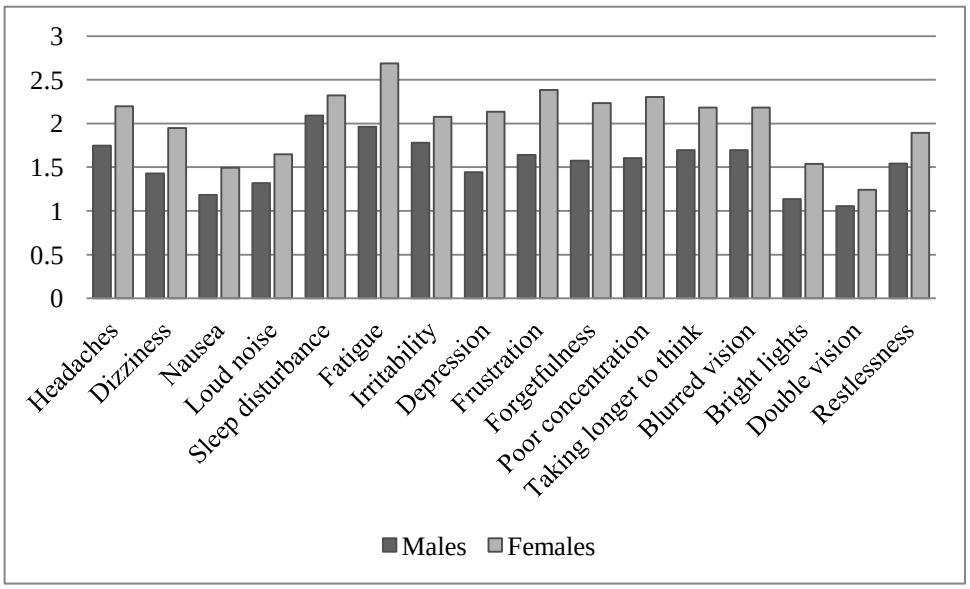
In the analyses of individual items, there was no main effect of condition on headaches ($F_{2,144} = 2.20$, ns), though there was a significant difference for both dizziness ($F_{2,145} = 4.92$, p=.013) and nausea/vomiting ($F_{2,144} = 3.45$, p=.034), indicating that mean scores reliably differed across the groups on these items only. Further planned comparisons revealed a significant difference between the complicated mTBI group and the orthopaedic group for headaches, $F_{1,144} = 3.39$, p=.048, with the complicated mTBI group rating this symptom as more severe, though no such difference was reliable between the two mTBI samples, $F_{1,144} = .511$, ns. There were robust differences in severity of dizziness between the complicated mTBI and both the orthopaedic controls ($F_{1,144} = 7.40$, p=.007) and the uncomplicated mTBI group ($F_{1,144} = 7.04$, p=.009). Similarly, significant differences were evident in nausea/vomiting between the complicated mTBI group and both the orthopaedic group ($F_{1,144} = 6.45$, p=.012) and the uncomplicated mTBI

group $F_{1,144} = 4.40$, p=.038). Means are displayed in Table 2, which also presents standard deviations. Again, ANCOVAs were not performed for the same reasons as stated regarding the item-level analysis of the RPQ13.

Gender differences

Gender differences are repeatedly found in PCS severity, with women reporting more severe problems than men. On the RPQ13, the main effect of gender was significant, $F_{1,138} = 8.78$, p=.004, as was its interaction with the scale, $F_{7.82,1051.21} = 2.83$, p=.005, indicating robust gender differences both in the average symptom severity for the scale, with women rating problems as worse than men (men M=1.54, SE=0.12; women M=1.97, SE=0.09), and in the pattern of the symptomology across the measure. That is, this interaction effect shows that different symptoms were consistently rated as more severe between men and women. However, the interaction between gender and condition was not significant, $F_{2,138} = .027$, ns, with no reliable changes in the difference in overall symptom severity between men and women across the diagnostic groups. Again, on the RPQ3, women rated symptoms as more severe than men (men M=1.44, SE=0.13; women M=1.94, SE=0.14), $F_{1,144} = 9.44$, p=.003, though the patterns of symptom severity between the genders were not reliably different across this measure as the interaction with the scale was not significant, $F_{2,254.56} = 1.15$, ns. Again, the interaction between condition and gender was not significant on the RPQ3, $F_{2,144} = .130$, ns, indicating that diagnostic group did not alter the differences between men and women. In support of previous work and our current hypothesis, women consistently rated PCS symptoms as more severe than men and this pattern was the same regardless of the diagnostic group they were in. Symptom scores for males and females are displayed in Figure 3 below.

Figure 6 Gender differences on the mean symptom scores for the RPQ.



Rates of clinically significant PCS

Using the cutoff described above, symptoms scores were dichotomised into the presence or absence of a significant problem. In line with Stulemeijer et al. (2008), participants reporting three or more significant problems were classified as presenting with clinically significant PCS. Almost a third of the complicated mTBI group (30.3%, n=10) presented with symptomology severe enough to be classified as clinically important, compared to 18.2% (n=8) of orthopaedic controls and 15.7% (n=11) with an uncomplicated mild mTBI. There were no significant differences between the three groups ($\chi^2 = 3.11$, df = 2, ns), although the planned comparison between the complicated and uncomplicated injury groups approached significance ($\chi^2 = 2.94$, df = 1, p=0.086).

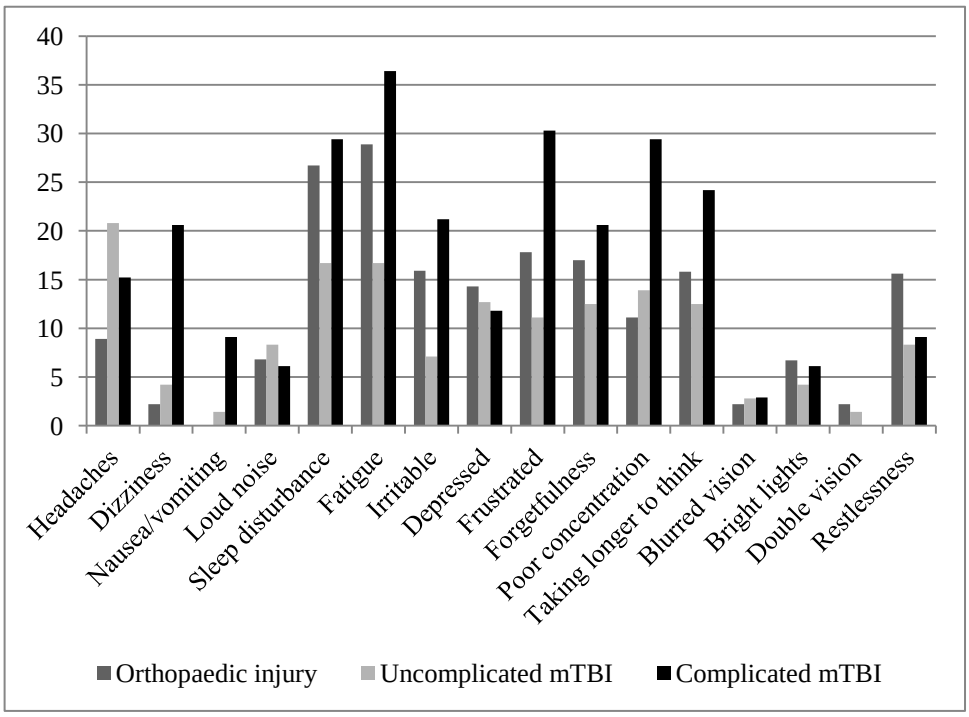
The rates of those reporting clinically significant symptoms can be found in Table 3, whereas Figure 4 displays these as percentages of the diagnostic group for greater ease of comparison Our hypothesis that the complicated mTBI group would have a higher rate of problems on the items of headaches, dizziness and nausea compared to the orthopaedic controls was tested using chi-square contingency tests and Fisher's exact tests when observed values were below 5. No significant difference was found for headaches, but was found for dizziness p=0.018, with nausea/vomiting being marginally significant, p=0.072. The complicated mTBI group had a higher rate in both instances. After looking at the data, we thought the complicated mTBI group may have a greater rate of concentration difficulties than the orthopaedic controls, which was confirmed with a post-hoc comparison ($\chi^2 = 4.22$, df = 1, $p<0.05$).

Table 3 Rates of clinically significant PCS symptoms across the diagnostic groups.

	Orthopaedic injury n=47 n (%)	uncomplicated mTBI n=76 n (%)	complicated mTBI n=34 n (%)
Headaches	4 (8.9)	15 (20.8)	5 (15.2)
Dizziness	1 (2.2)	3 (4.2)	7 (20.6)
Nausea/vomiting	0 (0.0)	1 (1.4)	3 (9.1)
Upset by loud noise	3 (6.8)	6 (8.3)	2 (6.1)
Difficulty sleeping	12 (26.7)	12 (16.7)	10 (29.4)
Fatigue	13 (28.9)	12 (16.7)	12 (36.4)
Irritability	7 (15.9)	5 (7.1)	7 (21.2)
Depressed	6 (14.3)	9 (12.7)	4 (11.8)
Impatience	8 (17.8)	8 (11.1)	10 (30.3)
Forgetfulness	8 (17.0)	9 (12.5)	7 (20.6)
Poor concentration	5 (11.1)	10 (13.9)	10 (29.4)
Taking longer to think	7 (15.8)	9 (12.5)	8 (24.2)
Blurred vision	1 (2.2)	2 (2.8)	1 (2.9)
Upset by bright lights	3 (6.7)	3 (4.2)	2 (6.1)
Double vision	1 (2.2)	1 (1.4)	0 (0.0)
Restlessness	7 (15.6)	6 (8.3)	3 (9.1)

The number of participants involved in the above analyses occasionally differed from the overall sample n due to lack of responses for certain items.

Figure 7 Percentage of group with clinically meaningful symptomology



DISCUSSION

The analyses on the RPQ13 (the Rivermead Post-concussion Questionnaires, excluding the items measuring headaches, dizziness and nausea) indicate that this instrument is largely unhelpful for disambiguating those with more complicated mTBIs from either very mild mTBI or orthopaedic controls with no mTBI. Those with complicated mTBI appear almost identical to orthopaedic controls on this measure of PCS, except on concentration difficulties. Because this subscale comprises 13 out of a total of 16 items, analysing the RPQ as a single continuous measure is similarly unhelpful. In stark contrast, and in line with our predictions, the RPQ3, measuring

headaches, dizziness and nausea/ vomiting, is able to distinguish those with complicated mTBI from both other trauma patients with no injury to the head (the orthopaedic group) and those with very minor mTBIs. Greater symptomology was reported by the complicated mTBI group across the items than by orthopaedic controls, and on all but headaches when compared to the uncomplicated mTBI group. This pattern of results was still obtained when controlling for extraneous variables and the age difference between the groups using analyses of covariance. Women consistently rated symptoms as more severe than men across both subscales of the RPQ. However, there were no interactions between gender and diagnostic group. Thus the effects of gender were found to be independent of the effects of injury group in this investigation; in other words, being female is an additive risk factor.

The analysis of clinically meaningful PCS, i.e. those that experienced at least three symptoms as severe, supported these findings. Nearly a third of complicated mTBI participants (30.3%) met this cut-off, compared to 18.2% of orthopaedic controls and 15.7% of the uncomplicated mTBI group, though these differences were not found to be reliable in this sample. Significantly more problems with headaches, dizziness and nausea (i.e. all those on the RPQ3) were experienced by the complicated group than orthopaedic controls. Dizziness and nausea also distinguished between the two mTBI samples, with the uncomplicated group experiencing these symptoms less often. Out of the symptoms on the RPQ13, only concentration difficulties was useful for differentiating between the groups, again being a problem more often in the complicated mTBI sample compared to either of the other groups.

This study provides preliminary evidence that treating mTBI as a homogenous group is not prudent, and may explain the similar rates of PCS between mTBI samples and control groups. Those with complicated injuries had significantly more sleep disturbance, fatigue, concentration difficulties, dizziness and nausea/vomiting. We had a very broad complicated head injury group, which consisted of anyone with any sign of complication. We think it likely that a less broad complicated mTBI group, consisting of those with a combination of GCS, LOC or PTA issues, would have increased the disparity in reported symptom severity between the complicated mTBI group and both the orthopaedic and uncomplicated mTBI groups.

The majority of the current literature regarding treatment of persistent PCS primarily focuses on the benefits of early interventions to reduce likelihood of persistence and improving recovery (typically in the acute phase post-injury). Such approaches address management of somatic problems, such as those symptoms measured by the RPQ3 (headaches, dizziness, nausea), cognitive problems and affective complaints within a CBT framework (Williams, et al., 2010). Findings suggest some amelioration of symptoms and reduction of PCS symptoms in the longer term. In general, interventions for minimising PCS work by allowing a graded means for enabling compensation for any underlying neurocognitive deficit and for improved tolerance of such issues as fatigue, for example, then enabling resumption of activities. However, these interventions also allow means for testing and challenging mood related concerns and beliefs about one's competence and abilities. Our findings would indicate complicated mTBI could be more systematically screened for so that those with such symptoms could be effectively identified for intervention. One promising intervention route may be provision of information on possible symptoms, which has been found to have a moderate, positive effect size of 0.32 in

terms of resolution of PCS symptomology by a meta-analysis of five studies (Mittenberg, Canyock, Condit, & Patton, 2001).

A caveat for providing information on brain injury for all survivors of mTBI is that there may be a risk of "expectation as aetiology". For example, Whitaker and Kemp, and House (2007) found that, following a mTBI, those who appraised their symptoms as likely to have serious, negative consequences were at significantly heightened risk of persistent PCS. Our findings would, as we note, aid better screening for those with mTBI for them to be given appropriate advice. This may help practitioners not to "over-prescribe" brain injury information for those with psychogenic forms of PCS. However, of course, survivors of trauma may well need some other form of informational advice for aiding their adjustment. We therefore suggest that more research is needed to identify the likely psychological factors causal of PCS such that more appropriately targeted interventions can be developed. One likely psychological factor that may influence development and/or maintenance of PCS is post-traumatic stress disorder (PTSD), which is common following even minor injuries seen at the ED (e.g. Mayou, Black, & Bryant, 2000; Mayou & Bryant, 2001) and has been found to be co-morbid with PCS (Belanger, Kretzmer, Vanderploeg, & French, 2010; Bryant, Marosszeky, Crooks, Baguley, & Gurka, 1999; Dikmen, Machamer, Fann, & Temkin, 2010; Hoge, et al., 2008; Lippa, Pastorek, Benge, & Thornton, 2010). Negative appraisals of the sequelae of traumatic events, such as investigated by Whitaker and colleagues (Whittaker, et al., 2007) described above, are also a core component of PTSD (American Psychiatric Association, 1994; Ehlers & Clark, 2000). Studies should seek to identify psychological factors that lead to acute PCS and how these go on to affect the persistence of such symptoms.

A limitation of this study is a low response rate that led to significant differences in age and gender distribution between responders and non-responders. As such, it is possible that our sample is not representative of the general population, containing less men and being older than the overall population of those leaving the ED that could have been followed up. As the above results show, female gender was consistently related to worse symptomology, and age was found to be negatively associated to PCS and was used as a covariate, which could have led to over-estimates of PCS symptomology. However, a 17.8% response rate and age and gender biases for research following up patients leaving an ED is consistent with past studies.(e.g. Whittaker, et al., 2007) Our study was also not seeking to investigate prevalence of symptomology, but rather provenance; to look at differences between groups and symptom clusters. The gender differences described above were consistent across the diagnostic groups, as indicated by non significant interactions between gender and condition on both the RPQ13 and the RPQ3, so over-estimates of symptomology levels are not so important. Similarly, adding age as a covariate also did not qualitatively change the pattern of results. Age was found to be positively associated with PCS symptomology when investigating possible covariates, with older age predictive of worse PCS. Since the complicated mTBI group were the youngest group, it is possible that the differences we found would be more marked in a sample with non-significant age differences.

Additionally, a strength of this study is the recruitment of consecutive attendances to an ED, which circumvented sample biases present in some studies in the literature, where participants were sampled from those seeking care for PCS symptomology or because they are involved in litigation. A further strength is that we demonstrate clinically-relevant intergroup differences on a popular and established measure of PCS. We also utilised a control sample that was matched

for severity of minor injuries, rather than a healthy comparison sample, so that the effect of injury to the head alone could be investigated.

CONCLUSION

Acute post-concussion symptoms of headaches, dizziness, nausea/vomiting and concentration difficulties appear to be neurogenic, as these were common in those with mTBI, but significantly less so in those with traumatic injuries not involving the head, and thus are less attributable to a psychological vector. They are also all immediate symptoms of mTBI commonly seen on admission to EDs and have been found to predict persistent PCS.(de Kruijk, et al., 2002; McCrory, et al., 2004a; Stulemeijer, et al., 2008a) On the other hand, the majority of symptoms commonly held to be post-concussive were not specific to those with mTBI; being experienced at similar levels in orthopaedic controls, and are likely to be psychogenic. Therefore, terming this constellation of symptoms "post-concussive" would appear to be highly misleading. The term "post-traumatic complaints" may be more helpful, though this could also cause confusion, as "trauma" has the multiple meanings of "injuries due to forces" and "psychological distress". Whether their basis is neurogenic or psychogenic, these symptoms are a source of significant morbidity to those with traumatic injuries and future work should seek to predict who will develop persistent PCS, regardless of whether the injury involved the head or not. Nevertheless, these results should help clarify differences between those with and without injury to the head, especially those with more complicated mTBI, which should aid interpretation and design of prognostic models. Furthermore, future work is needed to test the effectiveness of early

interventions for PCS and whether neurogenic and psychogenic symptoms indeed require separate strategies for amelioration.

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Study Two - The Prospective Course of Persistent Post-Concussion Symptomology and Its Influences: the Role of Post-Traumatic Stress

ABSTRACT

Background

The development of persistent post-concussive symptoms (PCS) following mild traumatic brain injury (mTBI) remains controversial, with PCS not being found to be specific to mTBI, but also following other minor injuries. Elevated rates of PCS have been found in those with post-traumatic stress disorder (PTSD) following mTBI in military samples. Our aim was twofold, first to compare the change over time in PCS from the acute phase post-injury to three months between civilians with mTBI or minor injury sparing the head. We expected controls to have similar levels of PCS to those with a more complicated mTBI, apart from on symptoms of headaches, dizziness and nausea, which we propose to have a neurological vector. We also expected those with PTSD symptomology to have increased PCS, poorer recovery over time, and for those with complicated mTBI with co-morbid PTSD to be most at risk of poor outcome. Secondly, we explored the influence of PTSD on persistent PCS, controlling for demographic, pre-injury and injury related variables.

Method

Consecutive adult attendees of an Emergency Department with mTBI or orthopaedic injury were prospectively recruited and completed the Rivermead Post-concussion Questionnaire (RPQ) and Trauma Screening Questionnaire (TSQ) at two weeks and three months post-injury. The sample at the second time point consisted of 18 with complicated mTBI, 43 with uncomplicated mTBI and 33 orthopaedic controls.

Results

Three or more PCS symptoms were experienced at three months post-injury in 29.4% of complicated mTBIs and 21.3% of orthopaedic controls, representing very little change over time, though recovery was more evident in the uncomplicated mTBI sample. Elevated severity levels of symptoms were only evident in those experiencing at least three PTSD symptoms. Headaches dizziness and nausea were only more problematic in those with complicated mTBI with this level of PTSD symptomology. A hierarchical linear regression, controlling for demographic, pre-injury and injury related variables, found that acute PCS symptomology was most predictive of persistent PCS symptomology, but persistent PTSD symptomology was also highly related. A path analysis suggested acute PTSD symptomology has an indirect role in the maintenance of PCS.

Discussion

PTSD symptomology appears to have a key role in the genesis and/or maintenance of PCS in both those with mTBI and minor injuries not involving the head. Headaches, dizziness and

nausea, found to be specific to mTBI and which do not overlap with PTSD symptomology, are nonetheless exacerbated by PTSD after mTBI to the same extent as other PCS symptoms.

INTRODUCTION

Mild traumatic brain injury (mTBI) is a major public health concern globally (Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007), with 90% of all head injuries being classified as 'mild' (Kraus, McArthur, Silverman, & Jayaraman, 1996; Thornhill, Teasdale, Murray, McEwen, Roy, & Penny, 2000; Yates, Williams, Harris, Round, & Jenkins, 2006). In the United Kingdom, the annual incidence rate of hospital admission for head injury is 229/100,000 (Tennant, 2005). Disability rates in the UK one year after injury have been found to be as high after mTBI (47%) as in moderate (45%) and severe (48%) head injury (Thornhill, et al., 2000). A constellation of post-concussion symptoms (PCS), such as headaches, dizziness, fatigue and cognitive difficulties, are common in the acute phase post-injury (Binder, 1986; Bohnen & Jolles, 1992; Mounce, Williams, Jones, Harris, Haslam, & Jetten, submitted), although these usually resolve by 1-3 months (Binder, 1986; Carroll, Cassidy, Peloso, Borg, von Holst, Holm, Paniak, & Pepin, 2004; McCrea, Guskiewicz, Marshall, Barr, Randolph, Cantu, Onate, Yang, & Kelly, 2003; Ponsford, Willmott, Rothwell, Cameron, Kelly, Nelms, Curran, & Ng, 2000). However, a substantial subset of individuals may be left with persisting PCS at 3 months (Meares, Shores, Taylor, Batchelor, Bryant, Baguley, Chapman, Gurka, Dawson, Capon, & Marosszeky, 2008) to over a year later (Dikmen, Machamer, Fann, & Temkin, 2010). Given the

frequency of mTBI in the population, a clear understanding of the provenance of persistent PCS is needed to reduce long-term morbidity.

Although such symptoms following head injury have been acknowledged for a long time (e.g. see Srauss & Sevitsky, 1934), it has been the recent wars in Afghanistan (Operation Enduring Freedom) and Iraq (Operation Iraqi Freedom) that have brought them to widespread interest (Hoge, McGurk, Thomas, Cox, Engel, & Castro, 2008; Lippa, Pastorek, Benge, & Thornton, 2010; Stein & McAllister, 2009). Currently, a lack of clarity still pervades the literature in some key areas. Firstly, according to recent work (Boake, McCauley, Levin, Contant, Song, Brown, Goodman, Brundage, Diaz-Marchan, & Merritt, 2004; McCauley, Boake, Pedroza, Brown, Levin, Goodman, & Merritt, 2005), there is limited agreement on diagnostic criteria between the two main classification systems; "post concussive syndrome" in the International Classification of Diseases 10th revision (ICD-10, World Health Organization, 1992) and "post concussive disorder" from the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV, American Psychiatric Association, 1994). Both require a history of TBI and the presence of a number of symptoms, but the ICD-10 does not set a symptom threshold of onset or duration, require measurable cognitive deficit, clinical significance or discrimination from other disorders. The same sample can produce vastly different incidence rates according to these two systems, with no clear evidence as to which is preferable, potentially leading to different clinical decisions (Boake, et al., 2004). Furthermore, many researchers use alternative classifications developed for specific measures of symptoms associated with PCS based on frequency/severity/number of symptoms, or they use total scores to quantify severity of symptomology instead (Dikmen, et al., 2010; Hoge, et al., 2008; King, 1996; Meares, Shores, Taylor, Batchelor, Bryant, Baguley, Chapman, Gurka, & Marosszeky, in press; Meares, Shores, Batchelor, Baguley, Chapman,

Gurka, & Marosszeky, 2006; Meares, et al., 2008; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009; Stulemeijer, van der Werf, Bleijenberg, Biert, Brauer, & E.Vos, 2006; Stulemeijer, van der Werf, Borm, & Vos, 2008).

Compounding this lack of clarity, work over the past decade has asserted that PCS may not even be specific to mTBI (Iverson, Zasler, & Lange, 2007; Williams, Potter, & Ryland, 2010), but rather due to a number of factors (Carroll, et al., 2004; Ponsford, et al., 2000). Similar rates of classification of persistent PCS or symptom severity have been found after traumatic injuries not involving the head at both the acute stage (Meares, et al., 2008; Mounce, et al., submitted) and several months post-injury (McLean, Kirsch, Tan-Schriner, Sen, Frederiksen, Harris, Maixner, & Maio, 2009; Meares, et al., in press; Mickevičiene, Schrader, Obelieniene, Surkiene, Kunickas, Stovner, & Sand, 2004), as well as a high base-rate found in the normative population (Garden & Sullivan, 2010). It may be that those with mTBI have a differing pattern of persistent PCS symptomology, such as more headaches, dizziness and nausea (Mounce, et al., submitted). The evidence for neuropsychological differences between mTBI patients with persisting PCS symptomology and controls is inconsistent, with some studies reporting equal performance (Meares, et al., 2008) and others reporting differences on some measures (Bazarian, Wong, Harris, Leahey, Mookerjee, & Dombovy, 1999; Ponsford, et al., 2000). In contrast, there is a great deal of evidence that psychological factors play a key role in the development of persistent PCS, most notably the presence of pre-injury mental health status (Dikmen, et al., 2010; McLean, et al., 2009; Meares, et al., in press) and post-traumatic stress disorder (PTSD) symptomology in the acute phase (Meares, et al., in press; Stulemeijer, et al., 2008) and longer term (Hoge, et al., 2008; Lippa, et al., 2010). Demographic factors, such as female gender, may also predict long term PCS (Bazarian, et al., 1999; Dikmen, et al., 2010; Meares, et al., in press; Mickevičiene, et

al., 2004; Ponsford, et al., 2000), as has the pursuit of litigation (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Carroll, et al., 2004), but again the findings are not consistent.

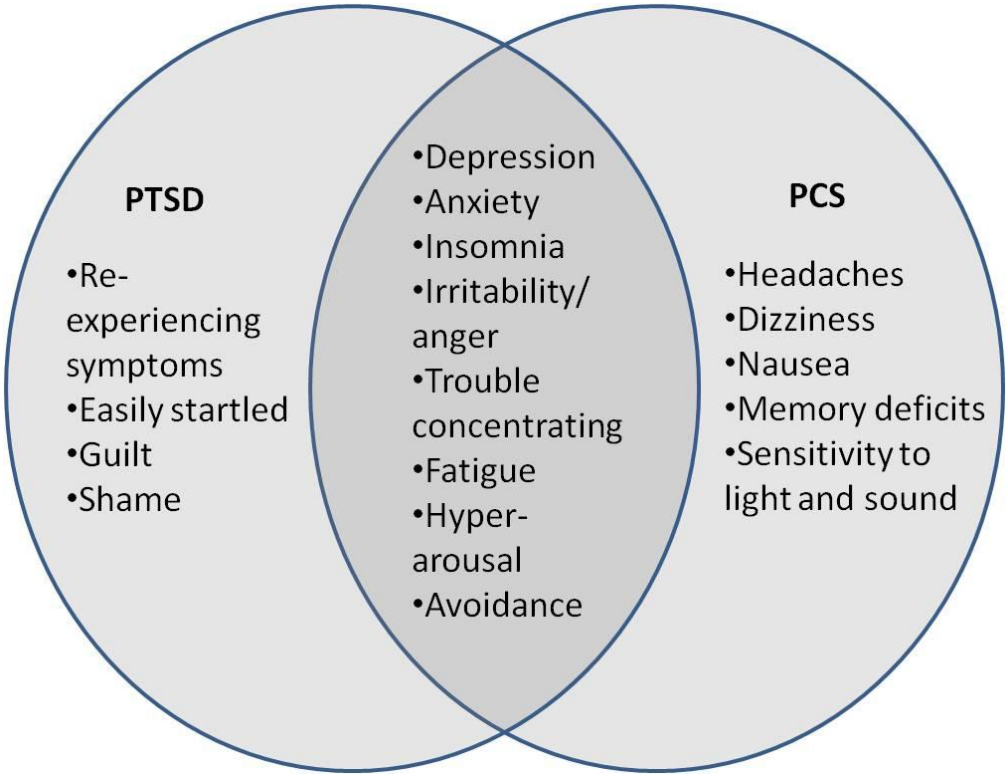
Comparing 62 mTBI patients with 58 non-brain-injured controls with other minor injuries, Meares et al (in press) found that at, three months post-injury, 50.0% of the mTBI group received a classification of PCS compared to 48% of trauma controls. They found the presence of a pre-injury depressive or anxiety disorder, post-traumatic stress, pain and female gender to be predictors, but not head-injury. However, Dikmen et al (2010), using a much larger, and thus more representative, sample of 732 patients with TBIs of all severities (the vast majority being mild) and 120 age and gender matched trauma controls, found that TBI was associated with significantly greater PCS symptomology at both one month and one year post-injury, with 53% of TBI patients having at least three persisting symptoms at one year compared to 24% of controls. Age, gender, pre-injury alcohol abuse and psychiatric history were found to be most predictive of poor outcome. Post-traumatic stress was not measured in this study.

Hoge et al (2008) investigated physical outcome, including post-concussive symptoms, in a large sample of 2,525 soldiers; 124 with injuries involving loss of consciousness, 260 with injuries involving altered mental status and 435 with other minor injuries. Soldiers experiencing a loss of consciousness were at far greater risk of PTSD, and had significantly worse physical outcomes and PCS than those with other minor injuries. However, when the effects of post-traumatic stress and depression were controlled for, mTBIs were only uniquely associated with persistent headaches, but no other physical outcomes differentiated them from other groups. Similarly, Lippa et al (2010) found that post-traumatic stress accounted for a substantial portion of the

variance of PCS severity in veteran outpatients with a history of mTBI. Again looking at combat-related TBIs, Belanger, Kretzmer, Vanderploeg, and French (2010) found that mTBI patients reported significantly more PCS symptomology than those with more severe TBIs, but this difference vanished when post-traumatic stress was controlled for. Although differences may exist between military and civilian samples, this work suggests the importance of investigating PTSD symptomology after non-combat-related injuries, especially as PTSD and other psychiatric symptomology are also common following civilian injury and are as common, if not more so, in mTBI (Mayou, Black, & Bryant, 2000; Mayou, Bryant, & Ehlers, 2001). Indeed, Bryant and Harvey (1999) found that civilian mTBI patients with PTSD reported significantly more PCS at six months than non brain-injured controls.

One obstacle that research into the co-occurrence of PCS and PTSD has to overcome is the overlapping nature of the symptomology between the two conditions, which Figure 1 below highlights. The more neurogenic post-concussive symptoms, such as headaches, dizziness and nausea (de Kruijk, Leffers, Menheere, Meerhoff, Rutten, & Twijnstra, 2002; Mounce, et al., submitted), are likely to be unique to PCS, as there seems little reason for these to be caused by psychological stress rather than trauma to the head. On the other hand, for PTSD, the re-experiencing symptoms, such as flashbacks and physical sensation felt during the trauma, as well as associated guilt and shame, should be unique, as these are not biomechanical in origin. However, both PTSD and PCS include symptoms such as depression, anxiety, irritability, trouble concentrating and difficulty sleeping. Differentiating whether these symptoms are due to one condition or the other, or both, is extremely difficult. Therefore, where possible, investigation should try to limit confounding findings due to this overlap by careful selection of measures and analyses used.

Figure 8 Overlapping symptomology between PCS and PTSD



Studies have sought to investigate the provenance of persistent PCS classification or symptomology, or examine the factors influencing a PCS classification. Few studies have aimed to both look at change over time in PCS and investigate the predictors of poor outcome in the same sample (Dikmen, et al., 2010; Meares, et al., in press). Studies often also lack of well-matched control samples (Belanger, et al., 2010; Lippa, et al., 2010). This study aims to further our understanding of the prospective course of PCS symptomology and classification by comparing mTBI patients to trauma controls without injury to the head. We also split the mTBI group into those with and without "complicated" injuries, as there is evidence that mTBI should not be treated as a homogenous group (Iverson, 2006; Lange, Iverson, & Franzen, 2009; Mounce,

et al., submitted). A prospective design was used and participants were recruited consecutively, then followed-up at two weeks (time 1, T1) and three months post-injury (time 2, T2) to assess change over time. We then investigated the associations between PCS classification and PTSD classification at both time points. In order to understand the influences on persistent PCS symptomology, we established a predictive model using demographic, pre-injury, injury-related and post-injury factors. Unlike other work, we were not predicting a classification of PCS, because there is no standard classification system and using the continuous variable of symptomology total scores allowed a more thorough investigation of the variance in the data. Finally, we present a model of these influences, established with a path analysis.

Based on previous findings, we made the following predictions: 1) significant decreases in PCS symptomology or 2) classification rates would not be evident between two weeks and three months for the complicated mTBI or control groups. 3) Complicated mTBI patients would not differ in overall symptomology or rates of classification from trauma controls, but would rate symptoms of headaches, dizziness and nausea as more severe. 4) Those with a classification of PTSD at three months post-injury would have more severe PCS than those without, and 5) that those with PTSD would also have a poorer recovery trajectory over time. Additionally, in line with findings discussed above (Belanger, et al., 2010; Bryant & Harvey, 1999; Hoge, et al., 2008; Lippa, et al., 2010), 6) we expected an interaction between mTBI and PTSD, such that complicated mTBI patients with PTSD at T2 would have worse overall PCS symptomology than both those without and trauma controls, regardless of PTSD classification. 7) Acute PTSD classification was expected to be highly related to both acute and 8) persistent PCS classification, and likewise, 9) persistent PTSD classification would also be very associated to PCS

classification at three months. 10) Acute PCS classification should also be highly related to persistent PCS.

METHOD

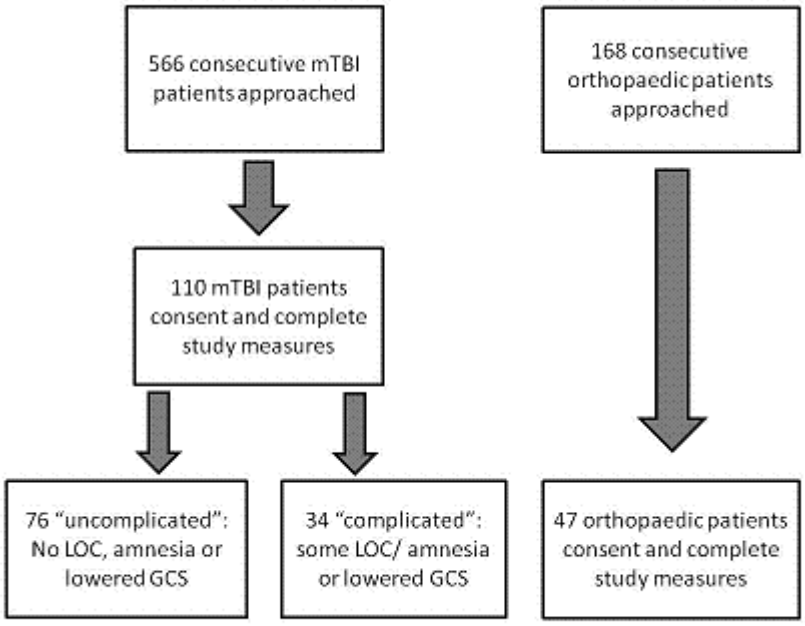
This investigation is an extension of the study reported in Mounce et al. (submitted). Participants were prospectively recruited from consecutive admissions to the ED of the Royal Devon and Exeter Hospital between November 2008 and October 2009 with either mTBI or orthopaedic injury. Participants were approached for recruitment at two weeks post-injury (time 1, T1) and were contacted for a follow-up assessment at three months post-injury (time 2, T2). Informed written consent was obtained prior to participation. The study was approved by the regional National Health Service Research Ethics Committee. Patients were eligible for participation if they were aged between 18-65 years and had received a diagnosis of either mTBI or an upper limb fracture. Exclusion criteria were attendance as a result of domestic violence or sexual assault, previous attendances within the past 5 years for similar injuries (as an indicator of domestic violence), attendances for urgent care for a pre-existing medical condition, significant history of mental health problems or learning disabilities and inability to complete questionnaires due to non-fluency in English.

The sample

Sample for time 1: two weeks post-injury

As reported in the previous study, a total of 157 attendees accepted the invitation to participate, 110 with mTBI and 47 with orthopaedic injury. The recruitment rate was a little higher for the orthopaedic group than for the combined mTBI sample (21.9% vs. 16.1% respectively), though this difference was not significant ($\chi^2 = 3.681$, df = 1, ns), and was 17.5% overall. The mTBI group was split into two subgroups; those with uncomplicated mTBI and those deemed to have complicated mTBI based on a GCS of 13-14 and/or reported LOC or amnesia in their medical notes. The final sample consisted of 47 orthopaedic controls, 76 with uncomplicated mTBI and 34 with complicated mTBI. See Figure 2 for a flowchart of recruitment into the study. As can be seen in Table 1, the groups did not differ significantly in terms of the ratio of men to women ($\chi^2 = 3.365$, df = 2, ns), or highest educational attainment ($\chi^2 = 1.920$, df = 4, ns), but reliable differences were evident in age ($F_{2,144} = 4.833$, p=0.009), with the complicated group tending to be younger than the other two diagnostic groups. Chi-square tests did not reveal any significant differences between the diagnostic groups in rates of those who had experienced three pre-trauma factors: previous stress/ trauma ($\chi^2 = .551$, df = 2, ns); previous need for mental health support ($\chi^2 = 2.914$, df = 2, ns); and previous admission for a head injury ($\chi^2 = .298$, df = 2, ns).

Figure 9 Flowchart describing the recruitment of participants and the final samples.



Non-responders with mTBI could not be divided into complicated and uncomplicated subgroups, as permission was not obtained to access their medical records (see below for the study procedure), so comparisons between our sample and non-responders use a combined mTBI group. The only data available for non-responders, other than injury type, was their age and gender. Chi-square tests found that responders were more likely to be women in both the orthopaedic control group ($\chi^2 = 7.519$, df = 1, p=.006) and the combined mTBI group ($\chi^2 = 11.595$, df = 1, p=.001). Independent samples t-tests also found that responders were significantly older for the orthopaedic sample (t_{213}=3.599, p<.001), as well as the mTBI group (t_{673}=5.676, p<.001). See Table 1, copied from Mounce et al. (submitted), for descriptive data.

Table 4 Demographic and pre-injury characteristics of the samples.

Responders n=157		**Orthopaedic injury n=47**	**uncomplicated mTBI n=76**	**complicated mTBI n=34**
	Mean age (SD)	47.80 (13.42)	45.18 (14.09)	38.12 (14.68)
	Men (%)	15 (33.9)	37 (48.7)	14 (41.2)
Highest level of education (%):	Secondary school	12 (27.3)	25 (35.2)	8 (23.5)
	College	18 (40.9)	27 (38.0)	16 (47.1)
	University	14 (31.8)	19 (26.8)	10 (29.4)
Suffered major stresses / trauma prior to injury		9 (20.5)	11 (15.9)	7 (20.6)
Previous need for mental health support		3 (7.0)	6 (8.7)	6 (18.2)
Previous mTBI		5 (11.4)	10 (14.7)	4 (12.1)
Non-responders n=734		**Orthopaedic injury n=168**	**Combined mTBI n=566**	
	Mean age (SD)	39.36 (14.77)	34.36 (13.53)	
	Men (%)	88 (52.4)	363 (64.1)	

The number of participants involved in the above analyses occasionally differed from the overall sample n due to lack of responses for certain items.

Sample for time 2: three months post-injury

Of this original sample, 59.9% completed the study at three months post-injury. The sample for the second time point was comprised of 43 with uncomplicated mTBI, 18 with complicated mTBI and 33 orthopaedic injured controls. As shown in Table 2, there were no differences in the proportion of those who responded at three months across the diagnostic groups ($\chi^2 = 3.12$, df=2, ns), nor were there differences in the ratio of men to women ($\chi^2 = 0.25$, df=1, ns) or in highest educational attainment ($\chi^2 = 2.25$, df=2, ns) between responders and non-responders. However, those who responded at time 2 were significantly older ($t_{145} = -2.86$, p=0.005) than those who did not complete the follow up measures. Importantly for the analyses in this investigation, there were also no differences in the proportions of those meeting cut-off criteria for likely PTSD and PCS two weeks post-injury across the diagnostic groups between those who took part at three months post-injury and those who did not. The procedure for making these classifications is described below. Within the responders at three months post-injury, there were no reliable differences between the diagnostic groups in any of the demographic or pre-injury variables. Descriptive data for these analyses can be found in Table 3.

Table 5 Demographic characteristics of responders compared to non-responders at three months post-injury

	Responders n=94	Non-responders n=63	p-value
Diagnostic group (%):			
Orthopaedic injury	33 (70.2)	14 (29.8)	
Uncomplicated mTBI	43 (56.6)	33 (43.4)	.211
Complicated mTBI	18 (52.9)	16 (47.1)	
Mean age (SD)	46.99 (13.59)	40.18 (14.76)	.005
Men (%)	38 (40.4)	28 (44.4)	.616
Highest educational attainment:			
Secondary school	27 (31.4)	18 (28.6)	
College	31 (36.0)	30 (47.6)	.751
University	28 (32.6)	15 (23.8)	
Met cut-off for PCS at two-weeks (%)	17 (20.0)	12 (19.4)	.923
Met cut-off for PTSD at two-weeks (%)	34 (43.6)	24 (41.4)	.797

Table 6 Demographic characteristics of the samples at three months post-injury.

	Orthopaedic injury n=33	uncomplicated mTBI n=43	complicated mTBI n=18	p-value
Mean age (SD)	49.10 (13.83)	47.46 (12.83)	42.28 (13.59)	.230
Men (%)	11 (33.3)	19 (44.2)	8 (44.4)	.588
Highest educational attainment (%):				
Secondary school	8 (26.7)	14 (36.8)	5 (27.8)	
College	12 (40.0)	12 (31.6)	7 (38.9)	.902
University	10 (33.3)	12 (31.6)	6 (33.3)	
Suffered previous trauma/stress (%)	8 (26.7)	5 (13.5)	4 (22.2)	.394
Previous need of mental health support (%)	2 (6.9)	3 (8.1)	2 (11.8)	.844
Previous hospitalisation for mTBI (%)	5 (16.7)	6 (16.2)	1 (5.9)	.540

Assessment procedure

Trained research assistants working at the hospital identified those who met the study's inclusion/exclusion criteria from the medical records of patients of the ED. A study information pack was sent via post to those identified as eligible for participation at two weeks post-injury,

explaining the nature and aims of the research and inviting them to take part, as well as including a consent form and the study questionnaire. The consent form also asked for permission for the researchers to access their medical records. Those that wished to participate completed the questionnaire and signed the consent form, then returned these to the researches by post. Non-responders were therefore those that did not wish to take part in the research. The same questionnaire was sent again at three months post-injury to those that had consented to take part at T1.

Participants were asked to complete the Rivermead Post-concussion Questionnaire (King, Crawford, Wenden, Moss, & Wade, 1995). The RPQ consists of 16 items assessing the presence and severity of symptoms common in persistent post-concussion syndrome, such as headaches, dizziness and concentration problems, on a 5-point scale ranging from "1 - no problem" to "5 - severe problem". Participants reported their demographics and answered three questions relating to their pre-injury status, all of which required yes/no responses. These were "had you suffered a previous stress or trauma prior to this incident?", "had you needed any mental health support?" and "had you ever had a head injury that needed hospitalisation?". We also asked participants to report their highest education level completed, with options of "Secondary school", "College" and "University". Additionally, they were asked to complete the Traumatic Stress Questionnaire (TSQ, Brewin, Rose, Andrews, Green, Tata, McEvedy, Turner, & Foa, 2002), a 10 item measure of post-traumatic stress that has been found to possess excellent psychometric properties and agreement to clinical interviews. Participants were asked to report which symptoms they had experienced at least twice in the past week, in relation to their injury-incident. The first 5 items measure re-experiencing symptoms, such as flashbacks and reliving feelings felt at the event, and the last 5 measure hyper-arousal, such as being easily startled.

Access to participants' medical records was required in order to provide detailed information on the nature of their state on attendance at the ED, such as GCS, LOC and presence of amnesia for the mTBI group, which was used to determine whether the participant had a complicated mTBI, as outlined above. Participants gave their consent for this access on their study consent form.

Data analysis

The RPQ was designed to be used as a single scale (King, et al., 1995). However, Eyres, Carey, Gilworth, Neumann and Tennant (2005) suggest, and findings from our previous work (Mounce, et al., submitted) support, that treating the RPQ as a single construct is unwise as it does not posses unidimensionality. Rather the scale should be split into two subscales, one comprising of the items measuring headaches, dizziness and nausea/vomiting (henceforth termed the RPQ3) and the other comprising the remainder (henceforth the RPQ13). Differences in mean RPQ3 and RPQ13 scores between the three diagnostic groups, men and women, and those with and without PTSD (see below), were thus compared using analyses of variance (ANOVAs) across the two time points. We used a 2(time post-injury: two weeks, three months) x 3(diagnostic group: orthopaedic, uncomplicated mTBI, complicated mTBI) x 2(RPQ scale: RP3, RPQ13) x 2(gender: men, women) x 2(PTSD classification at three months: no, yes) mixed factorial design, with diagnostic group, gender and PTSD classification as between subjects factors, and RPQ scale and time post-injury as repeated measures. Whenever we use the term "overall symptomology", we are referring to the whole RPQ. Although the full RPQ was not entered as a variable, the main

effects of the other variables in our model were compared on the mean of the two subscale means and thus reflect overall symptomology. This ANOVA will allow the testing of hypotheses 1-6.

Our sample had no differences in the proportion of people reporting pre-injury stress, mental health support needs or head-injury so these were not included as covariates. There were significant age differences between the time one and time two samples, however age was not found to correlate with either two week, or three month PCS scores and thus was judged to not be needed as a covariate.

In addition to looking at mean symptom severity, participants can be classified as having likely PCS or not by using established cut-off scores for the RPQ (Stulemeijer, et al., 2008). Symptoms were classified as 'mild' if participants rated them as 1-3 on the 5-point scale, whereas if they were rated as 4-5 they were classified as 'severe'. Participants who experienced three or more 'severe' symptoms met our cut-off for having PCS. Similarly, on the TSQ, if participants reported the presence of three or more PTSD symptoms (out of a possible ten) then they were classified as having likely PTSD, as suggested by Brewin et al. (2002). Note that although we refer to those meeting the cut off as having PTSD, this is not a true diagnosis, but rather reflects the high level of PTSD symptomology. Hypotheses 7-10 were tested by examining the relative proportions of participants passing the cut-off criteria for these conditions using Fisher's Exact Tests.

A more thorough investigation of how all these factors taken together relate to persistent PCS is required to obtain a comprehensive picture. Therefore a hierarchical linear regression was conducted, first entering the demographic and pre-injury variables, then whether they suffered a complicated mTBI or not and if they were seeking compensation, then their two week total RPQ mean scores, then their two-week TSQ score and finally their three-month TSQ score. Due to the overlapping symptomology between PCS and PTSD, which was reflected in similar wording between three TSQ hyper-arousal items and items on the RPQ, the TSQ items "difficulty falling or staying asleep", "irritability or outbursts of anger" and "difficulty concentrating" were not used when calculating their total TSQ score for the regression. See Figure 1 for a representation of possibly overlapping symptoms between PCS and PTSD. Finally, the results of this regression were used to postulate a model of factors influencing persistent PCS, which was then subjected to a path analysis to show the strength of associations in the pathways.

This exploratory work required a number of comparisons. Due to the main effects of our treatment variables being significant, the follow-up pair-wise comparisons between groups were protected from inflated Type 1 error rates, according to Fisher's Least Significant Difference theory.

RESULTS

Prospective course of PCS symptomology and classification

Using the mixed factorial design ANOVA described above, there was no evidence of a reduction in symptomology between two weeks (*M*=1.795, *SE*=.083) and three months (*M*=1.795, *SE*=.070) post-injury, $F_{1,72}$ = .434, ns. This pattern was consistent across the diagnostic groups, as the interaction between the main effects of time and condition was also non significant, $F_{2,72}$ = .914, ns. See Table 4 and Figure 4 for descriptive data. However, the interaction between time point and gender was reliable, $F_{1,72}$ = 8.81, *p*=.004, with women's symptomology having decreased over time (T1 *M*=1.96, *SE*=.097; T2 *M*=1.83, *SE*=.082), whereas men's symptomology increased (T1 *M*=1.60, *SE*=.141; T2 *M*=1.75, *SE*=.118), see Table 4 and Figure 5. This pattern of differences did not vary across the diagnostic groups, as the three-way interaction between time post-injury, gender and condition was not significant, $F_{2,72}$ = .090, ns.

Table 7 Means and standard errors across the time points, split by RPQ scale, for the diagnostic groups and gender.

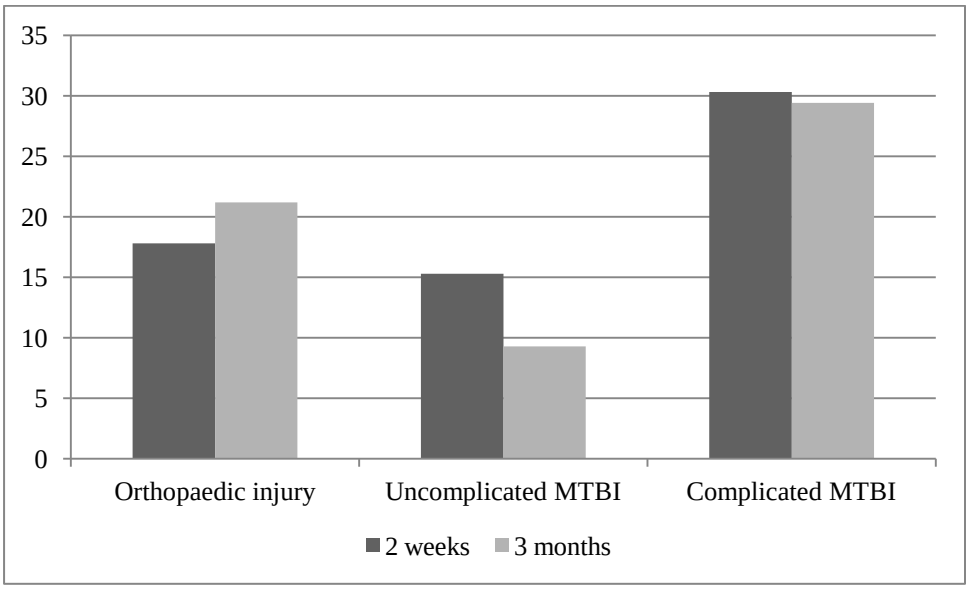
Sample	Two weeks post-injury			Three months post-injury		
	RPQ3	RPQ13	Total	RPQ3	RPQ13	Total
Comp. mTBI	2.11 (.19)	2.07 (.18)	**2.09 (.17)**	2.01 (.16)	2.12 (.16)	**2.07(.14)**
Uncomp. mTBI	1.58 (.14)	1.72 (.14)	**1.65 (.12)**	1.59 (.12)	1.82 (.11)	**1.71 (.10)**
Trauma controls	1.41 (.14)	1.77 (.14)	**1.59 (.12)**	1.36 (.12)	1.74 (.11)	**1.55 (.10)**
Men	1.56 (.16)	1.65 (.15)	**1.60 (.14)**	1.55 (.13)	1.95 (.13)	**1.75 (.12)**
Women	1.87 (.11)	2.04 (.11)	**1.96 (.10)**	1.79 (.09)	1.87 (.09)	**1.83 (.08)**
Full sample	1.73 (.09)	1.86 (.09)	**1.80 (.08)**	1.68 (.08)	1.91 (.08)	**1.79 (.07)**

N.B. The RPQ symptoms are rated between "1 – no problem at all" to "5 – severe problem"

We also investigated the prospective course of PCS classification. At T1, 29 participants (19.3%) were classified as having PCS compared to 121 without, whereas at T2 16 (18.4%) received a PCS classification compared to 71 without, of which 5 (31.3%) were new cases, having not received a classification of PCS at two weeks. A chi-square test found no reduction in the proportion receiving a PCS classification between T1 and T2, $\chi^2 = <.001$, df.=1, p=.995. As reported in Mounce et al. (submitted), 30.3% of the complicated mTBI received a classification of PCS, compared to 15.3% of the uncomplicated mTBI group and 17.8% of the trauma controls. By three months post-injury, there were significantly fewer uncomplicated mTBI patients with PCS (9.3%) than in the complicated mTBI group (29.4%), $\chi^2 = 3.86$, df.=1, p=.049. The proportion of new cases was roughly equal across the conditions (complicated mTBI: 8.0%, uncomplicated mTBI: 6.1%, controls: 8.3%). There were also very similar rates of those receiving a classification at both time points for the complicated mTBI group (80.0%) compared to the trauma control group (83.3%), but 66.7% of the uncomplicated group who

received a classification at T1 had recovered by T2. Figure 3 displays the percentage of participants within each diagnostic group receiving a classification of PCS at T1 and T2. Of the orthopaedic control group, 21.2% met the cut off for PCS at T2.

Figure 10 Percentage receiving a classification of PCS across the diagnostic groups at T1 and T2



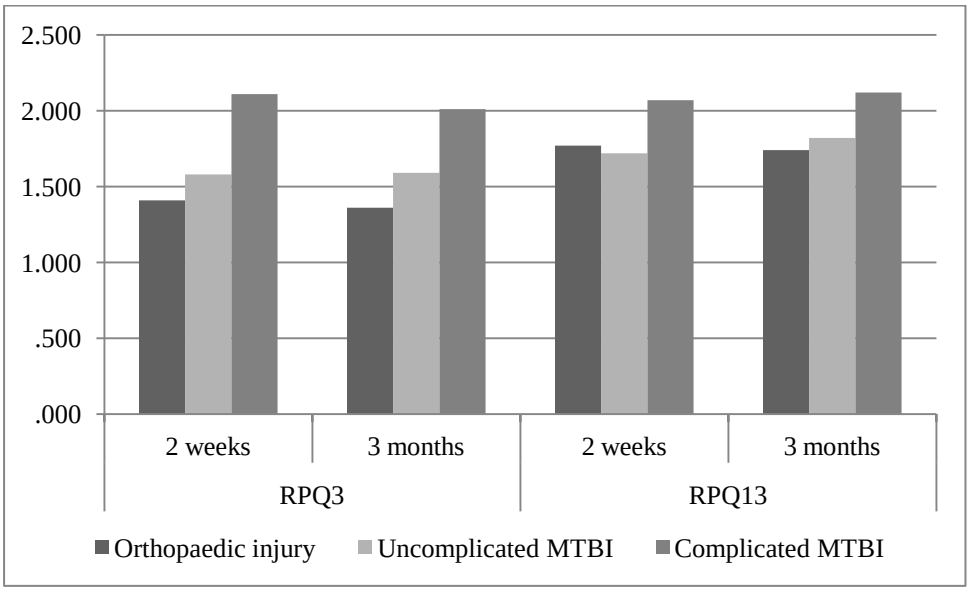
Headaches dizziness and nausea

As advised by Eyres et al. (2005), the 16 items on the RPQ were split into two subscales. The items measuring headaches, dizziness and nausea/vomiting formed the RPQ3. These three symptoms are also more obviously neurogenic, rather than psychological in nature, and as such are of particular interest. The remainder formed the RPQ13. A significant main effect of RPQ scale was found on the mean symptom severity scores, $F_{1,72} = 11.826$, p=.001. Overall, the

severity of headaches, dizziness and nausea/vomiting (*M*=1.70, *SE*=.079) was less than the other symptoms (*M*=1.89, *SE*=.078). This difference was not found to alter between two weeks to three months post-injury, as the interaction between time and RPQ scale was non significant, $F_{1,72}$ = 2.678, ns.

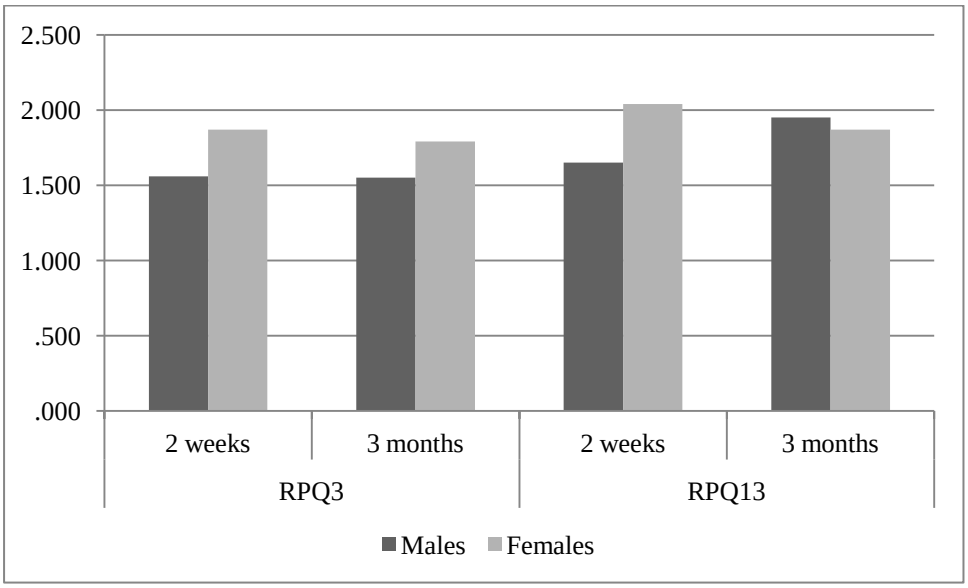
The main effect of condition was found to be significant, $F_{2,72}$ = 3.529, *p*=.035, meaning that overall symptom scores varied reliably across the groups (complicated mTBI: *M*=2.079, *SE*=.147; uncomplicated mTBI: *M*=1.68, *SE*=.107; controls: *M*=1.57, *SE*=.107). The interaction between RPQ scale and condition was also significant, $F_{2,72}$ = 5.527, *p*=.006, indicating that the difference in symptom severity between the RPQ3 and the RPQ13 varied according to the diagnostic group, see Table 4 and Figure 4. In order to test our prediction that the complicated mTBI group would have more severe headaches, dizziness and nausea/vomiting than the trauma controls, but similar levels of symptomology on the rest of the scale, we excluded the uncomplicated mTBI group and re-ran the ANOVA to look for an interaction between condition and RPQ scale. Firstly, the main effect of condition was still significant, $F_{1,37}$ = 4.129, *p*=0.049, with the complicated mTBI group having reliably more severe overall symptomology than controls. The interaction of interest was also significant, $F_{1,72}$ = 9.498, *p*=0.004, with the means supporting our prediction (again, see Figure 3) This pattern of differences did not change from T1 to T2, as evidenced by a non significant triple interaction of condition (complicated mTBI, controls), RPQ scale and time, $F_{1,72}$ = .111, ns.

Figure 11 RPQ scale scores at T1 and T2 across the diagnostic groups



The main effect of gender was not significant, $F_{1,72} = 2.530$, ns, indicating that overall symptom severity did not differ between men (*M*=1.68, *SE*=.122) and women (*M*=1.89, *SE*=.085), nor were there gender differences in the symptomology between the two RPQ scales, $F_{1,72} = 3.366$, ns. However, the triple interaction between gender, RPQ scale and time was significant, $F_{1,72} = 7.568$, *p*=.008, indicating that the change in the pattern of differences in mean symptom scores from T1 to T2 between men and women is itself different for the RPQ3 than for the RPQ13. As Figure 5 displays, whereas women's' scores decreased over time for both scales, men's scores decreased on the RPQ3, but increased on the RPQ13.

Figure 12 RPQ mean scale scores at T1 and T2 for men and women.



The effect of PTSD on symptom severity

We predicted that those with a classification of PTSD at three months post-injury would have more severe PCS symptomology. The main effect of PTSD confirmed this with a highly significant result, $F_{1,72} = 25.315$, $p<.001$; those with PTSD at T2 had considerably worse PCS symptomology (M=2.28, SE=.128) than those without (M=1.39, SE=.078). We also expected that this difference would increase over time. The interaction between PTSD and time since injury was significant, $F_{1,72} = 8.525$, p=.005, revealing that the symptomology of those without PTSD tended to decrease between two weeks to three months post-injury (T1 M=1.45, SE=.090; T2 M=1.33, SE=.076), but those with PTSD at T2 had increased in PCS symptomology by this time (T1 M=2.21, SE=.147; T2 M=2.35, SE=.124). Our prediction was confirmed, see Figure 6. Lastly, we expected that PTSD would especially exacerbate PCS symptomology in the complicated head injury group compared to trauma controls. This hypothesis was supported by a

significant interaction between condition (complicated mTBI, controls) and T2 PTSD classification, $F_{1,37} = 7.062$, p=.012, with the means being in the predicted direction, see Table 5 and Figure 7.

Figure 13 Difference in change over time in mean RPQ symptom scores between those with and those without PTSD at three months.

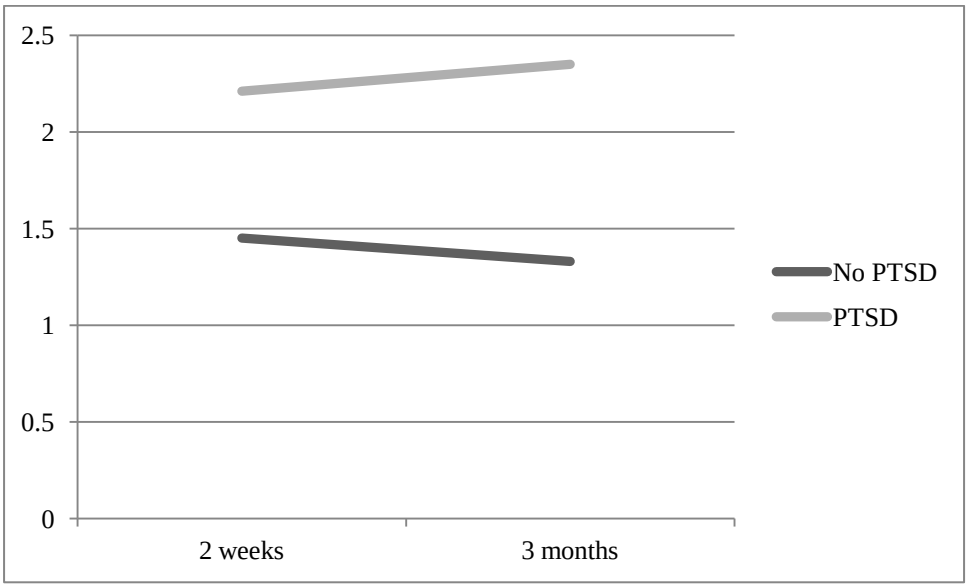
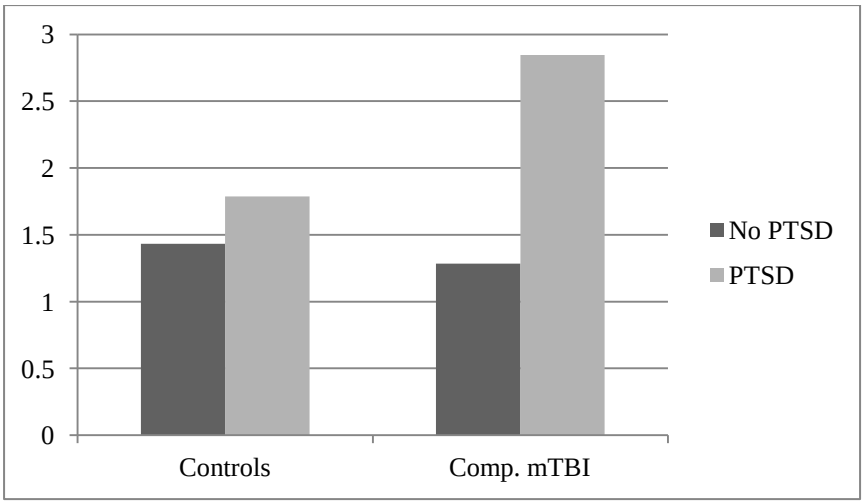


Figure 14 Mean RPQ symptom scores are especially increased in complicated mTBI patients with PTSD compared to those without and to controls with or without PTSD.



Further to what we predicted, the triple interaction between PTSD, time and condition (complicated mTBI, controls) was not significant, $F_{1.37} = .494$, ns, meaning that the interaction described above, whereby PTSD especially exacerbates PCS symptomology in complicated mTBI patients, did not reliably differ from T1 to T2. Interestingly, the triple interaction between RPQ scale, condition (complicated mTBI, controls) and PTSD was significant, $F_{1,37} = 5.820$, p=.021, with the direction of the means indicating that complicated mTBI patients with PTSD have more severe symptomology on both scales relative to those without, whereas controls with PTSD are only markedly worse on RPQ13 symptomology, which excludes headaches, dizziness and nausea/vomiting, see Figure 8. The three-way interaction between time, gender and PTSD classification was found significant, $F_{1,72} = 8.391$, p=.005, indicating that the change in the pattern of differences in PCS symptomology from T1 to T2 between men and women varied according to whether or not the participant had a T2 classification of PTSD. More specifically,

only men with PTSD experienced an increase in symptomology; men without PTSD and women with or without PTSD decreased in mean symptom severity. See Table 5 for descriptive data.

Figure 15 The interaction between condition, PTSD at T2 and RPQ scale (the RPQ3 measures headaches, dizziness and nausea/vomiting) on RPQ symptom scores.

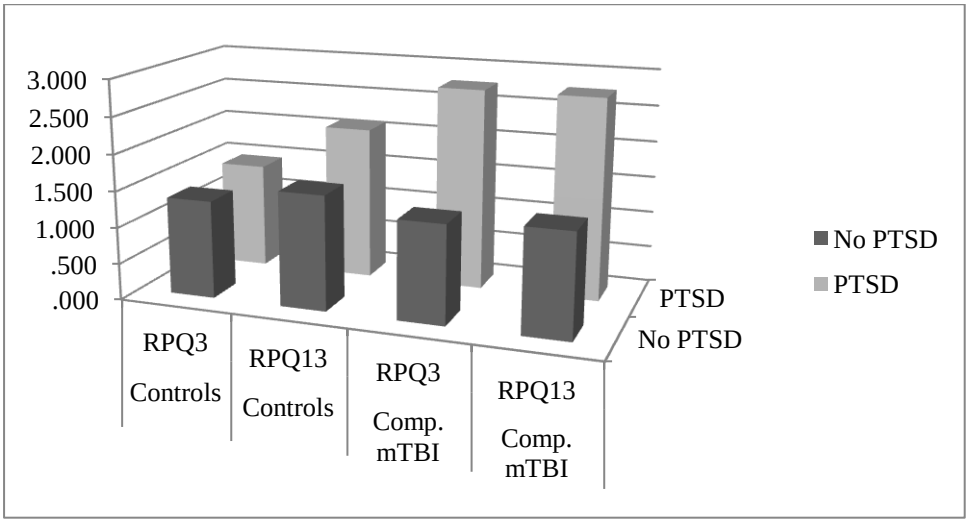


Table 8 Mean symptom scores and standard errors across time points, split by RPQ scale, between conditions and gender, for those with and without PTSD.

	Sample	Two weeks post-injury			Three months post-injury		
		RPQ3	RPQ13	**Total**	RPQ3	RPQ13	**Total**
No PTSD	Comp. mTBI	1.43 (.21)	1.55 (.21)	**1.49 (.19)**	1.27 (.18)	1.30 (.18)	**1.28 (.16)**
	Uncomp. mTBI	1.38 (.13)	1.36 (.13)	**1.37 (.12)**	1.27 (.11)	1.27 (.11)	**1.27 (.10)**
	Controls	1.38 (.16)	1.61 (.16)	**1.49 (.15)**	1.31 (.14)	1.55 (.14)	**1.43 (.12)**
	Total	**1.40 (.10)**	**1.51 (.10)**	**1.45 (.09)**	**1.28 (.09)**	**1.37 (.08)**	**1.33 (.08)**
PTSD	Comp. mTBI	2.79 (.30)	2.60 (.30)	**2.69 (.28)**	2.75 (.26)	2.94 (.26)	**2.85 (.28)**
	Uncomp. mTBI	1.79 (.24)	2.10 (.24)	**1.93 (.22)**	1.92 (.20)	2.38 (.20)	**2.15 (.18)**
	Controls	1.46 (.25)	2.11 (.24)	**1.78 (.23)**	1.46 (.21)	2.12 (.21)	**1.79 (.19)**
	Total	**2.12 (.16)**	**2.29 (.16)**	**2.21 (.15)**	**2.16 (.14)**	**2.55 (.14)**	**2.35 (.12)**
No PTSD	Men	1.33 (.15)	1.43 (.14)	**1.38 (.13)**	1.19 (.12)	1.32 (.12)	**1.26 (.10)**
	Women	1.47 (.14)	1.58 (.14)	**1.52 (.12)**	1.37 (.12)	1.42 (.11)	**1.39 (.10)**
PTSD	Men	1.89 (.32)	1.97 (.32)	**1.93 (.29)**	2.10 (.28)	2.90 (.27)	**2.49 (.24)**
	Women	2.28 (.17)	2.51 (.16)	**2.39 (.15)**	2.21 (.14)	2.32 (.14)	**2.27 (.13)**

N.B. The RPQ symptoms are rated between "1 – no problem at all" to "5 – severe problem"

Relationship between PCS classification and PTSD classification

The hypothesis relating to the relationships between T1 and T2 PCS and PTSD classifications were investigated using Fisher's Exact Tests. First, examining the relationship between T1 PCS and T1 PTSD, a highly significant result was found, $p<0.001$, with 92% of those with T1 PCS also having acute PTSD, compared to 31.5% of those without T1 PCS also presenting with co-morbid acute PTSD, see Figure 9. Of those with PCS persisting at three-months, 83.3% had presented with acute PTSD, compared to 36.4% of those without T2 PCS, see Figure 10. This

difference in proportion was again highly significant, p=0.004. Thus both hypotheses relating to acute PTSD were supported.

Figure 16 Proportion of patients with and without a T1 PCS classification with co-morbid acute PTSD.

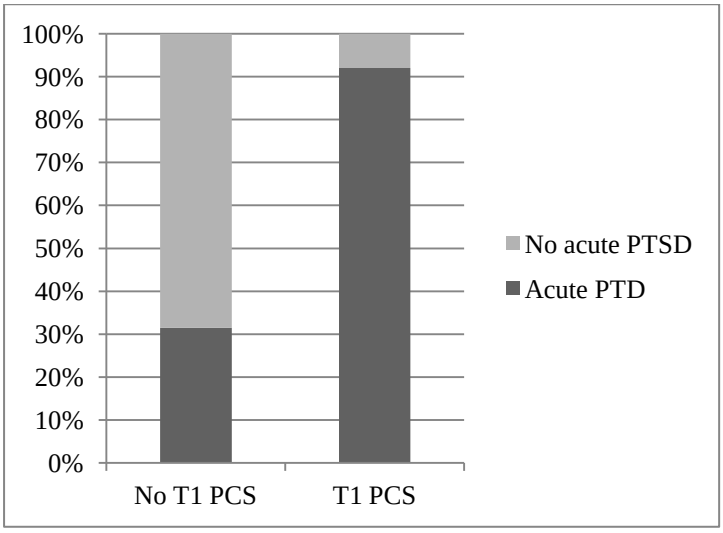
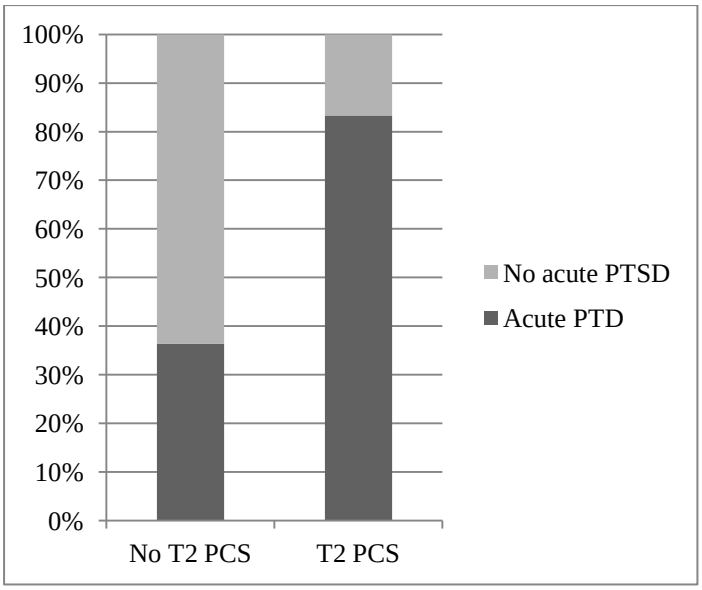


Figure 17 Proportion of patients with and without a T2 PCS classification with co-morbid acute PTSD.



Of those who met the cut off for T1 PCS classification, 64.7% developed persistent PCS, compared to just 7.1% of those who did not have acute PCS. Accordingly, 68.8% of those with persistent PCS had a T1 PCS classification and 31.3% of persistent PCS cases did not have clinically significant symptomology at two weeks. This difference in proportions, displayed in Figure 11, was highly significant, $p<0.001$, confirming our hypothesis. A highly significant association between PTSD classification and T2 PCS classification was also found, $p<0.001$, with 86.7% of those with persistent PCS having co-morbid PTSD, compared to 16.2% of patients without PCS having PTSD, supporting our hypothesis. These proportions are displayed in Figure 12.

Figure 18 Proportion of patients with and without a T2 PCS classification who presented with PCS at T1.

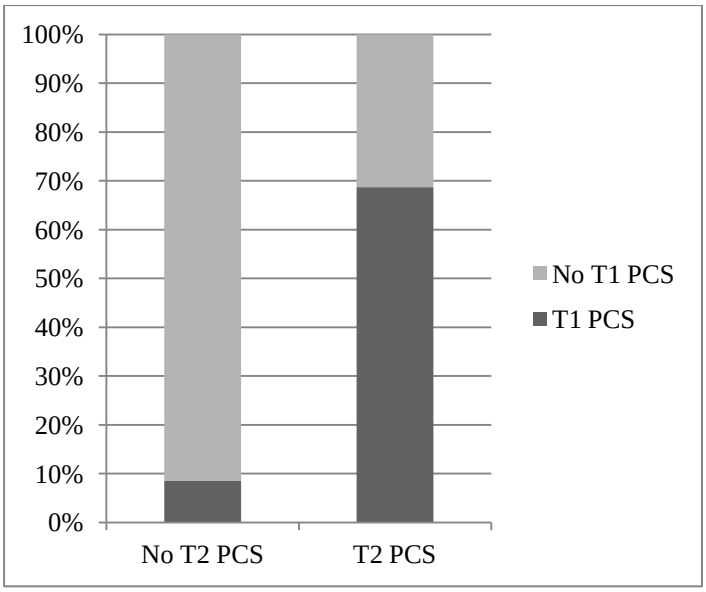
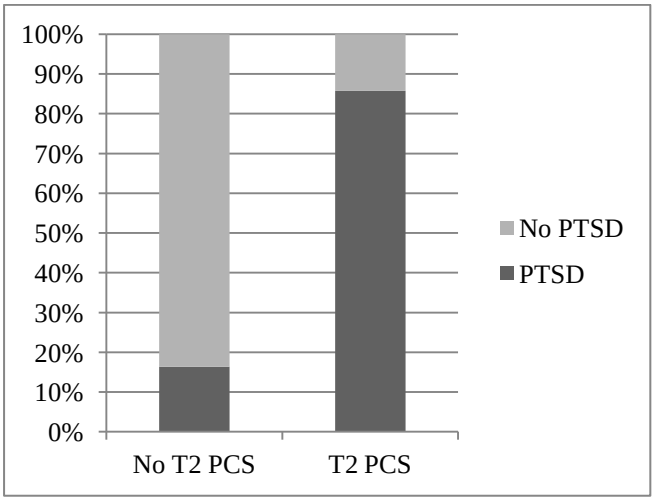


Figure 19 Proportion of patients with and without a T2 PCS classification who presented with co-morbid PTSD.



Investigating which factors are the most important influences on persistent PCS symptomology

The above analyses indicated that acute PCS, acute PTSD classification (acute PTSD) and persisting PTSD are all strongly associated to a classification of PCS at three months post-injury. However, a thorough investigation of the influences of these factors on persistent PCS needed to take into account demographic, pre-injury and injury-related factors. Also, using PCS symptomology, as opposed to classification, allows a more detailed understanding of changes in symptom severity. Therefore a hierarchical linear regression was performed on participants' total RPQ mean scores, using a blocking procedure. All participants were included as a higher n would facilitate a better model (by having more data in which to investigate variability in scores) and no reliable differences were evident between the diagnostic groups on the majority of the scales items (the RPQ13). Table 6 below shows the order in which items were entered into the model and the resultant R^2 and F changes. As mentioned above, items on the TSQ that elicited the presence of the same or similar symptoms as the RPQ were not included in participants TSQ scores.

Table 9 Details of the hierarchical linear regression investigating influences on persistent PCS symptomology

Block	Variables entered	R^2 change	F change	*p* value
1. Demographic and pre-injury variables	Age, gender, highest educational attainment, previous stress/trauma, previous mental health support and previous head-injury	.091	.617	.715
2. Injury-related variables	Compensation being sought, complicated MTBI or other diagnostic group	.029	.585	.563
3. Acute PCS symptomology	T1 total RPQ mean score	.434	33.106	<.001
4. acute PTSD symptomology	T1 TSQ score*	.025	1.963	.171
5. PTSD symptomology	T2 TSQ score*	.090	8.736	.006

As mentioned above in the Data Analysis section, items on the TSQ that asked about the presence of the same or similar symptoms as the RPQ were not included in participants TSQ scores.

The complete model was a good fit to the data, explaining 67.0% of the variance in the data (R^2 adjusted = .556), and was highly significantly associated to T2 PCS symptomology, $F_{11,32} = 5.89$, $p<.001$. As can be seen from Table 5, the only blocks producing significant changes in F ratio were T1 acute PCS symptomology scores and persistent PTSD symptomology. Although classification of acute PTSD was found to be significantly related to T2 PCS classification, in the presence of the other variables in our regression model, acute PTSD symptomology was not significantly associated to persistent PCS symptomology.

This regression suggested that T1 total RPQ mean scores and T2 TSQ scores (minus items that overlap with the RPQ) would produce the best model of T2 PCS symptomology. Entering just

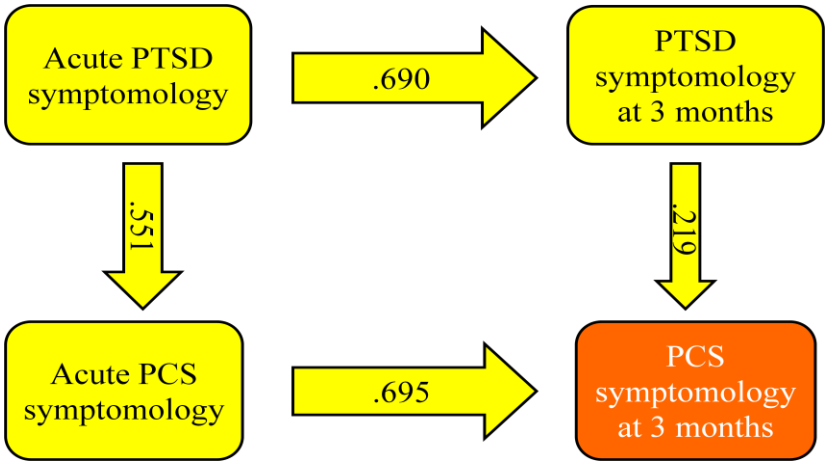
these two variables as predictors revealed they fit marginally better than the larger model, explaining 67.7% of the variance in the data (R^2 adjusted = .669), and are much more associated to T2 PCS symptomology, $F_{2,80} = 83.901$, $p<0.001$. With both variables entered, T2 total RPQ mean scores were positively associated to acute PCS symptomology, increasing by .65 points for every extra point on T1 total RPQ mean scores, and positively associated to persistent PTSD symptomology, increasing by 0.096 for every point on T2 TSQ scores. Both T1 total RPQ means ($t_{82} = 9.61$, $p<.001$) and T2 TSQ scores $t_{82} = 3.03$, $p=0.003$) were individually significantly associated to persistent PCS symptomology. Using a blocking procedure, we found that T1 total RPQ mean scores uniquely accounted for 37.3% of the variance in the data, whereas the unique variance of the T2 TSQ scores was 3.7%.

Establishing a model of influence of PTSD on persistent PCS symptomology

The above results suggested that the factors with the largest influence on persistent PCS symptomology are acute PCS symptomology and persistent PTSD symptomology. As shown earlier, acute PTSD classification (acute PTSD) appeared to be highly related to PCS classification at both time points, but, in the presence of other variables, acute PTSD symptomology did not predict T2 RPQ scores. Therefore we postulated an indirect effect of acute PTSD symptomology on persistent PCS by influencing both persistent PTSD and acute PCS symptomology. A path analysis was performed on the model displayed below in Figure 13. The standardised beta weights obtained from the regression of T1 total RPQ mean scores and T2 TSQ scores on T2 total RPQ mean scores (as above) and of T1 TSQ scores on T2 TSQ scores

and T1 RPQ total scores (without the items overlapping with the RPQ) are displayed on the model as representations of the strength of the association in the pathways.

Figure 20 Proposed model of influence of PTSD on persistent PCS symptomology.



DISCUSSION

The purpose of this study was twofold: first, to examine the change over time in post-concussion symptoms for adult patients with mTBI compared to trauma controls, for both PCS symptomology and classification rates; secondly to investigate the influences on persisting PCS symptomology. The main findings were that PTSD plays a key role in the provenance of persistent PCS, particularly in those with complicated mTBI. PTSD was associated with greater symptom severity and worsening symptomology over time, compared to those without PTSD, who showed a trend for decreasing symptom severity. For those without injury to the head,

PTSD was associated with increased symptomology for symptoms with a mainly psychogenic vector (the RPQ13), whereas in the complicated mTBI group PTSD exacerbated both psychogenic and neurogenic symptoms (headaches, dizziness and nausea, as measured by the RPQ3). As can be seen in the above model, persistent PTSD had a direct influence on persistent PCS, whereas acute PTSD had an indirect influence by contributing to acute PCS and persistent PTSD.

As we expected, there was no evidence for overall symptomology to decrease from two weeks (overall sample *M*=1.795, *SE*=.083) to three months post-injury (*M*=1.794, *SE*=.070), with this trend being consistent across the diagnostic groups. Similarly, there was no evidence of a decrease in rates of participants being classified as having PCS. At T1, 19.3% of the total sample had a classification of PCS (complicated mTBI: 30.3%, uncomplicated mTBI: 15.3%, controls: 17.8%), requiring rating at least three PCS-like symptoms as severe. This figure dropped slightly to 18.4% at T2 (complicated mTBI: 29.4%, uncomplicated mTBI: 9.3%, controls: 21.2%); the majority of the decrease being due to the recovery in the uncomplicated mTBI group. Of those receiving a classification of PCS at three months, 31.3% were new cases, having not been classified as having PCS at two weeks post-injury. A classification of PCS in the complicated mTBI or control group at two weeks tended to persist to three months (complicated mTBI: 80.0%, controls: 83.3%), whereas two thirds of the uncomplicated mTBI group who had an acute PCS classification had recovered by this time, although the proportion of new cases was roughly even across the diagnostic groups. Significantly fewer participants in the uncomplicated group received a classification of PCS than the complicated group at T2.

The lack of resolution of PCS in complicated mTBI and trauma controls is consistent with the literature. Meares et al. (in press), using a different system of PCS classification, found that at an average of 5 days post-injury 40.3% of mTBI patients and 50.0% of trauma controls had PCS, with little change by three months, as 46.8% of mTBI patients and 48.3% of controls had PCS at this stage. Sigurdardottir et al. (2009), using a very similar classification system with the RPQ to this study, investigated persistent PCS in a sample of 115 mixed severity TBI patients and found that 27.8% met the criteria for PCS at three months, with mild injuries more at risk than moderate to severe TBIs.

To date, this is the only study that has investigated differences in rates of persistent PCS classification between complicated and uncomplicated mTBI, with most papers splitting the mTBI group focussing on neuropsychological differences (Iverson, 2006; Lange, et al., 2009). We used a broad definition of "complicated" mTBI; classifying any patient with any sign of loss of consciousness, post-traumatic amnesia or lowered awareness on hospital presentation (Glasgow Coma Scale score of 13-14, rather than full awareness at 15) as "complicated". This was sufficient to differentiate between those with very mild TBI whose symptoms of PCS were largely resolved by three months, from those for whom nearly a third still experienced three or more persistent severe symptoms. This highlights how mTBI is not a homogeneous group (Iverson, 2006; Lange, et al., 2009; Mounce, et al., submitted) and indicates that future research should use caution in selecting mTBI samples and/or in drawing conclusions from mTBI samples that include a large proportion of very minor injuries with no sign of any complicating factors.

As expected, we did not find differences between the complicated mTBI sample and the trauma controls on rate of classification of PCS at either time point, although complicated mTBI did result in more severe overall symptomology scores. Presence of a complicated mTBI was not found to be significantly associated to three month PCS symptomology in our regression model. Our findings thus lend mixed support to the assertion that PCS is not specific to TBI (Iverson, et al., 2007; McLean, et al., 2009; Meares, et al., in press; Meares, et al., 2008), but that psychological factors rather than neurological ones play a dominant role in the genesis and persistence of many of the symptoms. Further weight is lent to this conclusion by the sizeable proportion of new cases of PCS not specific to mTBI, as discussed above, which is very similar to the 38.6% of new cases found at three months post-injury by Meares et al. (in press), again not unique to mTBI.

As noted, the complicated mTBI group were found to rate symptomology as more severe than trauma controls. Particularly, in accordance with our expectations, the symptom severity for headaches, dizziness and nausea/vomiting (the items forming the RPQ3) were rated as less severe in the control group than the remainder of the items (the RPQ13), whereas both scales were of roughly equal severity for the complicated mTBI group; a pattern consistent across the time points. This is in contrast to the trend for these three symptoms to be rated as less severe overall (as shown by the RPQ scale main effect). These particular symptoms are commonly seen in the Emergency Department immediately after mTBI (McCrory, Johnston, Meeuwisse, Aubry, Cantu, Dvorak, Graf-Baumann, Kelly, Lovell, & Schamasch, 2004) and are highly predictive of PCS (de Kruijk, et al., 2002; Stulemeijer, et al., 2006; Stulemeijer, et al., 2008). They have also been found to be distinct from the other items in the RPQ when subjected to a factor analysis (Eyres, et al., 2005), hence the recommendation that they be analysed as a separate scale. Our previous

work (Mounce, et al., submitted) investigating PCS symptomology in the acute phase found that complicated mTBI patients could be differentiated from non brain-injured orthopaedic controls on these items. Also, these symptoms are key to PCS diagnosis in both the ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 1994), both of which require a history of head injury. These results, taken with the literature discussed above, reinforce the assertion that headaches, dizziness and nausea/vomiting are neurogenic, resulting from trauma to the head, rather than caused by psychological factors.

It is clear from our results, however, that psychological factors do play a key role in the provenance of PCS symptomology; specifically post-traumatic stress. In line with our expectations, participants who were classified as having PTSD at T2 experienced significantly more severe symptomology than those not receiving a classification. Indeed, as we anticipated, a trend was evident for symptomology to decrease from T1 to T2 in those without PTSD, but increase over time for those with this condition. Our examination of symptom severity scores supports predictive models of persistent PCS (Meares, et al., in press; Stulemeijer, et al., 2008), which have found PTSD to be a significant predictor of poor recovery.

Presence of PTSD at three months had a particular impact on the complicated mTBI group compared to the trauma controls. PCS symptomology in the complicated mTBI group with PTSD was significantly worse than in those without PTSD and than controls, regardless of PTSD. This pattern of results did not vary with time since the injury. This finding is in keeping with prior work both in military populations (Belanger, et al., 2010; Hoge, et al., 2008; Lippa, et al., 2010) and civilian samples (Bryant & Harvey, 1999), where PTSD in mTBI patients has been

linked to greater PCS symptomology than non-brain-injured controls. Investigating this result further, we found that PTSD exacerbates the symptomology of both the RPQ scales for those with complicated mTBI, but is not associated with worse headaches, dizziness or nausea/vomiting for controls. Thus, psychological distress did not interfere with the experience of these more neurological symptoms for those without mTBI, but it did appear to interact with other factors in the (complicated) mTBI group, worsening symptoms most likely due to a neurological vector. Headaches, dizziness and nausea do not overlap with PTSD symptomology, see Figure 1, and so the mere presence of PTSD does not explain them (Bryant & Harvey, 1999). This effect may be due to the increased cognitive load of dealing with PTSD symptomology decreasing resources to mitigate the neurological factors experienced after mTBI.

PTSD also had a differential effect in men compared to women, with women with and without PTSD, and men without, decreasing in symptom severity between T1 and T2, whereas men with PTSD increased overall. In particular, further analysis revealed that this increase was only on the RPQ13, not on the neurogenic symptoms of headaches, dizziness and nausea/vomiting. This pattern of increased symptoms with a psychological vector may be due to differing coping techniques between men and women, such as men not accessing social support to the same extent (Holeva, Tarrier, & Wells, 2001), avoiding talking through their trauma (American Psychiatric Association, 1994), which is known to be key in resolution of PTSD (Ehlers & Clark, 2000), or perhaps appraising the sequelae of their injury more negatively, leading to "expectation as aetiology".

It has been suggested that patients' perceptions of their likely recovery plays an important role in the persistence of PCS symptomology (Mickevičiene, et al., 2004). Whittaker, Kemp and House (2007) gathered data on PCS symptomology, illness perception, post-traumatic stress, anxiety and depression for 73 patients with mTBI shortly after injury and at three months post-injury. They found that those with acute PCS who believe that their symptoms have a serious detrimental impact on their life, and will continue to do so, are at heightened risk of persistent PCS. Adding in PTSD, anxiety and depression did not improve their model. Hence they conclude that negative appraisals of PCS symptomology and their recovery is the dominant psychological factor in PCS provenance. However, negative appraisals of the injury and its sequelae are, in fact, a well known aspect of PTSD (American Psychiatric Association, 1994). Thus it could be that this facet of PTSD is what particularly influences the persistence of post-concussion symptoms, with re-experiencing symptoms of PTSD possibly being taken as further evidence of poor recovery and thereby reinforcing negative appraisals and expectation (see Ehlers & Clark, 2000).

The second aim of the study was to investigate the major influences on persistent PCS classification and symptomology by examining the relationship of different factors to these variables. Classification of PTSD was found to be highly associated with classification of PCS. In the acute phase post-injury, over 90% participants with a PCS classification had acute PTSD, and 83% of those with three or more persistent PCS symptoms had acute PTSD. At both time points, around a third of those without PCS also had acute PTSD, so the specificity was not as high as the sensitivity. As expected, and suggested by the above discussion of results from the ANOVAs, persistent PTSD was also highly related to persistent PCS, with 87% of those with PCS at three months also having PTSD at this time. Only a sixth of those without persistent PCS

also had PTSD at T2. This relationship was stronger even than the association between acute PCS and persistent PCS. Thus, screening for acute PTSD may be especially useful clinically, as, aside from the direct psychological trauma of acute PTSD that could be treated, those identified are suggested by these results to be at high risk of persistent PCS and post-traumatic stress.

This picture was generally retained when the influences on persistent PCS symptomology were carefully investigated with a hierarchical linear regression. Demographic and pre-injury variables, including psychiatric difficulties, did not show any association to three month PCS symptomology at any stage of the hierarchical regression. This is not consistent with some of the literature, which has found demographics and pre-injury psychiatric difficulties to be important predictors (Bazarian, et al., 1999; Dikmen, et al., 2010; McLean, et al., 2009; Meares, et al., in press; Ponsford, et al., 2000), although this finding is consistent with other work (Stulemeijer, et al., 2008). Litigation and complicated mTBI status were also not found to be influential. Rather, the most influential factor on persistent PCS symptomology was acute PCS symptomology, with PTSD symptomology at three months, excluding items overlapping with PCS, also being highly related. With these factors controlled for, acute PTSD symptomology was not related to persistent PCS symptom severity, at odds with the highly significant relationship evident between acute PTSD classification with three month PCS classification described earlier. This finding of acute PTSD not having an independent contribution compared to persistent PTSD is consistent with Meares et al.'s (in press) finding that the strength of association between PTSD and PCS increases over time.

T1 PCS symptomology scores and T2 PTSD scores accounted for 67% of the variance in the data alone, with acute PCS symptomology uniquely accounting for 37% of the variance compared to 4% explained uniquely by T2 PTSD scores. This different strength of association is represented in our proposed model of the role of PTSD in persisting PCS. In our model, PCS severity in the acute phase post-injury plays the greatest role in the provenance of PCS severity at three months, with persisting PTSD also having a direct effect. We propose that acute PTSD also contributes, albeit indirectly, by influencing both the severity of PCS in the acute phase and persisting PTSD symptomology. This proposal is supported by the significant associations that we found between acute PTSD classification and both acute PCS classification and persistent PTSD classification. Acute post-traumatic stress symptomology is known to be a key factor in the development of persisting PTSD symptoms (Holeva, et al., 2001; Meiser-Stedman, Yule, Smith, Glucksman, & Dalgleish, 2005). Additionally, we postulate that such acute symptomology reduces cognitive resources and coping reserves, thus preventing resolution of acute PCS symptomology, which we find to be mostly psychological in nature, as discussed above (see Williams et al., 2010). Although persistent PTSD symptomology was significantly related to persistent PCS, the strength of the association was low and only 4% of variance in T2 PCS was explained by T2 TSQ scores. These findings suggest that, though the two conditions have some overlap in symptomology and are associated, PCS and PTSD are distinct conditions.

Future work should investigate further the influence of various psychological factors in the genesis and maintenance of persistent PCS. For example, there seems to be at least two routes by which post-traumatic stress symptomology could influence recovery; by contributing to a neurogenic process by lessening coping skills and cognitive resources, and/or by the negative appraisals of the trauma and its consequences leading to expectation as aetiology. A more

thorough examination of the psychological mechanisms involved in PCS development would thus be useful, especially if controlling for somatic factors, such as post-injury pain. Our results also suggest that treatment for PTSD may reduce PCS symptomology, even those symptoms that appear neurogenic (headaches, dizziness and nausea), as these symptoms were only elevated in the complicated mTBI group with likely PTSD. This assertion should be subjected to proper testing. Also, it is unclear from our results why males with PTSD should be at particular risk of worsening PCS, except headaches dizziness and nausea. More investigations into gender differences in recovery after minor injury are warranted.

This study prospectively recruited participants seen in the ED for mTBI or orthopaedic injuries, rather than sampling from those seeking clinical care for symptoms that developed later or those involved in litigation. This avoided artefacts due to such a sampling bias, such as heightened levels of symptomology of PTSD or PCS. The longitudinal design, as opposed to cross-sectional research, also adds strength to the analyses of differences between the time points. Our use of a control sample who sustained minor injuries sparing the head is another strength, as this allowed us to control for injury related variables, as well as demographic and pre-injury factors, enabling a clear investigation into the effect of sustaining an mTBI. Additionally, separating out the very mild, uncomplicated TBIs from the complicated mTBIs facilitated a more detailed exploration of those at risk in a group that is not homogeneous (de Kruijk, et al., 2002; Iverson, et al., 2007), but is often treated as such.

A limitation of the work, however, is the low response rate, especially for the complicated mTBI sample. The final sample used in our analyses was also significantly older than non-responders

and had a higher proportion of women. It is possible that these differences to the general population of patients seen at the ED for these injuries may make these results less generalisable. However, in the final sample on which the ANOVAs and regression were conducted, there were no inter-group differences in age, gender, highest educational attainment or rates of those experiencing pre-injury trauma/stress, head injury requiring hospitalisation or need for mental health support. Since the aim of our investigation was on differences between groups, rather than reporting prevalence rates, these responder biases should not impact the reliability of our findings due to the lack of differences between the groups. Also, gender effects were controlled for in the ANOVAs by entering gender as a between-subjects factor and age was not found to be related to persistent PCS and was therefore not required as a covariate. Furthermore, in our regression model, no demographic or pre-injury variables were found to be reliably associated to PCS at three months. Despite a low response rate, which is nevertheless typical of work following attendees at EDs (Whittaker, et al., 2007), differences were large enough to be evident and, for the most part, in line with our predictions and with the wider literature, as discussed above.

CONCLUSION

Three or more severe post-concussive symptoms are commonly experienced three months after injury by nearly a third of mTBI patients with any sign of complication and around a fifth of orthopaedic patients with a similar injury severity. There was very little change over time, with approximately 80% having three or more symptoms at two weeks continuing to have such

symptomology at three months. Noticeable recovery was only observed in mTBI patients with very mild injuries who experienced no LOC, PTA or amnesia. This further implies that treating mTBI as a homogenous group is unwise. Post-traumatic stress appears to have a key role in the genesis or maintenance of symptoms, with elevated PCS levels only evident in those with three or more PTSD symptoms. Persistent PTSD symptomology was strongly predictive of persistent PCS, whereas acute PTSD symptomology appears to play indirect role in the maintenance of PCS. Of particular note is that headaches, dizziness and nausea were only considered a problem for complicated mTBI patients with co-morbid PTSD. This suggests that psychological factors may be responsible even for symptoms commonly held to have a neurological vector. Further work should seek to better understand factors influencing PTSD after minor injury and investigate the effectiveness of psychological interventions on both PTSD and PCS.

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Study Three - Post-Traumatic Stress after Mild Traumatic Brain Injury: The Influence of Memory Quality

ABSTRACT

Background

The development of post-traumatic stress disorder (PTSD) symptomology following mild traumatic brain injury (mTBI) is controversial. Recent models of PTSD have highlighted quality of memory for the trauma, such that memories are hard to put into words, are highly sensory and fragmented, as a key factor in the maintenance of symptomology. We assessed change over time in PTSD symptomology in those with mTBI compared to a control group with other minor injuries. We also investigated differences in memory quality and used a stepwise linear regression to select the most influential predictors of persistent PTSD symptomology. We expected individuals with mTBIs to have similar levels of PTSD to orthopaedic injury controls, that mTBI would produce poorer memory quality and that memory quality would be an influential predictor of persistent PTSD symptomology.

Method

Consecutive adult attendees of an Emergency Department with mTBI or orthopaedic injury were prospectively recruited and completed the Trauma Screening Questionnaire (TSQ) and the Trauma Memory Quality Questionnaire (TMQQ), as well as event appraisals, at two weeks and three months post-injury. The sample at the second time point consisted of 18 with complicated mTBI, 43 with uncomplicated mTBI and 33 orthopaedic controls.

Results

No differences were found between the mTBI group and controls in overall symptomology, distribution of symptoms across the clusters of PTSD (re-experiencing and hyper-arousal), change of symptomology over time, or in characteristics of trauma memory. Poorer memory quality was highly correlated with worse PTSD symptoms on both clusters at both time points. Memory quality and attributions of blame to others were the only variables selected by the regression procedure as predictors of persistent PTSD symptoms.

Discussion

mTBI is not a protective factor for the development of PTSD, as had been claimed. The characteristics of trauma memory (i.e. memory quality) were highly influential in the development of PTSD symptomology, in support of cognitive theories. Our results suggest a need for meaning in explaining the trauma – a clear story of what happened – for better post-trauma recovery.

INTRODUCTION

Mild traumatic brain injury (mTBI) is a common injury in adults and represents a major public health problem globally (Bruns & Hauser, 2003; Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007). It is estimated that 6.6% of those attending Emergency Departments (EDs) in a given year have a TBI (Swann & Walker, 2001), of which 80-90% are 'mild' (Kraus, McArthur, Silverman, & Jayaraman, 1996; Thornhill, Teasdale, Murray, McEwen, Roy, & Penny, 2000; Yates, Williams, Harris, Round, & Jenkins, 2006). In the United Kingdom, the annual incidence rate of hospital admission for head injury is 229/100,000 (Tennant, 2005), although the rate of unattended and ED-managed injuries is likely to be much higher (Bruns & Hauser, 2003). Disability rates one year after injury have been found to be as high after mTBI (47%) as in moderate (45%) and severe (48%) head injury (Thornhill, et al., 2000). Diagnosis of mTBI typically involves a brief loss of consciousness (less than half an hour), a short period of posttraumatic amnesia (PTA) - a confusional state in which memory formation is disturbed – and altered levels of awareness, as measured by the Glasgow Coma Scale (American Congress of Rehabilitation Medicine, 1993; Vos, Battistin, Birbamer, Gerstenbrand, Potapov, Prevec, Stepan, Traubner, Twijnstra, Vecsei, & von Wild, 2002). It is not unusual for someone with TBI to have amnesia for all or part of the incident in which they received their injury. It is for this reason that it was proposed that post-traumatic stress disorder, which is based on memory of a traumatic event, could not be experienced after even mild TBI (Mayou, Bryant, & Duthie, 1993; Spordone & Liter, 1995).

After head injury, an individual usually experiences various cognitive, psychological and somatic difficulties, such as poor concentration, memory difficulties, headaches and irritability (Binder, 1986; Bohnen & Jolles, 1992). These are usually short-lived and resolve within a month, but they may persist as post-concussion syndrome (PCS) in a significant minority (American Psychiatric Association, 1994; Dikmen, Machamer, Fann, & Temkin, 2010; Iverson, Zasler, & Lange, 2007; Mounce, Williams, Jones, Harris, Haslam, & Jetten, unpublished; World Health Organization, 1992). Post-traumatic stress disorder (PTSD) is a common psychological consequence of the kind of incidents that mTBIs are typically caused by, e.g. road traffic accidents, assaults and military conflict. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994), PTSD may develop after the experience of actual or threatened loss of life or serious injury to oneself or others, where this experience was accompanied by feelings of intense fear, helplessness and horror. Incidents that result in mTBI may well qualify as such antecedents. In order for PTSD to be diagnosed, symptoms across the three domains of re-experiencing (e.g. flashbacks), avoidant behaviour/emotional numbing and hyper-arousal (e.g. difficulty sleeping) must be present for longer than one month and must cause significant functional impairment.

The role of memory has been emphasised in recent accounts of the underlying mechanisms of PTSD. Ehlers and Clark (2000) have put forward a comprehensive cognitive model for persistent PTSD, based on previous theoretical and empirical work, which postulates that symptoms result from a sense of serious current threat. This persistence sense of current threat is argued to result from three main cognitive mechanisms; poor quality of memory for the trauma, excessively negative appraisals of the trauma and its consequences, and coping strategies that prevent change in the nature of the traumatic memories and appraisals. Data-driven processing during the

trauma, characterised by overwhelming sensory impressions, is proposed to result in memories for the traumatic event that are poorly elaborated and integrated with other autobiographical memories, such that they are not contextualised within their correct place in the past. Memories of this nature are thought to be predominantly sensory based (seeing, hearing or smelling aspects of the event during recall) and harder to verbalise into a narrative. These qualities make memories more likely to be intrusive. Additionally, they propose the presence of strong stimulus-response and stimulus-stimulus associations.

Similarly, but taking a neuroscientific approach, Brewin and colleagues (Brewin, 2001; Brewin, Dalgleish, & Joseph, 1996) have proposed that separable brain regions may be involved in two distinct memory systems; one for verbally accessible memories (VAMs) and a second for situationally accessible memories (SAMs). Whereas VAMs are easily accessible by conscious though and readily verbalised, as is normal for autobiographical memories, SAMs encode different sensory and physiological aspects of events and are not readily accessible for conscious amendment and editing, leading to the characteristic re-experiencing central to PTSD.

Initial work has provided support to the assertion that memories' phenomenological quality plays a key role in the genesis and maintenance of PTSD. Symptoms of PTSD have been found to be predicted by more disorganised and more sensory-based memories in a prospective sample of adult survivors of assault (Halligan, Michael, Clark, & Ehlers, 2003). A further analysis of the same set of data revealed that it was the qualities of the intrusive memories that were more predictive of PTSD, rather than just the presence of intrusive memories (Michael, Ehlers, Halligan, & Clark, 2005). Hellawell and Brewin (2004) asked 62 participants with a diagnosis of

PTSD to write a detailed account of their trauma. They were then asked to identify which sections of their account were written whilst experiencing a flashback and which were in periods of ordinary memory. Those written in a period of flashback were more perceptually detailed, made more mention of death, fear, helplessness and horror and made greater reference to the present tense. In contrast, ordinary memory sections made more mentions of secondary emotions, such as anger and guilt. A study into acute stress disorder (ASD) in children and adolescents, using a measure of memory quality based on the theories outlined above, found this construct to be significantly capable of distinguishing between those with and without an ASD diagnosis (Meiser-Stedman, Dalgleish, Smith, & Yule, 2007a).

As noted above, initial empirical studies seemed to suggest that PTSD did not occur after mTBI (Mayou, Bryant, & Duthie, 1993). It was then proposed that PTSD and injury to the head causing loss of consciousness were mutually exclusive diagnoses (Spordone & Liter, 1995), because "patients who sustain PTSD simply cannot 'forget' the traumatic event, whereas patients who sustain mTBI (e.g. cerebral concussion) have no recollection of the event" (p.406). However, recent research has shown that sustaining an mTBI results in a similar prevalence of PTSD to those with other injuries not involving the head (Glaesser, Neuner, Lutgehetmann, Schmidt, & Elbert, 2004; Jones, Harvey, & Brewin, 2005; Mayou, Black, & Bryant, 2000). Indeed, using a sample of 1148 adult admissions after road traffic accidents, Mayou et al (2000) found that a brief period of unconsciousness, as incurred due to mTBI, significantly increased PTSD symptomology relative to those without a period of unconsciousness, or even injury to the head, marking a complete contrast to their previous study cited above. There is, then, an apparent paradox, with the nature of memory for the event at the centre of the controversy.

Several authors have sought to explain this paradox (Bryant, 2001; Harvey, Brewin, Jones, & Kopelman, 2003; Harvey, Kopelman, & Brewin, 2005; Joseph & Masterson, 1999). McMillan, Williams and Bryant (2003) review four ways in which those who were unconscious for a traumatic event or have amnesia as a result of TBI could still develop PTSD. Firstly, it is possible that declarative memories of events surrounding the trauma may be a basis for re-experiencing, such as seeing an approaching collision or coming round in hospital. Secondly, there may be "islands of memory", where patches of declarative memory where laid down as someone drifted in and out of consciousness. Thirdly, there may be "affect without recollection" (King, 2001), whereby strong stimulus-response and stimulus-stimulus associations produce re-experiencing symptoms even with complete amnesia for what actually transpired. Lastly, re-constructed memory, pieced together from others' reports, can form the basis of traumatic re-experiencing, just as PTSD may develop vicariously after hearing about the traumatic experience of a loved one (PTSD diagnosis, American Psychiatric Association, 1994).

Thus, although lack of memory for the traumatic event has been found to be a protective factor against PTSD in mTBI (Caspi, Gil, Ben-Ari, Koren, Aaron-Peretz, & Klein, 2005; Gil, Caspi, Ben-Ari, & Klein, 2006; Gil, Caspi, Zilberman Ben-Ari, Koren, & Klein, 2005; Glaesser, et al., 2004), mTBI does not necessarily mean one will not have any memory from which PTSD may result. Indeed, the similar or increased rates of PTSD following mTBI compared to non head-injured controls described above may be due to poorer quality of memory for the trauma, as described by Ehlers and Clark (2000) and Brewin et al. (1996), despite possibly less declarative memory. The memory disturbances associated with mTBI from PTA and amnesia shortly after injury, and persistent PCS, such as difficulty remembering and concentrating, may prevent proper encoding and integration of trauma memories into autobiographical memory, thus inhibiting

patients forming a clear 'story' of what happened to them, which is important for recovery from traumatic stress (Ehlers & Clark, 2000; Mayou, et al., 2000; McMillan, et al., 2003). However, there have been no studies investigating the influence of memory quality on PTSD in those with mTBI compared to those without. Recent work also suggests that mTBIs may be associated with a different distribution of symptoms across the three domains of PTSD; although less re-experiencing may develop, there may be greater levels of avoidance and hyper-arousal symptoms (Caspi, et al., 2005; Gil, et al., 2005; Jones, et al., 2005) and PTSD may diagnosable due to these.

This study, therefore, investigated the levels of PTSD symptomology in consecutive ED attendees with mTBI, compared to a control group with minor injuries not involving the head, at two weeks and three months post-injury. We particularly explored differences in quality of trauma memory between these groups – whether memories were clear, coherent and easily verbalised, or mainly sensory, with a sense of current threat and that were hard to put into words. The comprehensive memory quality measure developed by Meiser-Stedman and colleagues (Meiser-Stedman, Smith, Yule, & Dalgleish, 2007b) was utilised, as used in Meiser-Stedman et al. (2007a) discussed above . We further investigated the role that memory quality plays in the persistence of PTSD symptomology using a regression model, in addition to demographic, pre-injury and incident-related factors. We also explored the association of appraisals of the event, such as fear of death and/or injury, feelings of helplessness and attributions of blame to PTSD symptomology in this model, as these factors have previously been found to be highly predictive (Jeavons, Greenwood, & Home, 2000; Williams, Evans, Needham, & Wilson, 2002). Williams et al. (2002) found that external attributions of blame were associated to PTSD, despite injury severity, demographic and pre-injury variables not being significantly related.

Specifically, we expected 1) similar rates of PTSD symptomology in the mTBI group compared to controls and 2) that levels of PTSD symptomology would decrease between two weeks to three months post-injury. Based on previous work, we expected 3) that participants with mTBI would develop less re-experiencing symptomology and more hyper-arousal symptomology (our measure did not include the avoidance cluster). We predicted that, due to memory disturbances associated with mTBI, 4) participants in this group would have a poorer quality of memory for their trauma than controls. 5) We expected that memory quality would be significantly associated to PTSD symptomology at both time points, as evidenced by correlations, and 6) would be a useful factor in a model to predict symptomology.

METHOD

Participants were prospectively recruited from adult consecutive self-referrals to the Emergency Department (ED) of the Royal Devon and Exeter Hospital, UK, between November 2008 and October 2009 with either a mTBI or orthopaedic injury. Participants were approached for recruitment at two weeks post-injury (time 1, T1) via post and were contacted for a follow-up assessment at three months post-injury (time 2, T2). Informed written consent to participate and to access participants' medical records was obtained. The study was approved by the regional National Health Service Research Ethics Committee. Patients were eligible for participation if they were aged between 18-65 years and had received a diagnosis of either mTBI or an upper limb fracture. Exclusion criteria were attendance as a result of domestic violence or sexual

assault, previous attendances within the past 5 years for similar injuries (as an indicator of domestic violence), attendances for urgent care for a pre-existing medical condition, significant history of mental health problems or learning disabilities and inability to complete questionnaires due to non-fluency in English.

The sample

Sample for time 1: two weeks post-injury

As reported in (Mounce, et al., unpublished), 157 participants enrolled at the first time point. This included 110 with mTBI (16.1% response rate) and 47 orthopaedic controls (21.9% response rate), though this difference was not significant ($\chi^2 = 3.681$, df = 1, ns), which comprises an overall response rate of 17.5%. Chi-square tests revealed that there were no reliable differences in the initial sample across the two groups in ratio of men to women ($\chi^2 = 2.821$, df = 1, ns), highest educational attainment ($\chi^2 = 0.367$, df = 2, ns), or rates of those who had experienced three pre-trauma factors; previous stress/ trauma ($\chi^2 = .182$, df = 1, ns), previous need for mental health support ($\chi^2 = .748$, df = 1, ns) and previous admission for a head injury ($\chi^2 = .168$, df = 1, ns). An independent samples t-test found no significant age differences ($t_{145}=1.950$, ns), see Table 1.

Age and gender were the only variables known for non-responders at time 1, other than injury type. Chi-square tests found that responders at time 1 were more likely to be women in both the orthopaedic control group ($\chi^2 = 7.519$, df = 1, p=.006) and the mTBI group ($\chi^2 = 11.595$, df = 1, p=.001). Independent samples t-tests also found that responders were significantly older for the

orthopaedic sample (t_{213}=3.599, p<.001), as well as the mTBI group (t_{673}=5.676, p<.001). See Table 1 for descriptive data.

Table 10 Demographic characteristics of the samples at two weeks post-injury and differences between initial responders and non-responders.

Responders		Orthopaedic injury	mTBI
n=157		n=47	n=110
	Mean age (SD)	47.80 (13.42)	42.82 (14.61)
	Men (%)	15 (33.9)	51 (46.4)
Highest level of education (%):	Secondary school	12 (27.3)	33 (31.4)
	College	18 (40.9)	43 (41.0)
	University	14 (31.8)	29 (27.6)
	Suffered major stresses / trauma prior to injury	9 (20.5)	18 (17.5)
	Previous need for mental health support	3 (7.0)	12 (11.8)
	Previous mTBI	5 (11.4)	14 (13.9)
Non-responders		Orthopaedic injury	mTBI
n=734		n=168	n=566
	Mean age (SD)	39.36 (14.77)	34.36 (13.53)
	Men (%)	88 (52.4)	363 (64.1)

The number of participants involved in the above analyses occasionally differed from the overall sample n due to lack of responses for certain items.

Sample for time 2: three months post-injury

Of this original sample, 59.9% completed the study at three months post-injury. The sample for the second time point was comprised of 61 with mTBI and 33 orthopaedic injured controls. As shown in Table 2, there were no differences in the proportion of those who responded at three months between the two groups (χ^2 = 2.985, df=1, ns), nor were there differences in the ratio of men to women (χ^2 = 0.250, df=1, ns) or in highest educational attainment (χ^2 = 2.250, df=1, ns) between responders and non-responders for this time point. However, those who responded at time 2 were significantly older (t_{145} = -2.864, p=0.005) than those who did not complete the follow up measures. Importantly for the analyses in this investigation, there were also no differences in the proportions of those meeting cut-off criteria for likely PTSD two weeks post-injury between those who took part at three months post-injury and those who did not (χ^2 = .066, df=1, ns). The procedure for making this classification is described below. Within the responders at three months post-injury, there were no reliable differences between the diagnostic groups in age (t_{88} = 1.068, ns), proportion of men to women (χ^2 = 1.062, df=1, ns), highest educational attainment (χ^2 = .536, df=2, ns), pre-injury stress/trauma (χ^2 = 1.288, df=1, ns), pre-injury need for mental health support (χ^2 = .136, df=1, ns) or previous hospitalisation for head injury (χ^2 = .216, df=1, ns). Descriptive data for these analyses can be found in Table 3.

Table 11 Demographic characteristics of responders compared to non-responders at three months post-injury.

	Responders n=94	Non-responders n=63
Diagnostic group (%):		
Orthopaedic injury	33 (70.2)	14 (29.8)
mTBI	61 (64.9)	49 (44.5)
Mean age (SD) *	46.99 (13.59)	40.18 (14.76)
Men (%)	38 (40.4)	28 (44.4)
Highest educational attainment:		
Secondary school	27 (31.4)	18 (28.6)
College	31 (36.0)	30 (47.6)
University	28 (32.6)	15 (23.8)
Met criteria for PTSD at two-weeks (%)	34 (43.6)	24 (41.4)

***** Significant at $p<.05$

Table 12 Demographic characteristics of the samples at three months post-injury.

	Orthopaedic injury n=33	mTBI n=61
Mean age (SD)	49.10 (13.83)	45.88 (13.45)
Men (%)	11 (33.3)	27 (44.3)
Highest educational attainment (%):		
Secondary school	8 (26.7)	19 (33.9)
College	12 (40.0)	19 (33.9)
University	10 (33.3)	18 (32.1)
Suffered previous trauma/stress (%)	8 (26.7)	9 (16.4)
Previous need of mental health support (%)	2 (6.9)	5 (9.3)
Previous hospitalisation for mTBI (%)	5 (16.7)	7 (13.0)

Assessment procedure and measures

Participants were sent a questionnaire by post two weeks after injury, which included all the study measures. The same questionnaire was sent again at three months post-injury. Those that consented to take part completed the questionnaire and returned it to the researchers, along with a signed consent form. If they did not wish to participate, at either time point, they did not return

the questionnaire. Those that did not participate at T1 were not approached at T2. The questionnaire included the following:

Demographics and pre-injury status

Participants reported their age, gender and highest educational attainment and answered three questions relating to their pre-injury status, all of which required yes/no responses. These were "had you suffered a previous stress or trauma prior to this incident?", "had you needed any mental health support?" and "had you ever had a head injury that needed hospitalisation?" They were asked with what frequency they used non-prescribed drugs and/or alcohol, either "not at all", "sometimes" or "frequently".

Injury/incident related factors

Participants rated the severity of the incident that led to them being injured as either "minor", "serious", "severe" or "extreme" and indicated whether or not compensation was being sought. Participants then stated whether or not they had been unconscious and for how long. We then asked two general questions of our own devising about the state of their memory for the incident; which were answered yes or no; "I have a good memory of all that happened" and "my memory of what happened is based on what I was told afterwards". The former was included to investigate whether such a simple measure of memory quality could discriminate between values on a scale of post-traumatic stress and the latter assessed whether participants' had declarative memories of the incident, or whether they had pieced the story together from others' reports.

Participants were then asked to read a series of statements that probed the nature of their attributions of blame, controllability and fear during the event, which are associated with PTSD (Jeavons, et al., 2000; Williams, et al., 2002), and answer yes or no to whether they were true for them. These were "when it happened, I thought I would be seriously injured", "when it happened, I thought I would die", "I felt I had control over what happened", "I feel someone else was to blame", "I feel I was to blame for what happened", "the incident could have been avoided" and "I feel no one was to blame for what happened".

Post-traumatic stress

The questionnaire included the Traumatic Stress Questionnaire (TSQ, Brewin, Rose, Andrews, Green, Tata, McEvedy, Turner, & Foa, 2002), a 10 item measure of post-traumatic stress that has been found to possess excellent psychometric properties and agreement to clinical interviews. Participants were asked to report which symptoms they had experienced at least twice in the past week, in relation to their injury-incident. The first 5 items measure re-experiencing symptoms, such as flashbacks and reliving feelings felt at the event, and the last 5 measure hyper-arousal, such as being easily startled.

Trauma memory quality

The Trauma Memory Quality Questionnaire (TMQQ) is an 11 item instrument that measures the extent to which participants have a high-quality, well-elaborated memory of a traumatic event that is integrated properly into one's autobiographical memory, as opposed to memory that is incomplete, highly sensory and/or is not tied to a specific point in one's past (Meiser-Stedman, et al., 2007b). Its design was informed by Brewin et al.'s (1996) dual representation model of

memory in PTSD, as well as Ehlers and Clark's (2000) cognitive model of persistent PTSD, and is the only established questionnaire for memory quality. Items include "My memories of what happened are mostly pictures or images", "When I remember the event I feel like it is happening right now", "My memories of the event are very clear and detailed" and "I can talk about what happened very easily". For the purposes of this study, the item "I can't seem to put the frightening event into words" was omitted, as the aspect this item measures is also measured by another item ("I can talk about what happened very easily") and the length of the questionnaire needed to be kept to a minimum. Participants were asked to indicate how much they agreed with the item statement on a 3-point scale of "1 – No" , "2 – Not sure" and "3 – Yes".

Data analysis

The TSQ was designed to be analysed as a single scale (Brewin, et al., 2002), but it can also be split into two subscales; one measuring re-experiencing symptomology of PTSD and the other measuring the hyper-arousal cluster. As described above, all items on the TSQ require yes/no responses. "No" was coded as 0 and "yes" coded as 1, giving each subscale a range of 0-5, with higher numbers reflecting the presence of more symptoms. In order to assess whether there was change over time in PTSD symptomology across the two symptom clusters measured by the TSQ, we used repeated measures analysis of variance (ANOVA) with a 2(time post-injury; two weeks, three months) x 2(PTSD cluster; re-experiencing, hyper-arousal) x 2(diagnostic group; mTBI, control) x 2(gender; men, women) mixed factorial design. Time post-injury and PTSD cluster were entered as repeated measures and the remainder were between subjects factors. The main effect of time post-injury was used to investigate any change in TSQ scores between the

time points. The means displayed for this will be an average of the means for the two subscales. The main effect of PTSD cluster was used to assess whether, across both time points taken together, there were differences in the amount of symptomology endorsed between re-experiencing and hyper-arousal symptoms. The interaction between time post-injury and PTSD cluster allowed us to examine whether there were different changes over time between the re-experiencing and hyper-arousal subscales. The main effects of group and gender were used to investigate whether there were differences in overall PTSD symptomology between mTBIs and controls, and men and women respectively. Interactions between the main effects were also explored. No covariates were used as there were no differences between groups on any of the demographic or pre-injury factors, as reported above.

To examine differences in memory quality, we conducted another repeated measures ANOVA using T1 and T2 TMQQ scores, this time with a 2(time post-injury; two weeks, three months) x 2(diagnostic group; mTBI, control) x 2(gender; men, women) mixed factorial design, with time post-injury being a repeated measure and the rest being between subjects factors. The main effect of time post-injury allowed us to examine whether memory quality changed between two weeks and three months, whereas the main effects of diagnostic group and gender assessed whether there were differences between the levels of these factors on TMQQ scores across both time points taken together. Interactions between the main effects are also reported. Again, no covariates were selected due to lack of differences between the groups in the T2 sample. We also examined the relationship between memory quality and PTSD by correlating TMQQ scores with the total TSQ scores, and the subscales of re-experiencing and hyper-arousal, for both time points.

Lastly, to assess the influence of demographics, pre-injury status, injury/incident related factors, thoughts and feelings during the event, attributions of blame and memory quality on persistent PTSD symptomology, we used a multiple linear regression with a forward stepwise procedure to select the best subset of these factors. The full TSQ scale was used as the dependent variable, with a range of 0-10, with higher values indicating the presence of more symptoms. The stepwise procedure adds one variable at a time into a model, looking for the factor that produces the most significant change in F ratio for the model. At each step, it also considers removing variables from the model that become redundant on adding the new factor. The procedure stops adding variables to the model when a significant change in F ratio cannot be achieved by doing so. Thus, the procedure produces an efficient model, including only factors with a strong association to the dependent variable.

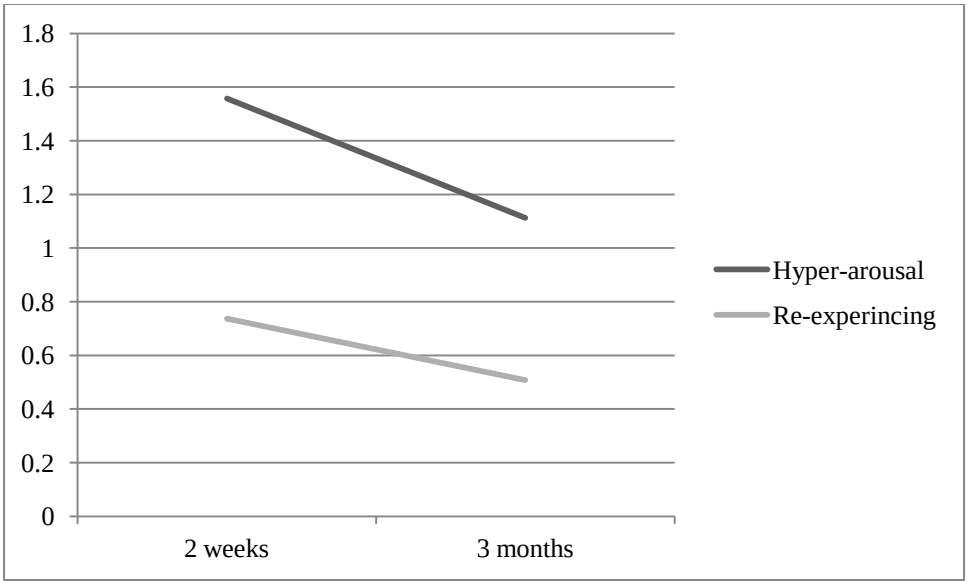
RESULTS

Differences in Post-traumatic stress symptomology

The main effect of time post-injury was significant, $F_{1,70}=7.323$, $p=.009$, revealing that mean PTSD symptom scores reliably decreased from two weeks post-injury ($M=1.147$, $SE=.158$) to three months post-injury ($M=.810$, $SE=.125$), supporting our prediction. Also in line with our expectations, there were no reliable differences between symptomology scores of those in the mTBI group compared to controls across both time points taken together, as evidenced by a non-

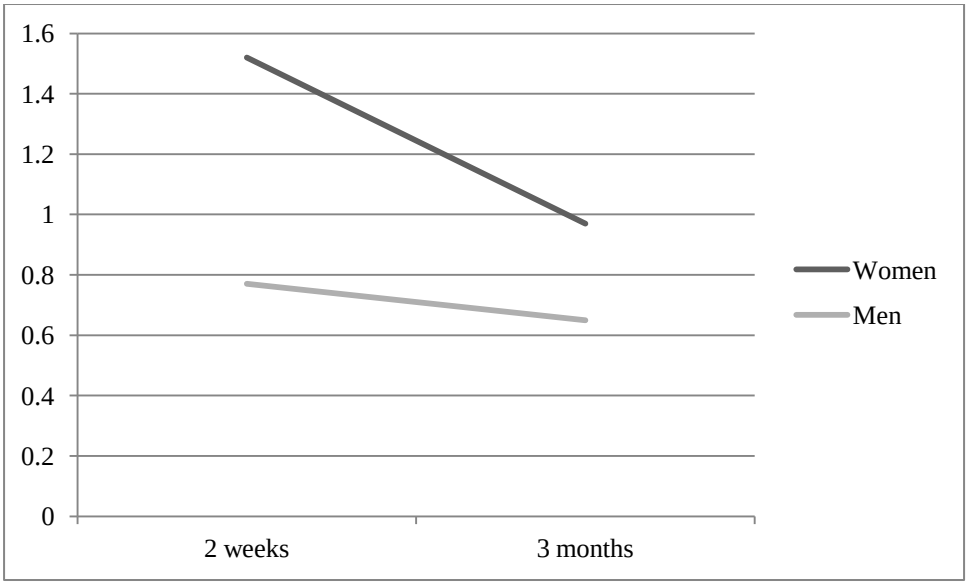
significant main effect of diagnostic group, $F_{1,70}$=.976, ns. The main effect of PTSD cluster was highly significant, $F_{1,70}$=25.689, p<.001, with more hyper-arousal symptoms experienced across groups (M=1.334, SE=.153) than re-experiencing symptoms (M=.623, SE=.140). The interaction between PTSD cluster and diagnostic group was not significant, $F_{1,70}$=.078, ns, indicating that both mTBIs and controls experienced the same pattern of more hyper-arousal symptoms than re-experiencing. Our third hypothesis that this would be true for the mTBI group is thus supported, though this result is not a distinguishing feature of this group. The reduction in symptomology over time did not vary between the PTSD clusters, as shown by a non significant interaction between time post-injury and PTSD cluster, $F_{1,70}$=1.469, ns (see Figure 1), nor did the mTBIs differ from controls in the decrease of overall symptomology between T1 and T2, as the interaction between time and diagnostic group was also not significant, $F_{1,70}$=1.156, ns.

Figure 21 Reduction in PTSD over time was the same for both symptom clusters.



The main effect of gender, however, was significant, $F_{1,70}$=4.301, *p*=.042, with women having reliably more symptoms overall (*M*=1.245, *SE*=.157) than men (*M*=.712, *SE*=.204). There was also a marginally significant interaction between gender and time post-injury, $F_{1,70}$=3.126, *p*=.081, with a trend for women to have greater reduction in symptomology over time (T1: *M*=1.524, *SE*=.193; T2: *M*=.966, *SE*=.153) than men (T1: *M*=.770, *SE*=.269; T2: *M*=.654, *SE*=.199). See Figure 2 below.

Figure 22 Differential reduction in PTSD over time between men and women.

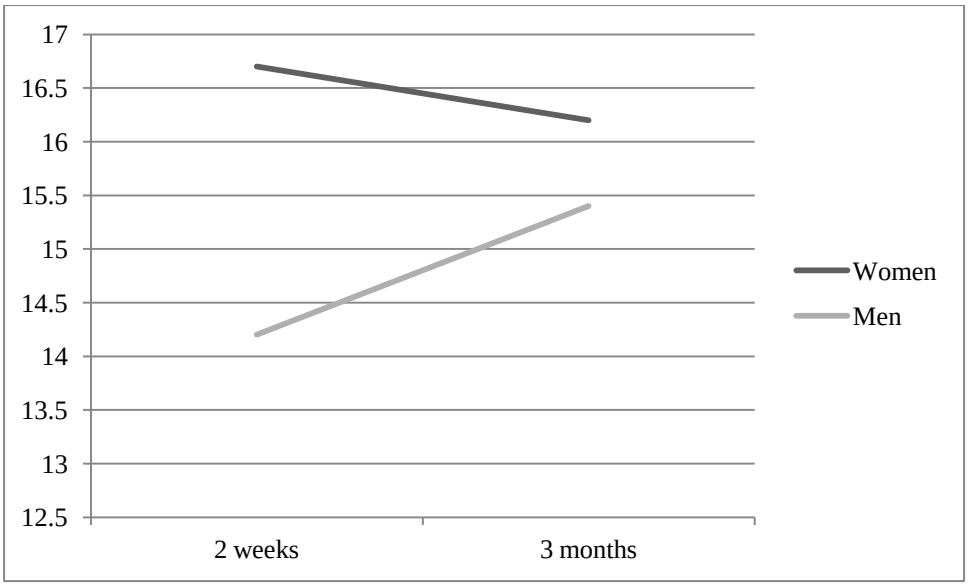


Differences in Quality of memory for the traumatic event

In the analysis of the TMQQ, the main effect of time was not significant, $F_{1,78}$=.823, ns, indicating that there were no reliable changes in memory quality between two weeks (*M*=15.473, *SE*=.407) to three months (*M*=15.894, *SE*=.467) post-injury. The main effect of diagnostic group

was not significant, $F_{1,70}$=.529, ns, meaning that the mTBI group (*M*=15.894, *SE*=.433) did not have significantly poorer memory quality than controls (*M*=15.394, *SE*=.661), so our hypothesis was not confirmed. Nor were there different changes in quality of memory over time between the groups, as the interaction between group and time was not significant, $F_{1,70}$=.769, ns. Once again, gender differences were apparent, with the women rating their memory as having a poorer quality (*M*=16.454, *SE*=.456), in terms of being more sensory, less complete and less easily verbalised, than men (*M*=14.833, *SE*=.645), $F_{1,78}$=4.204, *p*=.044 (note that higher means represent worse memory quality). The interaction between gender and time point was also significant, $F_{1,78}$=5.295, *p*=.024, indicating that the change over time of memory quality was different for men compared to women. Specifically, the means demonstrate that men's memory quality worsened over time (T1: *M*=14.229, *SE*=.667; T2: *M*=15.438, *SE*=.762), whereas women's tended to improve (T1: *M*=16.717, *SE*=.470; T2: *M*=16.192, *SE*=.539). Descriptive data are displayed in Figure 3 below.

Figure 23 Changes in memory quality over time for men and women (higher scores reflect poorer memory quality).



Associations between post-traumatic stress and memory quality

Bivariate correlations were performed to assess the degree of relationship between the TMQQ scores and the PTSD total scale score, as well as the re-experiencing and hyper-arousal subscales, at both time points. At two weeks post-injury, poorer quality of memory was highly associated to greater total PTSD symptomology (r=.510, p<.001), as well both more re-experiencing (r=.507, p<.001) and more hyper-arousal symptomology (r=.404, p<.001). By three months post-injury, the strength of these associations had increased further. Memory quality indicative of more perceptually based, less easily verbalised memories that seem current, rather than properly associated to a time in the past, was highly associated to more PTSD total symptomology

(r=.616, p<.001) , more re-experiencing (r=.623, p<.001) and more hyper-arousal (r=.503, p<.001).

Influences on persistent PTSD symptomology

In order to investigate which factors have the greatest influence on PTSD symptomology at three months post-injury, we used multiple regression with a stepwise procedure, as described above. This procedure aims to select the best subset of predictors from those available. The possible predictors were diagnostic group, gender, age, highest educational attainment, whether the participant had experienced pre-injury stress/trauma, whether they had required mental health support prior to their injury, whether they had sustained a previous head injury that required hospitalisation, whether they were seeking compensation for the incident, a self-rating of the severity of the incident, a self-report of whether or not they had lost consciousness (N.B. not whether loss of consciousness was in their medical records), whether or not they had a good memory of what happened, whether their memory was made up from what they had been told afterwards, whether they thought they would die or be injured, whether they felt they had control over what happened, whether they felt the incident could have been avoided, whether they blamed someone else for what happened, whether they blamed themselves, whether their memories of the event were clear and detailed and T1 TMQQ scores. The variable relating to whether the participants' memories of the event are clear and detailed is, in fact, an item from the TMQQ. We entered this separately into the available factors because we felt that this encapsulates whether a patient has a complete or patchy memory for what happened.

The stepwise procedure selected a three variable model, which had a poor overall fit, explaining just 32.2% of the variance in the data (R^2 adjusted = .287). The model was, however, highly significantly associated to T2 PTSD symptomology scores, $F_{3,58}$=9.199, p<.001. The three variables selected were 1) whether or not the participant felt someone else was to blame, 2) memory quality at T1 and 3) whether or not participants' memories of the event were clear and detailed. In the presence of the other variables, TSQ scores at T2 were 1.215 points higher for those who blamed someone else for the incident. T2 TSQ scores were positively associated to T1 TMQQ scores, increasing by .249 points for every extra point on the TMQQ, and were negatively related to clear and detailed memories of the event, such that TSQ scores decreased by .852 points for every extra point on the 3-point scale of "1 – no", "2 – not sure" and "3 – yes", when asked if that statement was true for them. Of these three predictors, only two were significantly associated to T2 TSQ scores; T1 TMQQ scores (t_{58}=3.314, p=.002) and having clear and detailed memories (t_{58}=-2.800, p=.007). The regression equation for this model is written below:

Total TSQ score at three months post-injury = 1.215(feel someone else was to blame) + .249(TMQQ score at two weeks post-injury) - .852(memories of the event are clear and detailed) – 1.535.

DISCUSSION

This study had two aims; first, to investigate differences in PTSD symptomology over time between those with mTBI compared to a control sample with minor injury not involving the head, and secondly to explore the influence of memory quality on outcome. As expected, we found no differences in the number of PTSD symptoms experienced between those with mTBI and controls. Additionally, symptomology decreased from two weeks to three months post-injury, and there were no reliable differences in the recovery rate of PTSD symptoms between these groups across the two time points. Our observed reduction in symptomology over time is to be expected, as such symptoms are common reactions to trauma in the first few weeks, but it is the persistence of symptoms for over a month that can be classified as being PTSD (American Psychiatric Association, 1994). There is a lack of clarity in the current literature as to the expected prognosis of those with mTBI compared to other minor injuries. Our findings support some previous findings, but are contrary to others. For example, Jones et al. (2005) also followed up 131 consecutive attendees of an ED after road traffic accidents, 66 of whom had mTBI and 65 did not, where mTBI was classified as PTA of less than 24 hours, with no PTA indicating no mTBI. There were no differences between these groups in levels of PTSD classification or symptom severity at 6 weeks or three months post-injury. This system of mTBI classification is different from the one used in this study, and it is likely that some of the participants in our mTBI group would not have been classified as such under the system used by Jones et al.

Other work has found mTBI to increase risk of PTSD. In one recent study (Bryant, Creamer, O?Donnell, Silove, Clark, & McFarlane, 2009), 11.8% of those with mTBI, using a similar

classification system for mTBI to the one used for our study, met criteria for PTSD at three months post-injury, compared to 7.5% of non head-injured controls. Similarly, Mayou et al. (2003) found that a brief period of unconsciousness, e.g. due to mTBI, was associated with greater psychological problems, including post-traumatic stress, after road traffic accidents. Despite this lack of agreement, these results taken together add further weight to the confutation of Spordone and Liter's (1995) assertion that PTSD could not develop following mTBI. Moreover, we found no evidence that those with mTBI differed in the number of symptoms experienced over time since the acute phase after injury, not just when symptomology can be called persistent.

We predicted that the mTBI group would have fewer symptoms of re-experiencing than hyper-arousal (we did not assess symptoms on the avoidance cluster of PTSD) and this pattern was consistent across the time points. Although this prediction was confirmed, the same was also true for the control sample, thus we did not find this to be a pattern unique to mTBI. One proposed resolution to the paradox of how those with little memory for a traumatic event, due to loss of consciousness and/or amnesia resulting from mTBI, can develop an anxiety disorder based of such memories is that PTSD diagnosis could be made from a differing symptom profile for mTBI. Specifically, those sustaining mTBI may indeed have less intrusive memories due to possible lack of declarative memories, yet develop greater levels of avoidance and hyper-arousal, which are the other core symptom clusters of PTSD (American Psychiatric Association, 1994), to the extent that diagnostic criteria are still met. This notion has received some support from the literature. Bryant et al. (2009) found that mTBI patients experienced more avoidance and hyper-arousal symptoms than non-mTBI patients, and that longer duration of post-traumatic amnesia was associated with less re-experiencing, though there were no differences between the groups on

the re-experiencing cluster. Neither this study, nor that or Bryant et al. (2009), recruited participants to the mTBI group on the basis of established loss of consciousness or lack of declarative memory for the event. Work in the literature that did seek to explicitly compare those with memory for the traumatic event to those without have found that re-experiencing symptoms are reported less frequently in those without, and that lack of declarative memories are a protective factors (Caspi, et al., 2005; Gil, et al., 2005; Glaesser, et al., 2004).

Although our work cannot extend this literature on the effect of having no memory for the event as we did not assess this, we have found interesting results on the influence of the *characteristics* of trauma memories. Recent theories of PTSD have asserted that poorly elaborated, disorganized, highly sensory memories, which are not properly contextualized with other autobiographical memories, play a pivotal role in the persistence of post-traumatic symptomology (Brewin, et al., 1996; Ehlers & Clark, 2000). Brewin and colleagues (1996) have proposed that memories of this nature are even handled by a separate memory system than other declarative memories. We found memory quality, as measured by the TMQQ, to be significantly related to the total number of PTSD symptoms experienced, as well as the symptoms experienced in both the symptom clusters (re-experiencing and hyper-arousal) assessed by the measure we used. Specifically, poorer memory quality, as evidenced by a difficulty in verbalizing memories, a more sensory nature, being poorly elaborated (e.g. appearing as a slideshow of pictures, as opposed to a complete film) and being out of temporal sequence (making one feel as if the memory was currently happening), was highly related to greater PTSD symptomology. This was true at both two weeks and three months post-injury. Furthermore, memory quality was selected by a forward stepwise regression procedure to be included in a model that was most associated to PTSD symptomology at 3 months post-injury, with only attribution of blame to others also being

included. This regression model also showed that asking whether memories are "clear and detailed" was helpful in predicting persistent symptomology, and maybe a useful screen for poor memory quality. This item is from the TMQQ, but we singled it out as a cardinal item that encapsulates much of the idea of memory quality.

It is worth noting that intrusive memories that lead to re-experiencing aspects of trauma are key symptoms required for a diagnosis of PTSD and, indeed, are iconic to the disorder, clearly distinguishing it from other anxiety disorders (Diagnostic and Statistical Manual IV, American Psychiatric Association, 1994). These symptoms and the characteristics of memories asked about in the TMQQ may appear synonymous, and thus the observed relationship of memory quality to PTSD could be perceived as an artifact of this. The TMQQ enables an assessment of whether certain characteristics of traumatic memories make such memories intrusive, in line with recent theory. Memories which are hard to verbalise, have a fragmented (appearing as a slideshow) and highly sensory nature were found to not only be related to the re-experiencing symptom cluster, but to a similar extent were also associated to hyper-arousal symptomology. These findings therefore support cognitive theories of the maintenance of PTSD.

Contrary to our expectations, we did not find differences between the mTBI group and controls on quality of memory. Our hypothesis was that the decreased awareness immediately after the injury, loss of consciousness, disturbance in memory due to post-traumatic amnesia and possible retrograde amnesia, as well as post-concussive symptomology following the injury, related to mTBI may interfere with proper encoding, elaboration and integration of memories for the event. We did not find support for this. However, we were not able in this work to fully assess LOC,

PTA or amnesia, as the length of these were not recorded in participants' hospital records, just whether they had been present or not. Future work, better able to control for such complicating factors in mTBI, may shed more light on whether injury to the head does impact the characteristics of traumatic memory, not just whether memory is present or not.

Although injury to the head was not found to be a risk factor, female gender was. Women consistently reported more PTSD symptomology than men and experienced poorer memory quality. Interestingly, both these relationships changed over time since injury. Women experienced a greater reduction in PTSD symptomology between two weeks and three months post-injury. Whereas women tended to improve slightly in memory quality over time, men's memories became more sensory and poorly elaborated. It is difficult to explain these results from the current study. It is possible that men's symptomology did not improve at the same rate as women's due to their decreasing quality of memory, which is associated with greater PTSD symptomology, as described above. Lending weight to this proposal is our finding that gender was not selected as a predictor for our model of three month PTSD symptomology by the stepwise regression procedure, though memory quality was. Another explanation is that, as men's symptomology was generally very low, this result could reflect an artifact of a "floor effect", whereby men's symptomology could not improve to the same degree. Why men's memory quality would worsen over time compared to women's is also not clear. Talking through one's traumatic experience, in order to gain a clear "story" of what happened, is thought to be key to amelioration of PTSD (Ehlers & Clark, 2000), especially following mTBI (McMillan, et al., 2003), which is one reason for the success of trauma-focused cognitive behavior therapy relative to other interventions (Bisson, Ehlers, Matthews, Pilling, Richards, & Turner, 2007). It is possible that men differ in coping style or in access to social support, which may diminish the

likelihood of resolving symptoms in this way, as sex differences in expression of emotion are well known and are can be conceptualized in a socio-relational framework (Vigil, 2009). Further investigation into individual differences in post-trauma responses is needed.

A further individual difference found to be influential to outcome after minor injury by our regression analysis was whether or not participants' attributed blame to another. Those that blamed someone else for their injury-incident were more likely to suffer from greater PTSD symptomology at three months post-injury, though blaming oneself was not found to be predictive. This is in keeping with other work. Williams, Evans, Needham and Wilson (2002) found external attributions of blame to be associated with greater PTSD symptomology (re-experiencing and avoidance clusters, hyper-arousal was not measured) in a community sample with TBI. They did not find the severity of the injury, as indexed by length of LOC and PTA, to be related to outcome, rather the nature of the traumatic event. Similarly, Janoff Bulman and Wortman (1977) found that blaming someone for a traumatic event and feelings that it could have been avoided where predictive or poor coping. In our findings, demographic characteristics, pre-injury trauma/stress, need for mental health support, participants' self-rating of injury severity and most event appraisals were not selected by the stepwise regression procedure for the model of persistent PTSD symptomology. Our finding that blame for another and poor memory quality were the only selected variables supports the literature arguing that people's need for meaning in explaining what happened to them is important in recovery post-trauma.

There are some limitations to this work that should be kept in mind. Firstly, we did not measure the avoidance cluster of PTSD symptoms. It is possible, as suggested by the literature discussed

above, that mTBI patients may have displayed a different profile to controls on this cluster in particular. Participants were asked to respond to the presence of certain event cognitions (e.g. fear of death) simply with yes or no. Fuller response scales may have enabled a greater investigation into the variability of individual differences and the influence of these in predicting PTSD symptomology. We did not recruit participants on the basis of a particularly stressful injury incident, such as only including those who were involved in a road traffic accident (RTA). Although some of our participants were involved in RTAs, assaults and other incidents with the potential to be highly traumatic, it is also true that others could have been injured in much more minor incidents. Similarly, our sample was significantly older than the general population seen at the ED. Younger people are more likely to be involved in highly traumatic incidents such as assaults and RTAs. These sample biases may mask the true influence of the factors we were investigating on the development of problematic post-traumatic stress, as, on average, only low levels of PTSD symptomology were experienced by our sample.

CONCLUSION

Investigating individual differences in post-trauma response and the factors that underlie them is important for theoretical understanding of resilience and vulnerability (Charney, 2004). It is also of great clinical importance to efficiently screen for those most at risk of significant morbidity as soon as possible post-trauma to enable appropriate service provision and well-informed interventions (Costello & Angold, 2000). Our study highlights two individual differences that

are key predictors of persisting post-traumatic stress symptomology; memory quality and external attribution of blame. Although levels of PTSD were found to decrease over time, having a poor quality of memory for the event, such that memories are hard to put into words, are highly sensory and fragmented, as well as attributing blame for the incident to others, were predictive of more persisting symptoms. These findings support Ehlers and Clark's (2000) cognitive model of maintenance of PTSD. Suffering mTBI was not a protective factor in the genesis or maintenance of symptoms, nor did it impact memory quality. Gender differences were found in both PTSD and memory quality. Further work is needed to investigate the individual differences at work in these findings.

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Appendices

APPENDIX 1: Study One as submitted for publication.

Neurogenic and Psychogenic Acute Post-Concussive Symptoms can be identified after Mild Traumatic Brain Injury

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ABSTRACT

Background

Provenance of post-concussion symptoms (PCS) after mild traumatic brain injury (mTBI) is controversial, similar rates found in other populations. Study aims to indentify which PCS specific to mTBI compared to controls. Also compared differences between complicated and uncomplicated mTBI. Headaches, dizziness and nausea expected to be more severe in complicated mTBI group compared to controls.

Settings

Adult individuals who sought care at an Emergency Department were consecutively recruited by post at two weeks post-injury.

Participants

34 complicated mTBI, 76 uncomplicated mTBI and 47 orthopaedic controls.

Main measures.

Rivermead Post-concussion symptom Questionnaire (RPQ). Pre-injury factors used as covariates.

Results

Complicated mTBI group reported greater severity of headaches, dizziness and nausea, as well as concentration difficulties, than orthopaedic controls, suggesting that these are neurogenic. Severity of other symptomology measured on the RPQ not significantly different between these groups, suggesting these are psychogenic. Differences were evident between the two mTBI samples on the items of dizziness, nausea, fatigue, sleep disturbance and concentration difficulties.

Conclusion

Neurogenic and psychogenic PCS were identified at the acute phase post-injury. Findings suggest treating mTBI as a homogenous sample not prudent. Should inform prognostic models and follow up support offered after leaving the Emergency Department.

BACKGROUND

Mild Traumatic Brain Injury (mTBI) is a major public health issue. Around 90% of all TBIs are classified as 'mild'.[1-3] There is still considerable confusion in the literature as to why some are left with persistent post-concussion symptoms (PCS).[4] This is in part due to PCS apparently not being specific to mTBI, but also occurring in other conditions, such as depression, post-traumatic stress and other traumatic injuries.[5-10] For example, Meares et al. [5] found that 43.3% of those with an mTBI met criteria for PCS on a self-report measure within the first 14 days of the injury, but so did 43.5% of controls with traumatic injuries not involving the head. Such findings raise questions as to the supposed neurological genesis of PCS. That is, it is not clear whether PCS are "neurogenic" and a result of trauma to the head, or whether they are "psychogenic", being caused by psychological factors.

One explanation for similar rates in diagnoses may be that the current criteria of PCS include generic post-traumatic symptomology as well as post-concussive symptoms. Many studies there have been attempted to predict whether or not a patient has a diagnosis of PCS based on symptomology passing a set criterion, i.e. using cut-offs. Diagnoses by these means for non-

head-injured populations might result from a different pattern of PCS symptomology than those with mTBI. This could mask persistent symptoms that have a genuine neurological basis, as opposed to a psychological basis. For example, Meares et al [5] classified participants as having PCS if 3 or more symptoms on a 13 items measure were rated as 3-5 on a 5 point scale of severity (5 being most severe). It is possible that the similar rates they found between mTBI patients and controls, discussed above, resulted from different clusters of symptoms being endorsed between the two groups.

More work is needed, therefore, to clarify which symptoms are a direct result of concussion, and, as such, can be correctly termed "post-concussive", by examining the symptom profiles of those with mTBI compared to controls. Research suggests at least three symptoms may be neurogenic: Headaches, dizziness and nausea/vomiting are all symptoms of PCS that are also commonly seen in the Emergency Department (ED) immediately after mTBI [11], which have also been found to be highly predictive of PCS. [12-14] These three symptoms have also been found to be separable from other post-concussive symptoms. The Rivermead Post-concussion Symptom Questionnaire [15] (RPQ) is one of the most widely-used, validated measures of PCS, but has been found to possess poor psychometric qualities if analysed as a uni-dimensional construct. [16] Having performed an exploratory factor analysis, Eyres et al. [16] suggest that the RPQ should be analysed as two separate scales; one comprising of the items measuring headaches, dizziness and nausea/vomiting (henceforth referred to as the RPQ3), and the second containing the remaining items (the RPQ13). This reinforces the assertion that these three symptoms specifically have a neurological vector.

A second reason for the comparable rates of PCS in mTBI patients and other populations may be that most studies have treated mTBIs as a homogenous group. There has been a growing awareness in the literature that mTBIs can be fairly heterogeneous and that injuries can be individualised and graded by severity.[17 18] For example, the European Federation of Neurological Societies (EFNS) guidelines split mTBIs into categories 0-3 representing increasing severity or complication of the injury.[19] Category 0 requires no loss of consciousness (LOC) or post-traumatic amnesia (PTA) or signs of TBI or other complicating factors and with a Glasgow Coma Scale (GCS) score of 15; the only requirement is traumatic injury to the head. Category 3, on the other hand, includes those with LOC, PTA, GCS of 13-14 and with or without risk factors (e.g. haemorrhaging). Little research has investigated the differences between category 0, "uncomplicated" mTBIs and those with more complex injuries, though there is evidence that indicators of complicated injury are associated with persistent PCS.[20] Not treating mTBIs as heterogeneous may therefore fail to accurately capture the risk of persistent PCS of those with more 'severe' mTBIs.

A more accurate diagnosis is crucial for appropriate management of symptoms at various points post-injury. An understanding of symptomology in the acute phase may prove particularly useful as this may have an immediate impact on recovery from the injury. Additionally, understanding the aetiology of symptomology at the acute stage may provide insight into the processes by which symptoms become persistent and thus aid identification of those at risk. Those at risk may then be followed up and provided with information, for example, for self-monitoring, to ensure that their recovery is maximised. [4]

The identification of early symptoms of persistent PCS using an established self-report measure is therefore critical. It is also important to include a control sample who have suffered an injury not involving the head in order to distinguish between symptoms which are truly "post-concussive", i.e. have a neurological cause, and those which are "general trauma" symptoms that may be experienced after any injury. More than this, research needs to investigate whether differences develop in acute outcome between those with complicated mTBI compared to uncomplicated mTBI.

In the present study we followed up ED attendees with mTBI or orthopaedic injuries at two weeks post-injury and assessed PCS using the RPQ. The mTBI sample was then divided into uncomplicated or complicated mTBIs based on neurological functioning on arrival. We intend to determine which symptoms on the RPQ are specific to mTBI and which are general trauma symptoms, as well as whether, on the basis of reported PCS, it is prudent to split mTBI samples into complicated or uncomplicated injuries. Due to the co-morbidity of PCS with affective disorders such as depression and PTSD, we collected information on pre-injury experiences, as well as previous hospitalisation for head-injury, in order to control for these extraneous effects.

We predicted that those with complicated mTBIs would report higher mean RPQ scores than uncomplicated mTBIs. However, we expected that complicated mTBIs will have comparable scores to orthopaedic controls on the RPQ13, though not on the RPQ3, which measures headaches, dizziness and nausea, as we believe these to be the symptoms most likely to be neurogenic. Based on many previous studies, we also expect women to report more severe symptomology than men [5 21], but this difference should be stable across diagnostic groups.

METHODS

Adults with mTBI or orthopaedic injuries were prospectively recruited from consecutive ED attendances between November 2008 and October 2009. They were approached to participate via post at two weeks post-injury. The study was approved by the regional National Health Service Research Ethics Committee and informed, written consent was obtained. Inclusion criteria were age between 18-65 and diagnosis of either mTBI or an upper limb fracture. Exclusion criteria were attendance as a result of domestic violence or sexual assault, previous attendances within the past 5 years for similar injuries (as an indicator of domestic violence), attendances for urgent care for a pre-existing medical condition, significant history of mental health problems or learning disabilities and inability to complete questionnaires due to non-fluency in English.

Participants

A total of 157 attendees accepted the invitation to participate, 110 with mTBI and 47 with OI. The recruitment rate was a little higher for the orthopaedic group than for the combined mTBI sample (21.9% vs. 16.1% respectively), though this difference was not significant ($\chi^2 = 3.681$, df = 1, ns), and was 17.5% overall. The mTBI group was split into two subgroups; those with uncomplicated mTBI and those deemed to have complicated mTBI based on a GCS of 13-14

and/or reported LOC or amnesia in their medical notes. Thus, for the purposes of this study, uncomplicated mTBI is equivalent to "category 0" of the EFNS guidelines for mTBI, having just traumatic injury to the head with no LOC, amnesia or lowered GCS, and those with complicated mTBI would fall in categories 1-3, including any implication of complication.[19] The final sample consisted of 47 orthopaedic controls, 76 with uncomplicated mTBI and 34 with complicated mTBI. See Figure 1 for a flowchart of recruitment into the study. As can be seen in Table 1, the groups did not differ significantly in terms of the ratio of men to women (χ^2 = 3.365, df = 2, ns), or highest educational attainment (χ^2 = 1.920, df = 4, ns), but reliable differences were evident in age ($F_{2,144}$ = 4.833, p=0.009), with the complicated group tending to be younger than the other two diagnostic groups. Chi-square tests did not reveal any significant differences between the diagnostic groups in rates of those who had experienced three pre-trauma factors; previous stress/ trauma (χ^2 = .551, df = 2, ns), previous need for mental health support (χ^2 = 2.914, df = 2, ns) and previous admission for a head injury (χ^2 = .298, df = 2, ns).

Non-responders with mTBI could not be divided into complicated and uncomplicated subgroups, as permission was not obtained to access their medical records (see below for the study procedure), so comparisons between our sample and non-responders use a combined mTBI group. The only data available for non-responders, other than injury type, was their age and gender. Chi-square tests found that responders were more likely to be women in both the orthopaedic control group (χ^2 = 7.519, df = 1, p=.006) and the combined mTBI group (χ^2 = 11.595, df = 1, p=.001). Independent samples t-tests also found that responders were significantly older for the orthopaedic sample (t_{213}=3.599, p<.001), as well as the mTBI group (t_{673}=5.676, p<.001). See Table 1 for descriptive data.

Figure 1. Flowchart describing the recruitment of participants and the final samples.

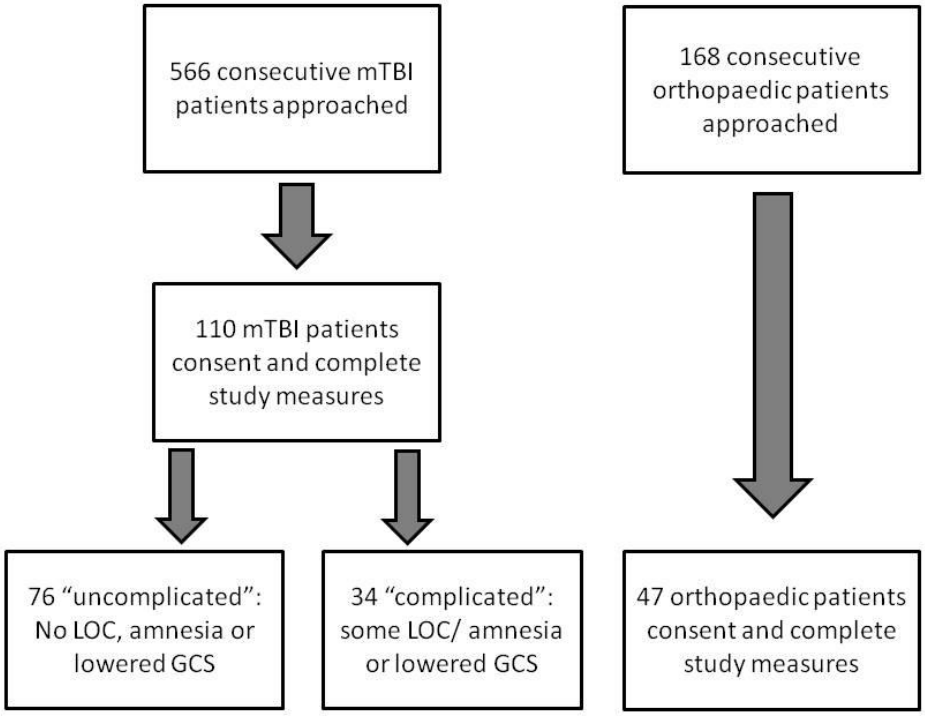

Table 1. Demographic and pre-injury characteristics of the samples.

Responders **n=157**		Orthopaedic injury n=47	uncomplicated mTBI n=76	complicated mTBI n=34
	Mean age (SD)	47.80 (13.42)	45.18 (14.09)	38.12 (14.68)
	Males (%)	15 (33.9)	37 (48.7)	14 (41.2)
Highest level of education (%):	Secondary school	12 (27.3)	25 (35.2)	8 (23.5)
	College	18 (40.9)	27 (38.0)	16 (47.1)
	University	14 (31.8)	19 (26.8)	10 (29.4)
Suffered major stresses / trauma prior to injury		9 (20.5)	11 (15.9)	7 (20.6)
Previous need for mental health support		3 (7.0)	6 (8.7)	6 (18.2)
Previous mTBI		5 (11.4)	10 (14.7)	4 (12.1)
Non-responders **n=734**		Orthopaedic injury n=168	Combined mTBI n=566	
	Mean age (SD)	39.36 (14.77)	34.36 (13.53)	
	Males (%)	88 (52.4)	363 (64.1)	

The number of participants involved in the above analyses occasionally differed from the overall sample n due to lack of responses for certain items.

Assessment procedure

Trained research assistants working at the hospital identified those who met the study's inclusion/exclusion criteria from the medical records of patients of the ED. A study information pack was sent via post to those identified as eligible for participation, explaining the nature and aims of the research and inviting them to take part, as well as including a consent form and the study questionnaire. The consent form also asked for permission for the researchers to access their medical records. Those that wished to participate completed the questionnaire and signed the consent form, then returned these to the researches by post. Non-responders were therefore those that did not wish to take part in the research.

Participants were asked to complete the Rivermead Post-concussion Questionnaire.[15] The RPQ consists of 16 items assessing the presence and severity of symptoms common in persistent post-concussion syndrome, such as headaches, dizziness and concentration problems, on a 5-point scale ranging from "1 - no problem" to "5 - severe problem". In addition to the RPQ participants reported their demographics and answered three questions relating to their pre-injury status, all of which required yes/no responses. These were "had you suffered a previous stress or trauma prior to this incident?", "had you needed any mental health support?" and "had you ever had a head injury that needed hospitalisation?". We also asked participants to report their highest education level completed, with options of "Secondary school", "College" and "University". In the UK, pupils sit exams at age 16 called "General Certificate in Secondary Education" (GCSEs), which are compulsory. They can then choose to go on to study Advanced Level courses (A-Levels), or equivalents, at college, which are 2-year courses that are required for entrance to most

university courses. Universities are separate to colleges in the UK; they provide higher education Bachelors degree courses, typically lasting 3 years, which can be taken after completing college (in most instances).

Access to participants' medical records was required in order to provide detailed information on the nature of their state on attendance at the ED, such as GCS, LOC and presence of amnesia for the mTBI group, which was used to determine whether the participant had a complicated mTBI, as outlined above. Participants gave their consent for this access on their study consent form.

Data analysis

There are a number of ways that the RPQ can be analysed. King et al (1995) designed the instrument to be used as a single measure of PCS and the mean scores of the 16 item scale (RPQ16). However, Eyres et al (2006) caution against this as they did not find the RPQ to possess unidimensionality. In accordance with their suggestions, the items measuring headaches, dizziness and nausea/vomiting were used as a separate scale from the remaining 13 items; forming the RPQ3 and the RPQ13 respectively. The items of each scale were entered as levels of a single repeated measure for the scale in an ANOVA, with condition (orthopaedic controls, uncomplicated mTBI, complicated mTBI) and gender as between subjects fixed factors. The main effect of condition and gender thus indicates whether there were differences between levels of these factors on overall symptomology for the scale, whereas the main effect of the scale (the repeated measure) indicates whether some symptoms were rated consistently more severe than

others. Of interest, the interaction between the repeated measure of scale and condition examines whether different patterns of symptomology are evident between the diagnostic groups. For example, complicated mTBI participants may consistently report different symptoms as more severe than those reported by orthopaedic controls. Using repeated measures is appropriate as the same variable of "symptom severity" is being measured over various "conditions" (i.e. the symptoms) for the same participant. This procedure also allows the above examination of differing symptom profiles across groups. Inter-group differences on the individual symptoms were also examined by performing ANOVAs on each symptom separately.

Additionally, pre-injury factors were controlled for by entering them as covariates. Linear regressions indicated that having had a major stress/trauma prior to the injury was the only predictor significantly associated with the total score of the RPQ13 and that previous use of mental health support was the only predictor significantly associated with the RPQ3. Accordingly, only the variable that was a significant correlate of the total score was entered as a covariate in Analysis of Covariance (ANCOVA) of the respective scale. Due to the significant age differences between the three diagnostic groups, the effect of age was also included as a covariate. Running the regression analyses detailed above with participants' age included revealed that age was significantly associated with both scales, even in the presence of the other predictors.

This exploratory work required a number of comparisons. Due to the main effects of our treatment variables being significant, the follow up pair-wise comparisons between groups were protected from inflated Type 1 error rates, according to Fisher's Least Significant Difference

theory. Where repeated measures are reported in the following ANOVAs and ANCOVAs, the Huyh-Feldt correction for sphericity will be used, and therefore degrees of freedom and *p*-values will be reported at the Huynh-Feldt criterion. All analyses were performed on Statistical Package for the Social Sciences (SPSS) version 18.0.

RESULTS

RPQ13

An ANOVA on the RPQ13, with all 13 items entered as separate levels of a single repeated measures factor, and gender (discussed separately below) and condition as between subjects factors, found the main effect of condition to be non significant, $F_{2,138} = 1.85$, ns, meaning that no reliable differences were found between the groups on overall mean symptom severity for this scale. However, the interaction between condition and the RPQ13 was significant, $F_{15.24,1051.21} = 2.10$, $p=0.008$, indicating that the diagnostic groups had reliably different patterns of symptom severity (see Figure 1 below), although overall symptom severity was not different (i.e. the non significant main effect). In other words, different symptoms on the RPQ13 were consistently rated as more severe in some groups than in others. See below for analyses on individual symptoms.

Planned contrasts investigated our hypotheses that i) the complicated mTBI group would not differ significantly from orthopaedic controls, but ii) they would have greater symptomology than

the uncomplicated mTBI group. The first hypothesis was confirmed, $F_{1,138} = 2.30$, ns, as no reliable difference was found between the complicated mTBIs and controls, and marginal support was found for our second hypothesis as the difference between the uncomplicated mTBI group and the complicated mTBI group approached significance, $F_{1,138} = 3.20$, p=.076. See Table 3 for means. Adding in the covariates of previous stress/trauma and age did not qualitatively alter these results.

Investigating differences on individual items, the main effect of condition was significant for just two of the thirteen items; sleep disturbance ($F_{2,145} = 3.64$, p=.029) and fatigue ($F_{2,144} = 3.40$, p=.024), indicating that reliable differences exist between the diagnostic groups scores for these symptoms. The condition main effect was also marginally significant for concentration difficulties ($F_{2,145} = 2.48$, p=.087). The nature of these differences was further explored by means of post-hoc comparisons. These indicated that sleep disturbance was greater for the complicated mTBI group compared to the uncomplicated mTBI group ($F_{1,145} = 5.47$, p=.021). The complicated mTBI group also experienced more fatigue ($F_{1,144} = 6.11$, p=.015) and poorer concentration ($F_{1,145} = 3.94$, p=.049) than the uncomplicated group, as well as poorer concentration than the orthopaedic group ($F_{1,145} = 4.03$, p=.048). Descriptive data are presented in Figure 2 and Table 2. Due to the lack of qualitative changes between the ANOVAs and ANCOVAs performed for the overall scale, and due to low observed power on adding in the covariates, ANCOVAs were not run on the individual items.

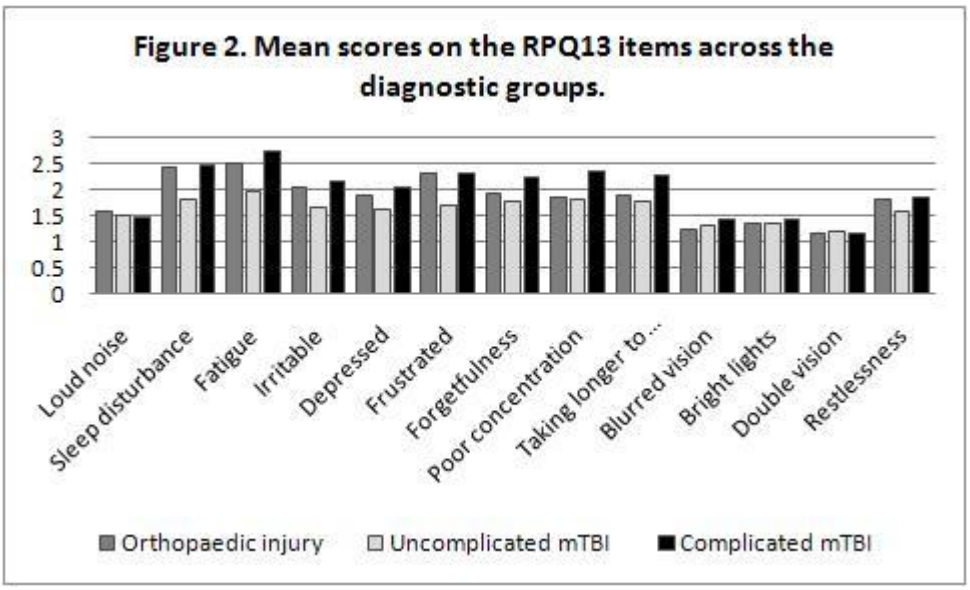
Figure 2. Mean scores on the RPQ13 items across the diagnostic groups.
3
2.5
2
1.5
1
0.5
0
Loud noise
Sleep disturbance
Fatigue
Irritable
Depressed
Frustrated
Forgetfulness
Poor concentration
Taking longer to ...
Blurred vision
Bright lights
Double vision
Restlessness
Orthopaedic injury
Uncomplicated mTBI
Complicated mTBI

Table 2. Means and standard deviations of the RPQ scale and item scores across the diagnostic groups.

	Orthopaedic Injury			Uncomplicated mTBI			Complicated mTBI		
RPQ scale/ item	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*
Total RPQ13	41	23.17	(10.74)	70	21.23	(10.77)	33	25.76	(10.79)
Upset by loud noise	45	1.57	(0.95)	72	1.51	(1.06)	34	1.45	(0.83)
Sleep disturbance [U]	45	2.42	(1.42)	72	1.82	(1.20)	34	2.47	(1.26)
Fatigue [U]	45	2.51	(1.38)	72	1.97	(1.22)	33	2.73	(1.42)
Irritable	44	2.05	(1.20)	70	1.66	(1.06)	33	2.18	(1.31)
Depressed	42	1.90	(1.14)	71	1.63	(1.09)	34	2.06	(1.13)
Frustrated	45	2.31	(1.26)	72	1.71	(1.11)	33	2.30	(1.49)
Forgetfulness	45	1.93	(1.23)	72	1.76	(1.13)	34	2.24	(1.23)
Poor concentration [U, C]	45	1.87	(1.14)	72	1.83	(1.16)	34	2.35	(1.39)
Taking longer to think	45	1.89	(1.17)	72	1.79	(1.11)	33	2.27	(1.23)
Blurred vision	45	1.22	(0.70)	72	1.32	(0.71)	34	1.44	(0.75)
Upset by bright lights	45	1.36	(0.93)	72	1.35	(0.82)	33	1.42	(0.90)
Double vision	45	1.16	(0.56)	72	1.19	(0.57)	33	1.15	(0.44)
Restlessness	45	1.82	(1.23)	72	1.60	(1.00)	33	1.84	(1.03)
Total RPQ3	45	4.49	(1.79)	72	4.86	(2.40)	33	5.91	(3.25)
Headaches [O]	45	1.76	(1.00)	72	2.04	(1.22)	33	2.27	(1.18)
Dizziness [U, C]	45	1.51	(0.79)	72	1.54	(0.90)	34	2.15	(1.40)
Nausea/vomiting [U, C]	45	1.22	(0.52)	72	1.28	(0.63)	33	1.61	(1.00)

[U] Means for the complicated and uncomplicated mTBI groups differ significantly

[C] Means for the complicated mTBI and orthopaedic control groups differ significantly

RPQ3

A different pattern of results was found when looking at the RPQ3, containing just the items measuring headaches, dizziness and nausea. The main effect of condition on the RPQ3 was significant, $F_{2,144} = 3.65$, p=.026, revealing that the mean scores for the scale varied between the diagnostic groups, though this time the pattern of differences did not differ between the groups, as the interaction was not significant. Once again, planned contrasts tested our hypotheses that the complicated mTBI group would have greater severity of symptoms on the RPQ3 than both other groups. Robust differences in the mean scores were found between orthopaedic controls and complicated mTBIs, $F_{1,144} = 7.20$, p=.008, and marginal differences were again evident between the mTBI groups, $F_{1,144} = 3.65$, p=.056, with those with complicated injuries experiencing more severe symptoms in both instances. See Table 2 for means and standard deviations. There were no qualitative differences in the ANCOVAs.

In the analyses of individual items, there was no main effect of condition on headaches ($F_{2,144} = 2.20$, ns), though there was a significant difference for both dizziness ($F_{2,145} = 4.92$, p=.013) and nausea/vomiting ($F_{2,144} = 3.45$, p=.034), indicating that mean scores reliably differed across the groups on these items only. Further planned comparisons revealed a significant difference between the complicated mTBI group and the orthopaedic group for headaches, $F_{1,144} = 3.39$, p=.048, with the complicated mTBI group rating this symptom as more severe, though no such difference was reliable between the two mTBI samples, $F_{1,144} = .511$, ns. There were robust differences in severity of dizziness between the complicated mTBI and both the orthopaedic controls ($F_{1,144} = 7.40$, p=.007) and the uncomplicated mTBI group ($F_{1,144} = 7.04$, p=.009). Similarly, significant differences were evident in nausea/vomiting between the complicated mTBI group and both the orthopaedic group ($F_{1,144} = 6.45$, p=.012) and the uncomplicated mTBI

group $F_{1,144} = 4.40$, p=.038). Means are displayed in Table 2, which also presents standard deviations. Again, ANCOVAs were not performed for the same reasons as stated regarding the item-level analysis of the RPQ13.

Gender effects

Gender differences are repeatedly found in PCS severity, with women reporting more severe problems than men. On the RPQ13, the main effect of gender was significant, $F_{1,138} = 8.78$, p=.004, as was its interaction with the scale, $F_{7.82,1051.21} = 2.83$, p=.005, indicating robust gender differences both in the average symptom severity for the scale, with women rating problems as worse than men (men M=1.54, SE=0.12; women M=1.97, SE=0.09), and in the pattern of the symptomology across the measure. That is, this interaction effect shows that different symptoms were consistently rated as more severe between men and women. However, the interaction between gender and condition was not significant, $F_{2,138} = .027$, ns, with no reliable changes in the difference in overall symptom severity between men and women across the diagnostic groups. Again, on the RPQ3, women rated symptoms as more severe than men (men M=1.44, SE=0.13; women M=1.94, SE=0.14), $F_{1,144} = 9.44$, p=.003, though the patterns of symptom severity between the genders were not reliably different across this measure as the interaction with the scale was not significant, $F_{2,254.56} = 1.15$, ns. Again, the interaction between condition and gender was not significant on the RPQ3, $F_{2,144} = .130$, ns, indicating that diagnostic group did not alter the differences between men and women. In support of previous work and our current hypothesis, women consistently rated PCS symptoms as more severe than men and this pattern was the same regardless of the diagnostic group they were in.

DISCUSSION

The analyses on the RPQ13 (the Rivermead Post-concussion Questionnaires, excluding the items measuring headaches, dizziness and nausea) indicate that this instrument is largely unhelpful for disambiguating those with more complicated mTBIs from either very mild mTBI or orthopaedic controls with no mTBI. Those with complicated mTBI appear almost identical to orthopaedic controls on this measure of PCS, except on concentration difficulties. Because this subscale comprises 13 out of a total of 16 items, analysing the RPQ as a single continuous measure is similarly unhelpful. In stark contrast, and in line with our predictions, the RPQ3, measuring headaches, dizziness and nausea/ vomiting, is able to distinguish those with complicated mTBI from both other trauma patients with no injury to the head (the orthopaedic group) and those with very minor mTBIs. Greater symptomology was reported by the complicated mTBI group across the items than by orthopaedic controls, and on all but headaches when compared to the uncomplicated mTBI group. This pattern of results was still obtained when controlling for extraneous variables and the age difference between the groups using analyses of covariance. Women consistently rated symptoms as more severe than men across both subscales of the RPQ. However, there were no interactions between gender and diagnostic group. Thus the effects of gender were found to be independent of the effects of injury group in this investigation; in other words, being female is an additive risk factor.

This study provides preliminary evidence that treating mTBI as a homogenous group is not prudent, and may explain the similar rates of PCS between mTBI samples and control groups. Those with complicated injuries had significantly more sleep disturbance, fatigue, concentration

difficulties, dizziness and nausea/vomiting. We had a very broad complicated head injury group, which consisted of anyone with any sign of complication. We think it likely that a less broad complicated mTBI group, consisting of those with a combination of GCS, LOC or PTA issues, would have increased the disparity in reported symptom severity between the complicated mTBI group and both the orthopaedic and uncomplicated mTBI groups.

The majority of the current literature regarding treatment of persistent PCS primarily focuses on the benefits of early interventions to reduce likelihood of persistence and improving recovery (typically in the acute phase post-injury). Such approaches address management of somatic problems, such as those symptoms measured by the RPQ3 (headaches, dizziness, nausea), cognitive problems and affective complaints within a CBT framework [4]. Findings suggest some amelioration of symptoms and reduction of PCS symptoms in the longer term. In general, interventions for minimising PCS work by allowing a graded means for enabling compensation for any underlying neuro-cognitive deficit and for improved tolerance of such issues as fatigue, for example, then enabling resumption of activities. However, these interventions also allow means for testing and challenging mood related concerns and beliefs about one's competence and abilities. Our findings would indicate complicated mTBI could be more systematically screened for so that those with such symptoms could be effectively identified for intervention. One promising intervention route may be provision information on possible symptoms, which has been found to have a moderate, positive effect size of 0.32 in terms of resolution of PCS symptomology by a meta-analysis of five studies [22].

A caveat for providing information on brain injury for all survivors of mTBI is that there may be a risk of "expectation as aetiology". For example, Whitaker and colleagues [23] found that, following a mTBI, those who appraised their symptoms as likely to have serious, negative consequences were at significantly heightened risk of persistent PCS. Our findings would, as we note, aid better screening for those with mTBI for them to be given appropriate advice. This may help practitioners not to "over-prescribe" brain injury information for those with psychogenic forms of PCS. However, of course, survivors of trauma may well need some other form of informational advice for aiding their adjustment. We therefore suggest that more research is needed to identify the likely psychological factors causal of PCS such that more appropriately targeted interventions can be developed. One likely psychological factor that may influence development and/or maintenance of PCS is post-traumatic stress disorder (PTSD), which is common following even minor injuries seen at the ED [e.g. 24 25] and has been found to be co-morbid with PCS [10 21 26-28]. Negative appraisals of the sequelae of traumatic events, such as investigated by Whitaker and colleagues [23] described above, are also a core component of PTSD [29 30]. Studies should seek to identify psychological factors that lead to acute PCS and how these go on to affect the persistence of such symptoms.

A limitation of this study is a low response rate that led to significant differences in age and gender distribution between responders and non-responders. As such, it is possible that our sample is not representative of the general population, containing less men and being older than the overall population of those leaving the ED that could have been followed up. As the above results show, female gender was consistently related to worse symptomology, and age was found to be negatively associated to PCS and was used as a covariate, which could have led to over-estimates of PCS symptomology. However, a 17.8% response rate and age and gender biases for

research following up patients leaving an ED is consistent with past studies.[e.g. 23] Our study was also not seeking to investigate prevalence of symptomology, but rather provenance; to look at differences between groups and symptom clusters. The gender differences described above were consistent across the diagnostic groups, as indicated by non significant interactions between gender and condition on both the RPQ13 and the RPQ3, so over-estimates of symptomology levels are not so important. Similarly, adding age as a covariate also did not qualitatively change the pattern of results. Age was found to be positively associated with PCS symptomology when investigating possible covariates, with older age predictive of worse PCS. Since the complicated mTBI group were the youngest group, it is possible that the differences we found would be more marked in a sample with non-significant age differences.

Additionally, a strength of this study is the recruitment of consecutive attendances to an ED, which circumvented sample biases present in some studies in the literature, where participants were sampled from those seeking care for PCS symptomology or because they are involved in litigation. A further strength is that we demonstrate clinically-relevant intergroup differences on use a popular and established measure of PCS.

CONCLUSION

Acute post-concussion symptoms of headaches, dizziness, nausea/vomiting and concentration difficulties appear to be neurogenic, as these were common in those with mTBI, but significantly

less so in those with traumatic injuries not involving the head, and thus are less attributable to a psychological vector. They are also all immediate symptoms of mTBI commonly seen on admission to EDs and have been found to predict persistent PCS.[11-13] The majority of symptoms commonly held to be post-concussive, on the other hand, were not specific to those with mTBI, being experienced at similar levels in orthopaedic controls, and are likely to be psychogenic. Therefore, terming this constellation of symptoms "post-concussive" would appear to be highly misleading. The term "post-traumatic complaints" may be more helpful, though this could also cause confusion, as "trauma" has the multiple meanings of "injuries due to forces" and "psychological distress". Whether their basis is neurogenic or psychogenic, these symptoms are a source of significant morbidity to those with traumatic injuries and future work should seek to predict who will develop persistent PCS, regardless of whether the injury involved the head or not. Nevertheless, these results should help clarify differences between those with and without injury to the head, especially those with more complicated mTBI, which should aid interpretation and design of prognostic models. Furthermore, future work is needed to test the effectiveness of early interventions for PCS and whether neurogenic and psychogenic symptoms indeed require separate strategies for amelioration.

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Appendix 2: The study questionnaire

Please note that the questionnaire was formatted for a different page layout than is required for the submission of this thesis.

The purpose of this study is to find out how people feel after sustaining an injury.

Below are questions asking for general background information and about your personal experiences before and after the incident that led to injury. Please tick the circle to indicate your response or write in the space provided. Please note that all of your responses are anonymous and confidential.

About you:

• Are you ○ Male ○ Female

• Date of birth ☐☐/☐☐/☐☐☐☐ Day Month Year

• Are you ○ ○ ○ ○ ○

Single Living Married Divorced Widowed

• Your current occupation is ……..

• Is this the same as before the incident? ○ Yes ○ No

• The highest educational level ○ Secondary school ○ College ○ University

that you have completed is:

Reason for attending Emergency Department:

• What happened to you (e.g. car accident, fall, assault)? …….

……..……

• Did you have any physical injuries? ○ Yes ○ No

• If yes, please describe:

……

• How serious was the incident? ○ Minor ○ Serious ○ Severe ○ Extreme

• Did you lose consciousness?

Yes

No

• If yes, for how long did you lose consciousness?

5 minutes

5 to 15 minutes

more than 15 minutes

• Are you seeking compensation as a result of your injuries?

Yes

No

• Had you suffered any major stresses or trauma before this incident?

Yes

No

• If yes, please describe:

……

……

Yes No

• Had you needed any mental health support?

Yes No

• Had you ever had a head injury that needed hospitalisation?

• If yes, please describe:

……

……

• Did you use non-prescribed drugs or alcohol?

Not at all Sometimes Frequently

Please consider the following statements about your memory of the incident.

	No	Yes
I have a good memory of all that happened.	○	○
My memory of what happened is based on what I was told afterwards.	○	○
When it happened, I thought I would be seriously injured.	○	○
When it happened, I thought I would die.	○	○
I felt I had control over what happened.	○	○
I feel someone else was to blame.	○	○
I felt I was to blame for what happened.	○	○
The incident could have been avoided.	○	○
I felt no one was to blame for what happened.	○	○

	No	Yes
Upsetting thoughts or memories about the event that have come into your mind against your will.	○	○
Upsetting dreams about the event.	○	○
Acting or feeling as though the event were happening again.	○	○
Feeling upset by reminders of the event.	○	○
Bodily reactions (such as fast heartbeat, stomach churning, sweatiness, dizziness) when reminded of the event.	○	○
Difficulty falling or staying asleep.	○	○
Irritability or outbursts of anger.	○	○
Difficulty concentrating.	○	○

Heightened awareness of the potential dangers to yourself and others.	○	○
Being jumpy or startled at something unexpected.	○	○

This section is concerned with your personal reaction to the incident. Please indicate whether you have experienced any of the following symptoms <u>AT LEAST</u>

Please consider the following statements about your memory <u>NOW</u> of the incident.

	No	**Not Sure**	**Yes**
My memories of what happened to me are mostly pictures or images.	○	○	○
When I have memories of what happened I sometimes hear things in my head that I heard during the incident.	○	○	○
When I remember the incident I feel like it is happening right now.	○	○	○
When I think about what happened I can sometimes smell things that I smelt when the actual incident occurred.	○	○	○
I can talk about what happened very easily.	○	○	○
I remember the incident as a few moments, and each moment is a picture in my mind.	○	○	○

(continued) **Please consider the following statements about your memory <u>NOW</u> of**

	No	Not Sure	Yes
My memories of the incident are like a film that plays over and over.	○	○	○
My memories of the incident are very clear and detailed.	○	○	○
Remembering what happened during the frightening incident is just like looking at photographs of it in my mind.	○	○	○
When memories come to mind of what happened, I feel my body is in the same position as when the frightening incident occurred.	○	○	○

Please consider the <u>LAST FOUR WEEKS</u> and answer the following questions by

	Worse	Same	Better
Been able to concentrate on what you're doing?	○	○	○
Lost much sleep over worry?	○	○	○
Felt you were playing a useful part in things?	○	○	○
Felt capable of making decisions about things?	○	○	○
Felt constantly under strain?	○	○	○
Felt you couldn't overcome your difficulties?	○	○	○
Been able to enjoy your normal day-to-day activities?	○	○	○
Been able to face up to your problems?	○	○	○
Been feeling unhappy and depressed?	○	○	○
Been losing confidence in yourself?	○	○	○

Been thinking of yourself as a worthless person?	○	○	○
Been feeling reasonably happy, all things considered?	○	○	○

Do you <u>CURRENTLY</u> experience any of the following symptoms?

	Not at all	A little bit	Moderately	Quite a bit	Severe
Headaches	○	○	○	○	○
Feelings of dizziness	○	○	○	○	○
Nausea and / or vomiting	○	○	○	○	○
Easily upset by loud noise	○	○	○	○	○
Sleep disturbance	○	○	○	○	○
Fatigue, tiring more easily	○	○	○	○	○
Being irritable or easily angered	○	○	○	○	○
Feeling depressed or tearful	○	○	○	○	○
	○	○	○	○	○

Feeling frustrated or impatient					
Forgetfulness, poor memory	○	○	○	○	○
Poor concentration	○	○	○	○	○
Taking longer to think	○	○	○	○	○
Blurred vision	○	○	○	○	○
Easily upset by bright lights	○	○	○	○	○
Double vision	○	○	○	○	○
Restlessness	○	○	○	○	○

In this section we would like you to think about the different group memberships that you may have had before and/or since the incident.

BEFORE the incident

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I was a member of lots of different groups.	○	○	○	○	○
I had friends in lots of different groups.	○	○	○	○	○
I received support from members of lots of different groups.	○	○	○	○	○

I got practical help from members of lots of different groups.	○	○	○	○	○

AFTER the incident

	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**
I still belong to the same group(s) that I was in before.	○	○	○	○	○
I still have friends in the same group(s) that I was in before.	○	○	○	○	○
I still receive support from the same groups I was in before.	○	○	○	○	○
I still get practical help from the same group(s) that I was in before.	○	○	○	○	○

SINCE the incident

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I am active in one or more new groups.	○	○	○	○	○
I have become friends with people in one or more new groups.	○	○	○	○	○
I receive support from people in one or more new groups.	○	○	○	○	○
I get practical help from people in one or more new	○	○	○	○	○

groups.					
My life has changed a lot.	○	○	○	○	○
The quality of my life is the same as it was before.	○	○	○	○	○
The quality of my life has improved.	○	○	○	○	○
I have high self esteem.	○	○	○	○	○
I have been discriminated against because of my injury.	○	○	○	○	○
I find it hard to tell people that I have had an injury.	○	○	○	○	○
I think of my injury as an invisible disability.	○	○	○	○	○

Please rate your CURRENT life experience

	Strongly Disagree	**Disagree**	**Neutral**	**Agree**	**Strongly Agree**

In most ways my life is close to ideal.	○	○	○	○	○
The conditions of my life are excellent.	○	○	○	○	○
I am satisfied with my life.	○	○	○	○	○
I enjoy my work.	○	○	○	○	○
I think the work I do is worthwhile.	○	○	○	○	○
My work is varied and interesting.	○	○	○	○	○

Thank you very much

Study phone number: 01392 262418

Study web site: http://www.psychology.ex.ac.uk/well-being-study

APPENDIX 3: Project protocol for ethics submission.

Please note that the protocol for the investigation carried out for this thesis was revised several times after submission to the National Health Service Research Ethics Committee and only the initial submission is available. Due to this document only being in Adobe Acrobat format, page numbers of the protocol do not follow from this thesis.