Social risk factors in the aetiology, maintenance and treatment of opioid use disorder

Submitted by Molly Carlyle, to the University of Exeter

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I certify that all material in this thesis which is not my own work has been identified and that any material that has previously been submitted and approved for the award of a degree by this or any other University has been acknowledged.

Signature:……

Abstract

Opioid use disorder (OUD) is a growing global concern as overdoses have drastically increased over recent years. There is an urgent requirement for novel and more effective treatments. Investigating the role of social factors in the onset and maintenance of OUD may be a promising approach. In **Chapter 1**, I review the role of social vulnerability factors in OUD, and how social functioning may be altered in opioid drug users via changes to the endogenous opioid system. In **Chapter 2**, I report greater pleasurable effects and reduced aversive effects of an acute dose of morphine in individuals with histories of childhood trauma (without histories of OUD). This suggested history of childhood trauma may increase the rewarding value of opioids, and therefore be a major vulnerability factor preceding OUD. Impairments to social functioning in those with OUD is then investigated in **Chapter 3**, where I report reduced empathy for others' emotions alongside greater anger following social exclusion. These findings indicate social risk factors and impaired social functioning as an important area that should be considered in the search for novel treatments for OUD. In **Chapter 4** I report on a brief intervention of compassion-focused therapy (CFT) for OUD, showing that this novel treatment is feasible and tolerable in this population. Another potential therapeutic avenue to improve social functioning is by using MDMA adjunct to psychotherapy, therefore in **Chapter 5** I examined whether social functioning is negatively affected by MDMA use. Low level, repeated MDMA use was associated with improved empathy and did not affect social distress, highlighting it as potentially suitable for treating social impairments in OUD. In **Chapter 6**, I discuss the wider theoretical implications and propose a social risk factor model for OUD. I also discuss the clinical implications of the findings, potential limitations to the work, and suggestions for future directions for improving social functioning in OUD. In conclusion, social functioning is disrupted in OUD, and experiences of childhood trauma and social stressors may prime people to the addictive effects of these drugs; however, CFT or MDMA-assisted psychotherapy may be beneficial for treating OUD.

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Author’s declaration

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The work in this thesis has given rise to the following publications:

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Carlyle, M., Stevens, T., Fawaz, L., Marsh, B., Kosmider, S., & Morgan, CJA. (2019). Greater empathy in MDMA users. *Journal of Psychopharmacology*, *33*(3), 295-304.

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The chapters are designed to be read as standalone chapters and hence there is some repetition between them.

Abbreviations

ACC	Anterior cingulate cortex
ACE	Adverse childhood events
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ACE	Adverse Childhood Experiences
ACTH	Adrenocorticotropic hormone
AI	Anterior insular
ASD	Autism spectrum disorder
BAC	Blood alcohol content
BMI	Body mass index
BOTSA	Brain Opioid Theory of Social Attachment
CBT	Cognitive behavioural therapy
CI	Confidence intervals
CFT	Compassion-focused therapy
CTQ	Childhood Trauma Questionnaire
DA	Dopamine
dACC	Dorsal anterior cingulate cortex
DASS	Depression, anxiety and stress scale
DEQ	Drug effects questionnaire
DOR	δ-opioid receptor
EOR	ε-opioid receptor
EFP	Empathy for pain
EMG	Electromyography
FSCRS	Forms of self-criticising/attacking and self-reassuring scale
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GSES	General self-efficacy scale
HPA	hypothalamic–pituitary–adrenocortical
IRI	Interpersonal Reactivity Index
IQR	Inter-quartile range
KOR	κ-opioid receptor
LEC	Life events checklist
LGCM	Latent growth curve models
M	Mean
MD	Mean difference
MDMA	3,4-Methylenedioxymethamphetamine
MET	Multifaceted empathy test
MI	Motivational interviewing
mm	Millimetres
mPFC	Medial pre-frontal cortex
MSPSS	Multidimensional scale of perceived social support
NAcc	Nucleus accumbens
NMDA	N-methyl-D-aspartate
NOR	Nociceptin opioid receptor
NMPOU	Non-medically prescribed opioid users
OCDUS	Obsessive-compulsive drug use scale
OSM	Opioid substitution medication
OT	Oxytocin
OUD	Opioid use disorder
PAG	periaqueductal grey

PANAS	Positive and negative affect schedule
PCS	Pain catastrophising scale
PET	positron-emission tomography
PFC	Pre-frontal cortex
POCQ	Post-ostracism Cyberball questionnaire
PRT	Progressive ratio task
PTE	Potentially traumatic events
PTSD	Post-traumatic stress disorder
RVM	Rostral ventromedial medulla
s	Seconds
SCS	Self-compassion scale
SD	Standard deviation
SEM	Standard error of the mean
SES	Socio-economic status
SNP	Single nucleotide polymorphisms
SOMSOM	State-dependent μ-Opioid Modulation of SOcial Motivation
SPSS	Statistical package for the social sciences
TSST	Trier Social Stress Test
UCLA LS	UCLA loneliness scale
VAS	Visual analogue scale
VTA	Ventral tegmental area

Chapter 1: Literature review

1.1 Opioid use: history and prevalence

Opium use has been reported for millennia. References to opium were made in classical antiquity, and it is generally believed that opium was first discovered and cultivated by the Sumerians in modern-day south Iraq (see Brownstein, 1993 for a review). Towards the end of the third millennium B. C, the Sumerians separated opium from the opium poppy, which was named 'Hul Gil', meaning 'plant of joy', and its use spread to other areas of Mesopotamia (see Brownstein, 1993 for a review). Its popularity grew vastly, and by the eighth century A.D. opium trade began to expand by the Silk Road trading route, connecting India, China and Europe. In the 17th century, it became popular to mix opium with tobacco (called 'madak'), which became a common method of use in China. During this time in China, rates of addiction soared and opium use began to be viewed unfavourably, leading to its recreational use being prohibited. This ban was lifted, however, following the forced authorisation of opium trade by the British East India Company, which were aptly called 'the Opium Wars'. Since then, demand for opium has boomed and spread worldwide for various uses, where it is the source for countless forms of opiate drugs.

The first opiate drug to be isolated from opium was morphine, discovered by Sertürner (1806), followed by the discovery of codeine shortly after, in 1832. Morphine makes up around 12% of the opium latex (the milky fluid expelled following damage), and its analgesic properties has transformed medicine: it was and still is often used to assist surgical procedures, and as a medication for pain. In early days, morphine was also proposed as a medication for addictions to opium and alcohol, unbeknown at the time that it was considerably more addictive than either of these substances. Both morphine and codeine are termed 'natural opiates', as they can be produced directly from opium. Many years later, in 1874, Wright (1874) first synthesised diamorphine (otherwise known as heroin), which was created by acetylating morphine. It was not until 1898, however, that heroin became produced commercially by the Bayer pharmaceutical company and marketed as a cough medicine, as seen in Figure 1.1 (see Brownstein, 1993 for a review). It was named after the German word 'heroisch', which translates as heroic and strong, and was mistakenly believed to be a non-addictive form of morphine. Since diamorphine derives

from the naturally occurring opiate morphine, heroin is termed a ‘semi-synthetic opiate’. Many more semi-synthetic opiates have since been produced, including oxycodone and hydrocodone, which are only two of many other congeners that fall into this category.

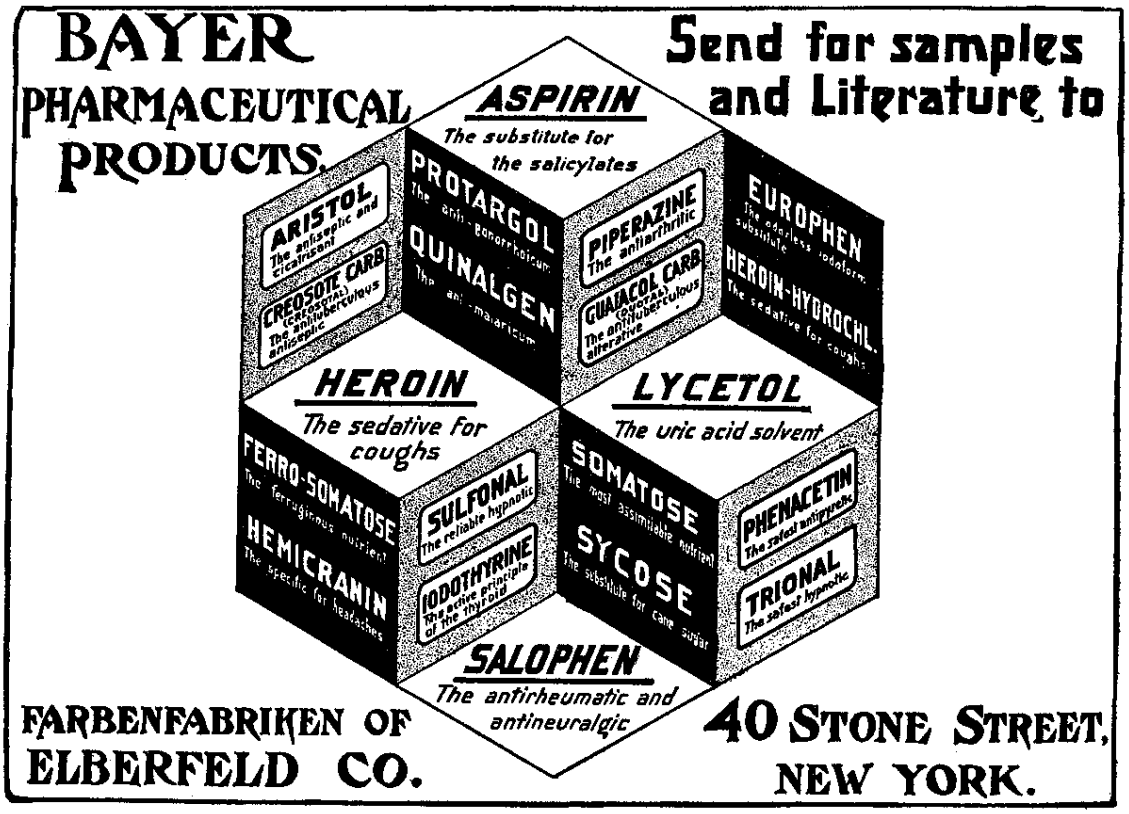


Figure 1.1. Heroin was originally advertised and sold as a cough medicine prior to realising its addictive potential. Image reproduced from Sneader, W. (1998). The discovery of heroin. *The Lancet, 352(9141)*, 1697-1699.

Over forty years later in 1939, the first fully synthetic opioid drug, meperidine, was chemically created in a laboratory (see Brownstein, 1993 for a review). This synthetic drug is structurally unrelated to opium-based analgesics, yet delivers similar pharmacological effects. Methadone was synthesised shortly after meperidine, which was shown to exhibit similar effects but to be longer acting. Other synthetic opioids have since been produced, such as buprenorphine and fentanyl. For clarity in the following thesis, the term opioid will be used as an overarching term that accounts for *all* opioid drugs: natural, synthetic, or semi-synthetic. The term opiates fall under this umbrella, however this term only refers to opioids that are derived from the opium plant.

Many of these opioid drugs have proved to be invaluable medicines that are used across the world, with several included under the WHO List of Essential Medicines. Opioids are among the most powerful analgesics available: they are considerably stronger than non-opioid acting painkillers such as paracetamol or aspirin, and their use in medicine to treat severe pain is diverse. Few examples of circumstances in which they are given include: post-surgery pain, pre-hospital physical trauma, labour, and during the treatment of cancer and palliative care. Hence, when used correctly, opioid drugs are extremely beneficial for treating a diverse range of medical problems. However, whilst considerably less common than the medical use of these drugs, their non-medical use has become universally widespread and is associated with a range of problems.

Opioid drugs are used recreationally to induce subjective feelings of euphoria and tranquillity, and ultimately almost all forms of opioid drugs can be abused. Their non-medical use is now a global problem that affects an estimated 34 million opioid users and 19 million opiate users worldwide, and is a major public health concern (United Nations of Office on Drugs and Crime, 2018). The health burden of opioids disproportionately exceeds that of any other illicit substance: 78% of all illicit drug-related deaths in the EU (European Monitoring Centre for Drugs and Drug Addiction, 2019) and 76% of worldwide (United Nations of Office on Drugs and Crime, 2018) detected the presence of opioids, and there has been a concerning increase in opioid-related deaths in recent years. To put this in context with legal drugs: alcohol and tobacco respectively account for 3.3 million and 6 million world-wide deaths per annum (World Health Organisation, 2014), whilst there are 207,400 drug-related deaths which are primarily due to opioids (United Nations Office on Drugs and Crime, 2016). Furthermore, within the UK, more people enter treatment services for opioid problems than any other illicit drug or alcohol combined, consequently accounting for a vast majority of treatment resources (typically in the form of opioid substitution treatments) (Health & Social Care Information Centre, 2016). The economic cost of opioid misuse on healthcare is thus vast, which is also increased by opioid-associated criminal behaviour. In the UK, 44% of all acquisitive crimes are drug-related to support drug use and are committed by opioid and/or crack cocaine users, which is estimated to cost £5.8 billion (Home

Office, 2013). Overall, the economic burden of opioid misuse is immense and overwhelmingly costly to healthcare and criminal justice systems.

The most common opioid to be used recreationally is heroin, with 78% of opioid users citing it as their primary drug (European Monitoring Centre for Drugs and Drug Addiction, 2019). For this reason, heroin has gained most public attention due to its profound negative impact on health and its association with wider socioeconomic problems. Although heroin accounts for the vast proportion of recreational opioid users, there has been an increase in the recreational use of synthetic opioids such as fentanyl in recent years (European Monitoring Centre for Drugs and Drug Addiction, 2019). There has also been a considerable rise in the nonmedical use of prescribed opioid drugs, particularly in the United States (known as the 'opioid crisis'), where the nonmedical use of prescription opioids can transition to illicit heroin use (Compton, Jones, & Baldwin, 2016). The increased use of fentanyl, a synthetic opioid with 50-100 times more potency than morphine (Pearson et al., 2015), has been responsible for a vast increase in overdose deaths in the United States. To contextualise this: 1,663 fentanyl-related deaths were reported 2011, which risen to 18,335 by 2016 (Spencer, Warner, Bastian, Trinidad, & Hedegaard, 2019). The astonishing increase in opioid use and overdose reports due to the opioid crisis is thought to be due to a myriad of factors. One contributor was the inaccurate opinion that opioids that are medically prescribed for pain do not carry risk of addiction (see deShazo, Johnson, Eriator, & Rodenmeyer, 2018, for a review). Although this was in the absence of scientific support, this opinion consequently influenced policy making that supported more lenient prescribing of opioids, and has contributed to the opioid crisis becoming considered a 'national emergency' (deShazo et al., 2018). These startling figures thus highlight the importance of identifying the indicators of risk of opioid addiction when prescribing opioid drugs.

In summary, opioids have been used for millennia, and these are essential drugs in many areas of medicine. Their recreational use, however, is associated with a vast array of problems; including a detrimental impact on health and high rates of mortality, as well as wider societal costs on the health care and criminal justice systems. Heroin is the most common illicit opioid used, however a rise in non-medical opioid use is also becoming a major concern. Understanding the

risk factors that precede opioid addiction, as well as factors involved in maintaining addiction are important for both enhancing treatments as well as reducing the economic burden of opioid use disorder. Social functioning has been highlighted as an important area for broadening our understanding of addiction due to high rates of social stress that are risk factors both pre- and post-drug use; however, addiction research has been criticised for overlooking the role of social factors and their neurobiological underpinnings (Heilig, Epstein, Nader, & Shaham, 2016). Understanding how social factors could both predate and be changed by opioid use could be important in the search for both prevention and intervention measures aimed at reducing problematic use.

This thesis aims to investigate the link between opioid use and social cognition in order to better understand how social factors are involved in the onset and maintenance of opioid addiction, and how understanding in these domains could be informative for developing novel treatments. Within this chapter, I will first provide a summary of the neurochemical action of opioid drugs (section 1.2), which will be important for providing context for the research discussed in the subsequent sections. This will be followed by an overview of specific social risk factors and that are relevant to opioid use disorder, and are central to the rest of this thesis (section 1.3). I will then explore the role of endogenous opioids in social cognition in pre-clinical and healthy volunteer studies, and how this may be altered in opioid users (section 1.4). Existing pharmacological and psychological treatments will then be discussed (section 1.5) before summarising and discussing the research questions for the current thesis (sections 1.6 and 1.7).

1.2 Neurochemical action of opioid drugs

The pharmacological effects of opioid drugs can largely be attributed to their influence over the opioid system, where they have greatest affinity for the μ-opioid receptors (MOR) (see Charbogne, Kieffer, & Befort, 2014 for a review). MOR is one of three major subtypes of opioid receptor, alongside δ-opioid receptors (DOR) and κ-opioid receptors (KOR). As mentioned, the vast majority of opioid drugs act as agonist primarily at MOR sites, but also to a lesser extent at DOR sites, and it is these sites which are thought to be responsible for the analgesic and euphoric properties of opioid drugs (Akil et al., 1998; Price, Von der Gruen, Miller, Rafii, & Price, 1985). All three of these opioid receptors are G

protein coupled receptors, and exert an inhibitory effect via cellular hyperpolarisation (see Al-Hasani & Bruchas, 2011, for a review). There are three main types of opioid ligands: endorphins, enkephalins, and dynorphins. Specifically, β-endorphin and Met-enkephalin have a strong affinity for both MOR and DOR, respectively (Akil et al., 1998), whilst dynorphin has a strong affinity for KOR (figure 1.2). Most opioid drugs are full agonists that mimic the actions of endogenous opioid peptides. Other opioid drugs may be slightly different, however, such as the partial agonist buprenorphine, which is both an agonist of MOR and an antagonist of KOR (Leander, 1987).

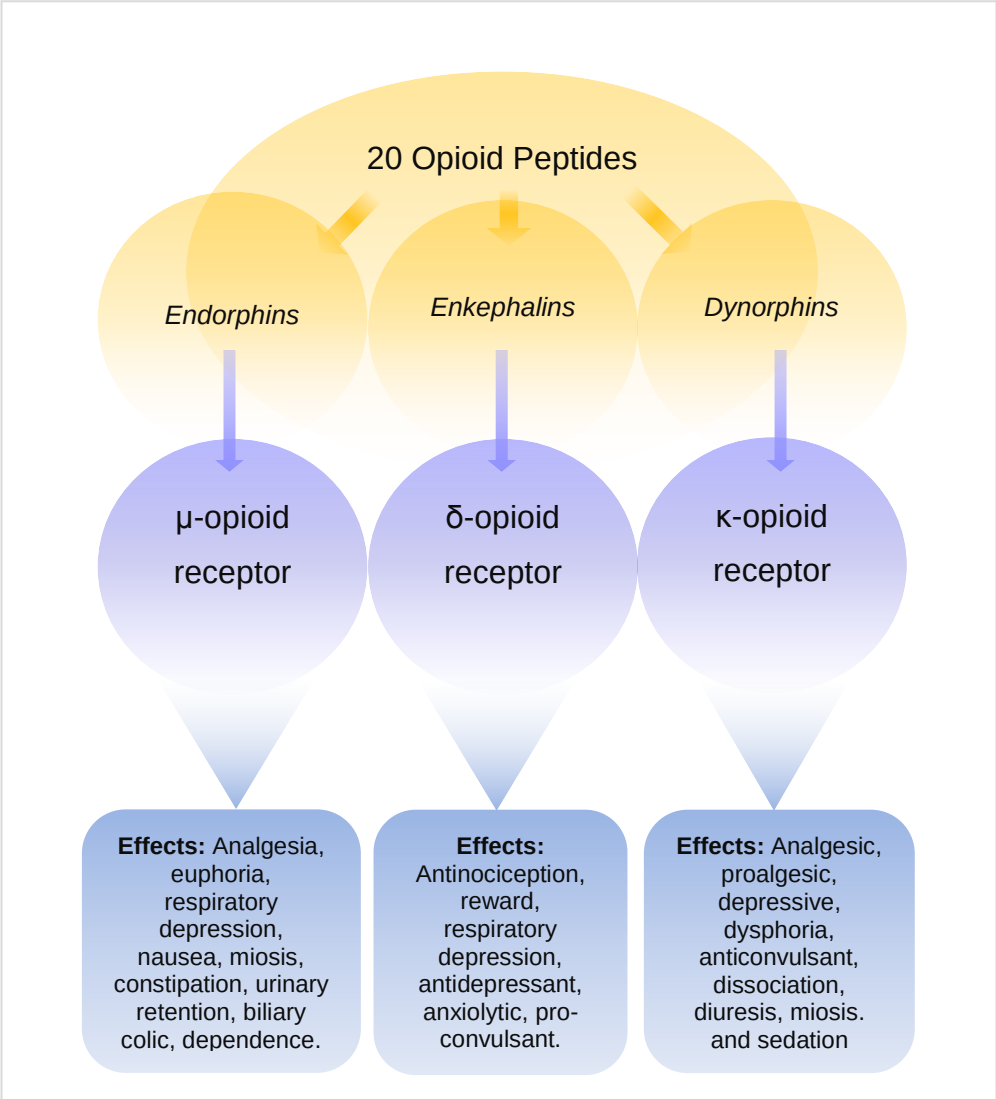


Figure 1.2. The endogenous opioid system. 20 opioid peptides (ligands) fall into three main categories, endorphins, enkephalins, and dynorphins, each of which have a high affinity for the three major opioid receptors: μ, δ and κ, respectively. These exert slightly different effects on other neurotransmitter systems, causing diverse physical and psychological effects. Figure made using multiple sources (Al-Hasani & Bruchas, 2011; Emery & Eitan, 2019; Grossman & Clement-Jones, 1983; Werling, Brown, & Cox, 1987).

Although opioid drugs generally act as MOR agonists, their exact actions on opioid receptors have subtle differences, possibly through differences in MOR subtypes as well as different intracellular responses (see Emery & Eitan, 2019; Pasternak, 2001, for reviews). There are multiple examples to exemplify such differences using animal models, such as inconsistent cross-tolerances to different MOR agonists: highly morphine-tolerant mice will still experience the analgesic effects of other MOR agonists, such as heroin and fentanyl (Rossi, Brown, Leventhal, Yang, & Pasternak, 1996). Furthermore, CXBK mice are

insensitive to the analgesic effects of morphine, but they retain the analgesic effects of other MOR agonists such as fentanyl and methadone (Chang, Emmel, Rossi, & Pasternak, 1998; Rossi et al., 1996). Additional to this, the analgesic effects of methadone are blocked by MOR antagonists, thus suggesting that these drugs act on the opioid system to produce analgesia in different ways (Chang et al., 1998). In addition to the animal models, human research also indicates subtle differences in the action of MOR agonists: In clinical settings, patients who have become tolerant to one MOR agonist are be prescribed a dramatically lower dose of a new MOR agonist (more than 50% smaller) when switching drug due to inconsistent cross-tolerances (Pasternak, 2001) which suggests different modes of action.

Furthermore, the subjective effects of different MOR agonists can also vary, for example between morphine, oxycodone, and hydrocodone (Stoops, Hatton, Lofwall, Nuzzo, & Walsh, 2010). Morphine is associated with higher subjective ratings of negative effects, whilst oxycodone is related to higher ratings in difficulty concentrating, and the subjective effects of hydrocodone were felt to dissipate more rapidly than the other two (Stoops et al., 2010). Thus, despite exerting the same agonist effects, different opioid drugs must activate the opioid pathways in marginally different ways. As well as subtle differences in the affinity for blinding to the different opioid receptors, there are also pharmacokinetic differences between these drugs that would account for experiential differences: including the speed in which these drugs pass the blood-brain barrier (molecules that are smaller and higher in lipophilicity diffuse across faster), and how they enter the body (route of administration e.g. orally versus intravenously) (Compton et al., 2016; Emery & Eitan, 2019).

Other potential opioid receptors have been proposed, however controversy has surrounded their categorisation as opioid receptors. The ε-opioid receptor (EOR) was identified and believed to be another opioid receptor subtype (Schulz, Wüster, & Herz, 1981), as it is stimulated by the opioid peptide β-endorphin and is involved in analgesia (Tseng, 2001). However, its categorisation as another opioid receptor subtype was questioned in a knockout study looking at animals lacking MOR, DOR and KOR, which found that the effects of β-endorphin-stimulation was eliminated (Contet, Matifas, & Kieffer, 2004). This suggests that the EOR is more likely a splice variant of one of the

main three opioid receptors, and hence does not function independently (Contet et al., 2004). Another proposed opioid receptor was the σ-receptor, however this was later found be non-specifically activated by substances that have no relation with opioids (such as phencyclidine), and hence was suggested as a different class of receptor associated with psychedelic effects (Bruce Vaupel, 1983; Sharp, 1997). The most recent opioid receptor to be discovered was the nociceptin opioid peptide receptor (NOP) (Mollereau et al., 1994), with nociceptin as the natural ligand (Henderson & McKnight, 1997). This opioid receptor has been linked to pain processing, anxiety, depression, epilepsy, and reward processing (see Chiou et al., 2007, for a review). Compared to the three classic opioid receptors, research into the NOP receptor is in its infancy, but holds promise for future therapeutic applications for treating mood disorders (Post et al., 2016), substance use disorders (Flynn et al., 2019), binge eating (Hardaway et al., 2016), PTSD (Tollefson, Himes, & Narendran, 2017), and schizophrenia (Khan, Boileau, Kolla, & Mizrahi, 2018) due to potentially antidepressant and anxiolytic effects, and reduced abuse potential.

Opioid receptors are widely distributed across the central and peripheral nervous system (Stein, 2016). Brain areas with particularly high density of opioid receptors include the insula, anterior cingulate cortex, prefrontal cortex, thalamus, and somatosensory cortices, all of which are involved in the perception and experience of pain (see Fischer et al., 2017, for a review). The brain areas most well understood in analgesia are the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM): stimulation of opioid receptors in the PAG inhibit excitatory ON-cells (involved in nociception) and indirectly disinhibits OFF-cells (involved in antinociception), causing a net inhibition on pain processing (Morgan, Whittier, Hegarty, & Aicher, 2008). The RVM then sends inhibitory signals to the dorsal horn (the spinal cord), where opioids reduce the nociceptive signal (see Fischer et al., 2017, for a review). These effects on nociception make opioid drugs highly effective analgesics, however due to the wide distribution of opioid receptors throughout the brain they also exert other side effects, such as respiratory depression. Opioid activation in the brainstem can affect respiratory rhythm and the amount of air inhaled: within the ventrolateral medulla, areas involved in inhalation are inhibited by opioids, whilst areas involved in exhalation are unaffected by them

(see Pattinson, 2008, for a review). This causes breathing so slow and become irregular, contributing to respiratory depression (Pattinson, 2008). Other side effects of opioid drugs include nausea. Nausea and sickness are believed to be controlled by the 'vomiting centre' within the brain, which is in the medulla oblongata (Hornby, 2001). Opioids receptors are stimulated at both the chemoreceptor trigger zone (involved in initiating sickness), as well as the vestibular apparatus (required for balance), which are partly thought to underlie opioid-induced nausea (see Porreca & Ossipov, 2009, for a review). Analgesia, respiratory depression, and nausea are all effects of opioid drugs, yet opioids also produce feelings of euphoria and pleasure which are important when considering the reinforcing effects of these drugs.

The reinforcing effects of opioid drugs also involves other neurotransmitters in brain areas important in reward and reinforcement, including dopamine (DA), glutamate, and gamma-Aminobutyric acid (GABA). Mesolimbic DA activity (connected with reward, motivation, and learning) was previously thought to be increased by exogenous opioids via activation of the opioid receptors located in the ventral tegmental area (VTA) and nucleus accumbens (NAcc) (Devine, Leone, Pocock, & Wise, 1993; Hemby, Martin, Co, Dworkin, & Smith, 1995). However, it is now believed that opioid drugs increase DA via a disinhibitory process involving GABA. As MOR inhibits tonic neural activity, it reduces GABA release and causes GABAergic disinhibition of DA, and this is suggested as the main mechanism in which opioids increase DA (Chefer, Denoroy, Zapata, & Shippenberg, 2009; Lecca, Melis, Luchicchi, Muntoni, & Pistis, 2012). Glutamate is also involved in this process: MOR activity also increases glutamate release by blocking inhibitory GABAergic interneurons, in turn stimulating DA release (Chen et al., 2015). The importance of glutamate in this process is supported by reduced DA firing in the VTA after morphine when glutamate antagonists are infused in this region (Jalabert et al., 2011). Thus, the effects of MOR stimulation on GABA and glutamate are important for increasing DA following MOR agonists, which aligns with a general consensus that DA is an important underlying factor in drug reward (Robinson & Berridge, 2006). More recently, however, the involvement of dopamine in opioid abuse has been questioned: DA blockade does not reduce reward-related behaviours towards opioid drugs in animals, nor are increases in DA observed

following opioid administration in addicted individuals (Van Ree & Ramsey, 1987; Watson et al., 2014), despite causing reported feelings of euphoria (see Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015 for a review). Hence, DA is not necessary for the rewarding effects of opioids, and thus may not play such a pivotal role in opioid addiction as initially suggested (Nutt et al., 2015). Alternatively, glutamate receptors, such as AMPA and NMDA, are now also being highlighted for their involvement in opioid addiction; particularly in regards to learned associations and drug-seeking behaviours (Reissner & Kalivas, 2010). In opioid-dependent animals, NMDA antagonists have been shown to eliminate the conditioned place preference for opioid-paired locations, attenuate the conditioned response to opioid-related cues, and also reduce the unpleasant effects of opioid withdrawal which has also been replicated in humans (Bossert, Liu, Lu, & Shaham, 2004; Glass, 2011).

In addition to these neurotransmitters, opioid drugs have also been shown to influence the peptide hormone oxytocin. Acute stimulation of the opioid receptors has been shown to inhibit oxytocin release (Bicknell & Leng, 1982), whilst blockade of opioid activity using the agonist naloxone conversely increases it (Neumann, Russell, Wolff, & Landgraf, 1991). Another study shown that prolonged opioid activation is associated with reduced oxytocinergic tone, where there is a reduction in oxytocin synthesis and plasma levels (Zanos et al., 2014). Vasopressin may also be affected by MOR activity (Lightman & Forsling, 1980), however another study reports vasopressin to be unaffected by endogenous opioids (Bicknell, Chapman, & Leng, 1985).

Thus, opioid drugs cause a neurochemical cascade which are believed to be related to their rewarding effects. Vulnerability to the rewarding effects of these drugs, however, may vary in the presence of many factors. As briefly introduced at the end of section 1.1, the role of social risk factors has been overlooked in opioid addiction research, and the following section will provide an overview of specific social risk factors and that are relevant to opioid use disorder.

1.3 Social risk factors for the initiation and maintenance of problematic opioid use

As humans operate in social groups, there is an innate fundamental need to belong that requires frequent, positive, and meaningful interpersonal interactions with others for emotional well-being (Baumeister & Leary, 1995). Social risk factors include adverse childhood experiences (such as interpersonal trauma history of abuse and neglect) as well as social stress (encompassing social deprivation, isolation, stigma, and stressful life events). Threats to social belonging all commonly activate the neurobiological pathways for stress, which is a common denominator that connects them; yet endogenous opioids can soothe the social distress evoked by these experiences (this is discussed further in section 1.4). However, when social stressors are encountered repeatedly, they can have adverse effects on the mental and physical functioning, and this 'allostatic load' has been suggested to partly drive drug reward. The neurobiological influence of stress on drug reward will be discussed in section 1.3.4.

1.3.1 Adverse childhood experiences

Epidemiological research suggests that childhood adversity is a disproportionately large predictor of developing opioid use disorder in later life (Dube et al., 2003). Numerous studies have found that most heroin addicts have experienced some form of childhood adversity, including trauma (Lake et al., 2015) or neglect (Gerra et al., 2014). To illustrate the extent of this, experiences of childhood physical and sexual abuse are 2.7 times higher among those with a history of heroin use than in the general population (Heffernan et al., 2000). Another study reported two thirds of opioid addicts have experienced adverse childhood experiences, compared to one third of the general population (Naqavi, Mohammadi, Salari, & Nakhaee, 2011). In this study, physical neglect was the most prevalent form of adversity reported by opioid addicts (51.7%), followed by emotional abuse (34%), and sexual abuse (31.6%). In addition, as severity of adverse childhood experiences increases, the age of first heroin use has been found to decrease (Taplin, Saddichha, Li, & Krausz, 2014). Thus, there is strong evidence to link these adverse childhood experiences with later opioid use.

Several sources of evidence suggest a mechanism for the link between childhood trauma and opioid use. Firstly, early life trauma has been shown to enhance the reward value of MOR agonists such as heroin in animals. For example, young rats who have experienced maternal separation (a paradigm known to model early life trauma) show a stronger place preference for morphine-paired areas than non-traumatised offspring (Michaels & Holtzman, 2008). This suggests that opioids may be particularly rewarding to those who experience early adversity as opioid drugs activate the system responsible for socially affiliative and soothing behaviours (Schindler & Bröning, 2015) (also discussed in section 1.4). This produces positive and rewarding feelings that may not have been commonly experienced in childhood. However, although opioids may emulate these positive and soothing feelings, research has also suggested that positive emotions that arise from feeling safe and secure can be frightening or aversive in people who have not had early nurturing experiences (Gilbert et al., 2012). This is because these feelings may be unfamiliar or associated with difficult memories where feeling safe does not last. Therefore, the heightened reward and pleasure from opioids may not be due to feeling safe and soothed as suggested by Schindler and Bröning (2015), but instead could be due to emotional numbing of difficult emotions. The ability to regulate negative affect is developed in childhood by nurturing environments, and is related to opioid activity; however, this system can become permanently dysregulated if the child's emotional needs are not met (Weller & Feldman, 2003). Thus, opioid drugs may be used as an external source of self-soothing and self-medication of distress in individuals who have deficits in emotion regulation.

Further evidence for the link between the endogenous opioid system and trauma comes from research using positron emission tomography (PET). Histories of trauma have been associated with reduced MOR availability in brain areas implicated in emotional processing, reward, and control, such as the amygdala, NAcc and the insular cortex (Liberzon et al., 2007). This study was conducted on patients with post-traumatic stress disorder (PTSD) related to military combat, however, which could have different effects than interpersonal traumas and childhood adversity. Another study compared post-mortem brain samples of individuals who committed suicide with and without histories of

childhood adversity, alongside healthy controls (Lutz et al., 2018). The authors reported epigenetic changes in the endogenous opioid system in those with childhood adversity, finding downregulated KOR in the anterior insula, suggesting lasting changes to opioid functioning due to early social experiences. Furthermore, pre-clinical research in rats has shown long-lasting reductions in both opioid and dopamine receptor density as a result of repeated maternal separation, which was directly linked with increased alcohol use later (Ploj, Roman, & Nylander, 2003). A further study similarly using maternal separation in rats reported epigenetic changes in gene expression coding for the different opioid receptor subtypes and their precursors, which influenced adult ethanol intake (Granholm et al., 2017). These studies suggest that other neurotransmitters are also affected by childhood adversity, such as dopamine, which are important in the reward system. Although Ploj et al. (2003) reported reductions in dopamine density in rats, a study using PET in humans reported increased striatal dopamine functioning in those with childhood adversity (Egerton et al., 2016), therefore suggesting that early adversity may have different effects on the dopaminergic system in humans.

Alterations in receptor functioning as a consequence of childhood trauma could also result in differing responses to drugs that act on those neurobiological systems. One study using PET assessed dopamine responses to amphetamine in individuals with childhood trauma, reporting a positive correlation between amphetamine-induced dopamine release in the ventral striatum (important for reward processing) and number of adverse childhood events (Oswald et al., 2014). In addition, childhood trauma was positively correlated with both D2 receptor availability and pleasant subjective effects in males, whereas a trend for the opposite was found in females. This finding is at odds with prior evidence linking lower receptor density with increased drug-induced pleasure from methylphenidate in healthy individuals (Volkow et al., 1999), suggesting that childhood trauma influences the early development of the dopamine system (potentially through epigenetic changes caused by early exposure to glucocorticoids), which could render a hypersensitivity to the rewarding effects that is not just through subjective pleasure. The gender differences here should be interpreted with caution, however, since there were only 9 females included in the study (Oswald et al., 2014). Another study found

neurological responses to naltrexone (an opioid antagonist) to be altered in those with childhood adversity and histories of drug and/or alcohol use disorders (Savulich et al., 2017). Naltrexone increased medial pre-frontal cortex activation (mPFC) when responding to negative emotional images in those with childhood adversity. Increased activity in this region have been linked with greater effort to engage in emotion regulation. Naltrexone also restored connectivity between the anterior cingulate cortex and hippocampus in those with childhood adversity. The authors highlight that this pathway is linked with relapse when hyperactive, as well as being linked to the reconsolidation of fearful memories. The findings not only highlight how naltrexone may work therapeutically in those with trauma histories, but they also suggest an underlying dysregulation of the endogenous opioid system in those with childhood trauma. Considering the strong links between childhood trauma and opioid use disorder, little is known about the impact of childhood trauma on endogenous opioid functioning, and the impact of this on the rewarding effects of opioids.

The research discussed strongly suggests that childhood adversity is a social risk factor that predates opioid addiction. These early experiences have been shown to affect neuroplasticity and the development of the endogenous opioid system, as well as the dopaminergic system, both of which are important in processing reward and reinforcement. The alterations of these neurobiological pathways may occur due to epigenetic changes via exposure to stress (Koob & Schulkin, 2018; Oswald et al., 2014), which may have negative repercussions on emotion regulation where opioids are used as a compensatory mechanism to self-soothe and cope. Additional to this, neurobiological alterations in these systems may facilitate the rewarding and reinforcing effects of opioid drugs. There are other social factors that are also affected as a consequence of opioid use, as covered in the next section.

1.3.2 Social deprivation, isolation, and stigma

Social deprivation encompasses a myriad of socioeconomic factors. In the UK, the English Indices of Deprivation (2015) summarises this multifaceted concept as comprising of: low income and unemployment; homelessness; lack of educational opportunities; poor health and premature mortality; acquisitive crime; and poor living environment (Department for Communities and Local

Government, 2015). Social deprivation has been identified as increasing the risk of drug abuse through a combination of poor social support, unemployment, feelings of helplessness, and increased exposure to drugs (Kendler, Ohlsson, Sundquist, & Sundquist, 2014). The sociodemographic distribution of opioid users tends to be individuals who belong to areas in which social deprivation is high, ultimately highlighting deprivation as a vulnerability factor for opioid use (Richman & Dunham, 1976). For example, unemployment was associated as a significant risk factor leading to the development of substance use disorders, as well as increasing relapse following abstinence (Henkel, 2011). In addition, socially deprived areas are also disproportionately affected by the poor health implications of drug use, as well as high levels of drug-related mortalities (MacGregor & Thickett, 2011), in what has been termed the “harm paradox” e.g. Bellis et al. (2016).

In addition to being a vulnerability factor preceding drug use, social deprivation can also act as a barrier for recovery from drug addiction. Research suggests that individuals with drug use disorders often experience financial difficulties, including debt, poor employability, and lack of job prospects within socially deprived areas (Department for Communities and Local Government, 2015). In such cases, there are often few alternative options or opportunities to improve quality of life, and individuals can find themselves trapped in a cycle of drug use to fill this void (MacGregor & Thickett, 2011). Heroin use in particular is pinpointed as particularly destructive to communities, on both an individual and societal level, further exacerbating areas of social deprivation by increasing levels of crime, antisocial behaviour, and prostitution (McKeganey, Neale, Parkin, & Mills, 2004). However, this cycle may be perpetuated by stigma, which can act as a barrier for opioid users to seek help or engage in safer drug use (i.e. needle syringe programmes) (Hurley, 2017). Stigma is discussed in more detail later in this section.

Experimentally-induced social deprivation in animal studies confirms its importance in initiating and maintaining drug using behaviour. Rats in socially-deprived environments have been shown to self-administer more morphine than socially-housed ones, which is exacerbated the longer social deprivation is prolonged (Consorti, Castellano, Oliverio, & Pavone, 1992). Furthermore, perhaps the most recognised set of experiments investigating this are called

‘Rat Park’ (see Alexander, 2001 for a review). In these series of experiments, rats were placed in a socially-stimulating, spacious, natural environments that contained many natural, positive reinforcements (such as the opportunity to breed), and rates of morphine self-administration was compared with socially-deprived, caged animals. In most cases, socially deprived animals consumed considerably more opioids than those in natural, socially-enriching environments (sometimes as much as 20 times more). It is important to note that this reduction in opioid use among animals exposed to socially enriching environments has not always been replicated, however, which suggests that addictive behaviours are not solely driven by these environmental factors (Petrie, 1996). Nonetheless, recent research has replicated the decreased acquisition of opioid self-administration in rats reared in socially enriching environments using the short acting MOR agonist remifentanil (Hofford, Chow, Beckmann, & Bardo, 2017). Another study reported no differences in cocaine self-administration between rats reared in socially deprived versus socially enriching environments, and surprisingly exposure to prolonged stress caused reduced self-administration irrespective of rearing environment (Hofford, Prendergast, & Bardo, 2018). Thus, the influence of social deprivation on reward sensitivity may be a contributory element within the multifactorial problem of opioid use, and may depend on the presence of other factors.

Once an opioid addiction has developed, users are often marginalised from the community, and can experience social isolation and stigmatisation as a consequence of their drug use (Buchanan & Young, 2000). Social exclusion has a longstanding association with problem drug use (Drugs & Crime, 2010; Unit & Britain, 2001), and is also linked to vulnerabilities to drug-related health issues (such as blood borne viruses, or HIV) as individuals engage in much riskier behaviours due to experiences of severe marginalisation (Shaw, Jolly, & Wylie, 2014). Social isolation is also related to an increased risk of suicide attempts among drug users, highlighting the protective factor of social connectivity in this vulnerable population (Rossow & Lauritzen, 1999). Hence, it has been proposed that social isolation plays a crucial role in catalysing the downwards trajectory of drug addiction, and that social connection and bonding is the key for improvement and recovery among these individuals (Maremmani et al., 2015). Opioid addiction is commonly associated with social disconnection and

isolation (Barry, McGinty, Pescosolido, & Goldman, 2014), and many argue that opioid use among this population is partly driven by the desire to alleviate feelings of social distress (Panksepp et al., 1978). By exogenously activating the opioid system, the effects of opioid drugs have been said to powerfully parallel the rewarding effects of positive social interactions (Burkett & Young, 2012), and hence potentially act as a substitute for a lack of social connection (Panksepp et al., 1978). Only recently are the importance of social isolation and its resulting effects on the endogenous opioid system being considered in addiction research (Heilig et al., 2016).

Experiences of stigma from the public and healthcare providers contribute to social isolation and can perpetuate drug use and reduce recovery success (Lloyd, 2013). Evidence suggests that substance use is associated with greater stigma than mental illnesses, particularly intravenous drug use (Decety, Echols, & Correll, 2010). People have been shown as less willing to welcome, work closely with, or offer help to addicted individuals, and are more inclined to act with discrimination and oppose policies focused on helping them (Barry et al., 2014). Stigma can perpetuate isolation, as individuals in recovery will often avoid contact with non-drug users due to feelings of anxiety and social distress (Jackson, Parker, Dykeman, Gahagan, & Karabanow, 2010). Stigmatisation thus hinders individuals from seeking help, which perpetuates isolation and drug use further (Volkow, Baler, & Goldstein, 2011)

1.3.3 Stressful life events in adulthood

It is unsurprising that stressful life events are related to the onset and maintenance of substance use problems, as stress has robustly been shown to trigger an overwhelming amount of poor mental health outcomes (Cooper & Marshall, 2013; Hammen, 2005; Lincoln, Peter, Schäfer, & Moritz, 2009; Ventura, Nuechterlein, Lukoff, & Hardesty, 1989). In the field of addiction, majorly stressful events, such as partner violence, sexual assault, and participation in war, have all been shown to predict later problematic drug use and relapse (Coker et al., 2002; Kilpatrick, Acierno, Resnick, Saunders, & Best, 1997; Seal, Shi, Cohen, & et al., 2012). Even minor stressful events, such as interpersonal problems, legal problems, or moving or living somewhere new, have been shown to elevate the risk of later opioid use problems (Myers, McLaughlin, Wang, Blanco, & Stein, 2014). Although stress affects all

populations, those belonging to the most socially deprived areas have been shown to experience the highest levels of psychosocial stress, which contributes to poor health outcomes (Steptoe & Feldman, 2001). Thus, stress, social deprivation, isolation and stigmatisation do not operate independently: they are inter-correlated, and their interactions contribute to problem opioid use.

To exemplify the complex interactions of social epidemiology in predicting problematic opioid use, a well-known study investigated the return of the US soldiers serving in Vietnam (Robins, Davis, & Goodwin, 1974). During service, 75% of soldiers were using opioids to the extent that they would fit the criteria of addiction. However, upon their departure home only 7% exhibited symptoms of addiction 8-12 months later. In this case, the best predictor of opioid addiction was whether individuals used drugs *before* military service. Such research indicates how it may be during times of stress that drug use is initiated and maintained, however, may dissipate in the presence of more positively enriching and reinforcing environments. Thus, opioid use is a multidimensional problem that encompasses multiple social stressors.

1.3.4 The neurobiology of social stress

In addition to lifestyle changes discussed above, social stressors such as childhood trauma, social isolation and deprivation, stigma and stressful life events also exert a vast influence on brain neurocircuitry. Some of these have been discussed, such as neuroadaptations to the opioid and dopamine system after childhood trauma, however one of the major underlying factors connecting these all is chronic activation of the hypothalamic–pituitary–adrenocortical (HPA) axis.

The chronic impact of these social stressors dysregulate the neurological and neuroendocrine systems involved in regulating the body's response to stress, which has consequences on behaviour and is linked with addiction. They contribute to 'allostatic load' which refers to the chronic activation of a normally fluctuating neuroendocrine responses to environmental demands, which has knock-on effects on immune functioning, neurobiological systems, and behaviour (Koob & Schulkin, 2018). Specifically the release of glucocorticoids such as cortisol, which are involved in immune functioning and inflammation, can become disrupted by social stressors. For example, social isolation is

related to higher cortisol awakening response (Chida & Steptoe, 2009), as well as increased levels of cortisol throughout the day (Grant, Hamer, & Steptoe, 2009). In addition to this, social isolation is related to higher night time cortisol, and a smoother diurnal slope, which is similarly related to poor health outcomes (Stafford, Gardner, Kumari, Kuh, & Ben-Shlomo, 2013). Stigmatisation, too, causes abnormalities in cortisol function: chronically stigmatised groups often show higher cortisol reactivity to social stressors (Juster et al., 2015; Schvey, Puhl, & Brownell, 2014; Townsend, Major, Gangi, & Mendes, 2011). On the contrary, social connectivity has been shown to remediate aberrations in cortisol activity when individuals face a social stressor, showing the protective benefit of positive social interactions (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). Links have been made between the activation of the neuroendocrine responses to stress and the rewarding effects of drugs, where greater allostatic load alongside a weakened anti-stress response can lead to negative affective state which can drive the negative reinforcement of drugs (see Koob & Schulkin, 2018, for a review) Social stressors thus cause disruptions to the HPA axis activity that controls the neuroendocrine response to stress, which has knock-on effects on other neurochemical systems such as dopamine and endogenous opioids.

Animal studies have indicated that social hierarchy can influence the availability of striatal D2/D3 receptors, which in turn may predict addictive behaviours: social sub-ordinance in both rats and primates has been shown to be related to lower striatal D2/D3 receptors, which is inversely related to levels of cocaine administration (Grant et al., 1998; Morgan et al., 2002; Nader et al., 2012). A similar finding has more recently been reported in rats, where socially subordinate individuals also show less D2/D3 binding; yet, contrary to the primate studies, socially dominant individuals were shown to self-administer *more* cocaine (Jupp et al., 2016). The relationship between social status and D2/D3 receptor availability has also been replicated in humans: individuals with low socio-economic status (SES) similarly show lower availability of striatal D2/D3 receptors (Martinez et al., 2010; Matuskey et al., 2015; Wiers et al., 2016). Both Matuskey et al. (2015) and Wiers et al. (2016) also investigated the effect of SES on D2/D3 specifically in chronic drug users, with divergent results: the former found that SES was positively related to D2/D3 availability in chronic

cocaine users, whilst this correlation was absent in the latter study. A recent study investigated social status in relation to endogenous opioids, finding that higher social status was related to lower KOR levels in humans (Matuskey et al., 2019), where KOR activity has been suggested as 'anti-reward' by decreasing dopamine. This is at odds with the relationship between SES and dopamine and highlights the intricate relationship between social stress and social behaviours. Thus, there is some evidence to suggest that SES/dominance is related to differences in striatal D2/D3 responsivity in both animals and humans, which interacts with the endogenous opioid system. However, the exact impact of this in drug-using populations are not so clear.

Research also indicates the endogenous opioid pathway is impacted by social stress. Since the opioid system is activated in response to physical pain, animal studies often use physical pain assessments as an indirect means of assessing opioid activity. Such studies have shown that the opioid pathway is activated during social stress, and pain processing is consequently affected. For example, following an aggressive social confrontation between resident and intruder mice, socially defeated individuals take three times longer when responding to a post-confrontation painful stimuli than their counterparts who have not been social defeated (Miczek, Thompson, & Shuster, 1982). This analgesic response to physical pain following a social stressor (an indirect measure of opioid activity) was only observed in the socially defeated individuals, despite both animals experiencing equal amounts of stress. This suggests that social stress, rather than stress generally, activates the opioid pathway. In relation to addictive behaviours, mice put under social stress exhibit a stronger place preference for cocaine-paired areas than unstressed individuals (McLaughlin, Li, Valdez, Chavkin, & Chavkin, 2006). These amplified drug-seeking responses in socially stressed animals are abolished both in 1) individuals lacking the ability to express the opioid peptide precursor prodynorphin, and 2) those given an opioid antagonist (McLaughlin et al., 2006). Thus, such studies identify the opioid system as important during the experience of social stress, and in turn its relationship with drug-using behaviour.

Endogenous opioid release during social stress has also been suggested from research in humans. It has been found that individuals have a higher pain

tolerance following social exclusion (DeWall & Baumeister, 2006), however pain tolerance is also influenced by other factors, such as competition during sports, and thus it is not specific to social exclusion (Sternberg, Bailin, Grant, & Gracely, 1998). Nonetheless, genetic differences in the MOR gene predict sensitivity to social exclusion, whereby those possessing the G allele, who have lower expression of receptors are more sensitive to the effects of social exclusion (Way, Taylor, & Eisenberger, 2009) (social exclusion, pain tolerance and genetic differences in endogenous opioid release are discussed in more detail in section 1.4). It is possible that greater pain tolerance following social exclusion could be due to stress-induced analgesia, which refers to the adaptive suppression of pain following a stressful event and occurs via activation of endogenous opioids (Butler & Finn, 2009) but also the endocannabinoid system (Hohmann et al., 2005).

A subject of much debate is whether both physical and social pain share similar neurocircuitry (Eisenberger, 2012; Eisenberger & Lieberman, 2004). Neuroimaging and lesioning studies support this overlap implicating the same brain regions – the dorsal anterior cingulate cortex (dACC) and anterior insula (AI) – in processing both social distress and the affective (rather than sensory) aspects of physical pain (see Eisenberger, 2015, for a review). Pharmacological evidence adds to this by alleviating both physical pain and social distress via stimulation of the endogenous opioid system (discussed in section 1.4 in more detail). Although this view of shared neural mechanisms between physical and social pain has been widely accepted, it has also received criticism, as the brain areas activated are not specific to pain but could also be due to cognitive processes involved in detecting, attending to, and reacting to salient events (Iannetti, Salomons, Moayedi, Mouraux, & Davis, 2013). In addition, it has been disputed due to being based on a reverse inference that activation in those brain regions reflects affective pain processing and social distress. The salience model, however, has been argued to lack support (Eisenberger, 2015), and a large-scale reverse inference analysis using 10,000+ fMRI studies suggests that dACC function is selective to pain processing (Lieberman & Eisenberger, 2015). Nonetheless, recent research reported dACC and AI activity as involved in responses to the salience of social evaluation from others, irrespective of whether or not this is positive or negative (Perini et al., 2018). Thus, self-

referential salience cannot be ruled out as responsible for activation of the 'social pain matrix' (Perini et al., 2018). Other researchers additionally argue that viewing the neural mechanisms of social pain to 'piggyback' those of physical pain underestimates the sophistication of the neural mechanisms in pain processing, and if there are specialised receptor systems for different forms of physical pain then it is likely that social pain also has its own neural architecture (Ferris, Jetten, Hornsey, & Bastian, 2019). The authors suggest that it is important to understand both the convergent and divergent qualities of both social and physical pain regarding attention, motivational state, and responses. It is possible that looking at neural connectivity rather than regions of interest (i.e the dACC and AI), may deepen our understanding of how social pain is neurologically organised.

Overall, negative social experiences such as deprivation, isolation, and stigmatisation can cause abnormalities in neurochemical brain function, which may render individuals vulnerable to addictive behaviours. Human beings are social creatures with an innate need for social connection and belonging, and threats to these processes can result in undesirable and problematic behaviours (Baumeister, 2011). The following section will discuss the importance of the endogenous opioid system in social and affiliative behaviours. It will first cover pre-clinical and healthy volunteer research, before discussing the potential deviations in endogenous opioid functioning and social behaviours in chronic opioid users.

1.4 The role of the opioid system in social cognition

Social cognition refers to the cognitive processes that underlie how an individual relates to others emotionally and behaviourally, encompassing processes such as emotion recognition and regulation, empathy, trust, co-operation, and social feedback and learning (assessing how an individual reacts to social cues as well as whether they are able to respond and reciprocate appropriately) (Patin & Hurlemann, 2015). The following section will discuss the importance of endogenous opioids in social cognition, and how these important social functions may become impaired in opioid use disorder.

1.4.1 Pre-clinical research

Animal studies have demonstrated the importance of MOR for forming and maintaining attachments (Cinque et al., 2012; Moles, Kieffer, & D'Amato, 2004), alleviating separation distress (Panksepp, Herman, Conner, Bishop, & Scott, 1978), and increasing positive affect through social bonding (Fabre-Nys, Meller, & Keverne, 1982). Labelled as the 'Brain Opioid Theory of Social Attachment' (BOTSA; Machin & Dunbar, 2011), it has been suggested that the endorphins are naturally released during romantic love, attachment, and other socially rewarding activities including social play (Panksepp & Bishop, 1981), and physical touch (Keverne, Martensz, & Tuite, 1989). Endogenous opioid release has thus been considered as an adaptive response that is fundamental for facilitating caregiving behaviours and creating fulfilling relationships (Machin & Dunbar, 2011).

Pharmacological studies support the importance of MOR in eliciting affiliative behaviours and alleviating social distress. Following social separation, opioid agonists (such as morphine; 0.125-0.5 mg/kg) have been shown to decrease separation distress in young animals, whilst opioid antagonists (such as naloxone; 1mg/kg) conversely increased distress (Panksepp, Bean, Bishop, Vilberg, & Sahley, 1980; Panksepp et al.,1978). The authors suggest that these contrasted effects occur because MOR agonists emulate the natural increase in endogenous opioids when the mother is present, which attenuates the social distress experienced by her absence. Yet, blockade of this activity conversely increases the distress and desire for her companionship. Reductions in social distress, measured by distress vocalisations, were observed following the administration of exogenous opioids has been replicated in a vast array of species, including infant rats (Carden & Hofer, 1990; Kehoe & Blass, 1986), rhesus monkeys (Kalin, Shelton, & Barksdale, 1988), chicks (Panksepp et al., 1980), and puppies (Knowles, Conner, & Panksepp, 1989). One possible problem with concluding that the attenuated social distress caused by opioids highlights this system as important in social bonding is that other anxiolytic drugs, such as benzodiazepines and barbiturates, have also been shown to reduce separation distress vocalisations in rat pups (Insel, Hill, & Mayor, 1986) and chicks (Feltenstein, Warnick, Guth, & Sufka, 2004). This could therefore indicate that MOR activation reduces distress generally rather than just socially,

or that social distress is not specifically alleviated by opioid drugs but also anxiolytics. Nonetheless, the dichotomous effect of MOR stimulation and blockade on social distress could still indicate the endogenous opioid system as important for social attachment.

Another study investigated social grooming following a period of social isolation, as a measure of social anxiety and desire for social affiliation in primates (Keverne et al., 1989). The authors found social grooming behaviour naturally increased MOR activation when monkeys were reunited with another monkey, measured via greater levels of β-endorphin in cerebral spinal fluid. However, social grooming was decreased following stimulation of MOR by morphine administration (2mg/kg), and is intensified following MOR blockade by naltrexone (0.5mg/kg) (Keverne et al., 1989). The effect of naloxone on intensifying desire for social comfort has been replicated in other primates, such as young macaques (Schino & Troisi, 1992) and rhesus monkeys (Martel, Nevison, Simpson, & Keverne, 1995). Overall, this supports the notion that increases in MOR activity emulate the effects of social affiliation and thus reduce the need for it; whereas blockade of MOR activity increases social anxiety and increases the compensatory grooming behaviours to alleviate this.

Whilst MOR activation is associated with reduced social distress and anxiety, it has also been shown to increase the desire to seek and solicit social interactions. One study investigated this by measuring the socially rewarding activity of social play: when given morphine (0.05–0.1 μg), adolescent rats demonstrate an increase in social play, however this behaviour is diminished when given naloxone (0.5 μg) (Trezza, Damsteegt, Achterberg, & Vanderschuren, 2011). This suggests MOR is involved in the reward associated with social play. As reward processing encompasses both hedonic (during social play) and motivational qualities (seeking social play), another study extended this by assessing whether MOR activity is also involved in the *motivation* to engage in social play (Achterberg, van Swieten, Houwing, Trezza, & Vanderschuren, 2018). This study reported that juvenile rats treated with morphine expressed more social play and stronger conditioned place preference for social play-associated areas, whilst those treated with naloxone expressed a reduced preference for social play-associated areas and were less motivated to respond for social play during a progressive-ratio reinforcement

schedule (Achterberg et al., 2018). This suggests the endogenous opioid system is involved in both the hedonic qualities and motivation to engage in social play. The dichotomous effect of morphine and naloxone on social play has also been replicated in other species, including primates (Guard, Newman, & Roberts, 2002). Thus, preclinical evidence indicates MOR activity is important for both reducing social distress, and enhancing the pleasurable and motivational aspects of social rewards.

The paradoxical effect that MOR activity can both decrease the need for social interactions (via reduced social distress) but also increase the desire to engage in them (via increased social rewards) has been suggested as due to differences in motivational state, named the State-dependent μ-Opioid Modulation of SOcial Motivation (SOMSOM) model (Loseth, Ellingsen, & Leknes, 2014). The model postulates that animals may seek comfort to alleviate negative emotion via MOR release through social contact (a negative motivational state), or they may seek social interactions where MOR release promotes the value of social rewards (a positive motivational state). Therefore, stimulating MOR via exogenous opioids when the animal is experiencing a negative motivational state can decrease social distress and reduce the need for social approach behaviours. However, when the animal is experiencing a positive motivational state MOR stimulation can increase social exploration and approach. Both scenarios are socially rewarding, yet social inhibition or approach caused by increased MOR activity is dependent on the animal's initial motivational state. Considering the prior research discussed, Loseth et al. (2014) suggest that greater distress vocalisations in infant animals and increased rates of social grooming in primates occurs following social isolation, which is a negative motivational state where the animals consequently seeks social comfort. On the other hand, increased social play in rodents is said to reflect a positive motivational state irrelevant of whether they have experienced social separation. This is because social separation is no longer distressing by the time rats are juveniles.

Genetic evidence further supports the notion that MOR moderates social cognition. Disrupting MOR activity using genetic knock-out studies in mice have shown that animals lacking MOR exhibit impairments in the ability to form and maintain bonds (Cinque et al., 2012). These impairments were identical to those

observed in healthy animals given the MOR antagonist, naltrexone. Furthermore, polymorphisms in the MOR gene are associated with differences in maternal care, in addition to mediating the activity of oxytocin (OT; a peptide involved in social bonding) during caregiving behaviours (Higham et al., 2011). Like opioids, OT has been connected with a vast variety of social behaviours. In animals, it has been shown to attenuate social separation distress, and modulate affiliative behaviours (see Nelson & Panksepp, 1998 for a review). Due to these overlapping factors, it is thought that endogenous opioids and OT are intrinsically linked by an overarching system which is responsible for driving social and affiliative behaviours (Nelson & Panksepp, 1998). There is little existing research, however, that investigates the impact of exogenous opioid drugs on OT activity and subsequent social behaviour.

The literature thus far indicates the opioid system as centrally important for the development and maintenance of affiliative and rewarding social behaviours. The above are only a few studies within a vast expanse of literature that supports this notion (see Machin & Dunbar, 2011, for a review). This evidence for the moderating effect of the opioid system on social processes is evident across many species of animals, and is now more recently has been demonstrated in humans.

1.4.2 Healthy volunteer research

Human studies have confirmed the importance of MOR in social bonding and reward (Inagaki, 2018). Since MOR activation has been shown to be related to social distress in animals, one study using positron emission tomography (PET) investigated whether MOR activation was related to social rejection and acceptance in humans using the PET radiotracer [^{11}C] carfentanil (a potent and highly selective MOR agonist) (Hsu et al., 2013). This study used a computerised task to emulate either social acceptance, rejection, or neutral, where individuals were told their personal computer profiles were either liked (acceptance) or disliked (rejection) by an individual whom the participant rated most highly on wanting to form a relationship with (the computer came up with ‘n/a’ on neutral conditions). As predicted, it was found that social rejection was related to higher MOR activation in the ventral striatum, amygdala, midline thalamus, and PAG, which are brain areas involved in affective processing of physical pain and distress. This suggested the protective involvement of MOR

in reducing the experience of social distress following rejection (Hsu et al., 2013). Conversely, during social acceptance, MOR was reduced in the midline thalamus and subgenial anterior cingulate cortex, and MOR increased in the amygdala and anterior insula. There was also a positive correlation between desire to socially interact and MOR activity during acceptance in the ventral striatum, which was even greater for those in relationships. The authors conclude that MOR activity in different brain regions during rejection and acceptance aligns with the preclinical studies showing that MOR has dual importance for both alleviating social distress and increasing social rewards.

Other studies using PET have reported the effects of MOR on social bonding activities such as laughter, and social touch. MOR activity has been shown to increase following laughter, and pre-existing MOR availability can predict the rate of social laughter, which refers to the involuntary and stimulus-driven laughter important for maintaining social bonds (Manninen et al., 2017). Another study investigating social touch reported increased subjective pleasure alongside increased MOR availability following caressing from a romantic partner (Nummenmaa et al., 2016). Although increased pleasure was expected due to the importance of social touch for affiliation and bonding, increased MOR availability was contrary to expectations. The authors suggest that, although primate research has reported increased solicitations to groom following MOR blockade (Keverne et al., 1989; Martel et al., 1995; Schino & Troisi, 1992), MOR activity is actually reduced when social touching occurs in humans. Other possible differences are that the primates are socially isolated before being socially reunited, putting them in a negative motivational state where grooming is increased to attenuate distress; yet humans in this study are not in a negative motivational state before social touching, and therefore are not seeking social comfort where increased MOR activity occurs (in line with the SOMSOM model). In addition, the individual in the scanner is a passive receiver of social touch, rather than actively initiating social touch, which is motivationally different. It would be interesting to replicate the primate studies more closely in humans by inducing a negative motivational state prior to social touch, for example by using social isolation or rejection. In addition, assessing MOR availability in the individual who actively initiates the touching may reveal differences in MOR activation.

Another study investigated opioid manipulation via morphine and naltrexone on touch pleasantness using brushing on the forearm (Løseth, Eikemo, & Leknes, 2019). The authors did not find an effect of morphine or naltrexone on ratings of touch pleasantness or wanting for more, contrary to expectations that morphine would increase pleasantness and naltrexone would decrease it. One potential reason highlighted by the authors is the role of context during social touch, where MOR responses may be sensitive to the relationship between individuals engaging in touch. In addition, they also highlight that participants were not socially isolated before touch as they are in the primate grooming studies, and MOR activation could increase as a consequence of being socially reunited with others. The relationship between MOR activity and social touch in humans may therefore depend on initial motivational state, the relationship between the individuals, and whether the person is giving or receiving social touch.

Other studies have investigated the role of MOR in socially rewarding functions by using pain tolerance as a proxy for MOR activity, where increased pain tolerance indicates increased activation of the endogenous opioid system. These studies have looked at human-specific bonding activities, and reported increased pain tolerance as a consequence of social laughter (Dunbar et al., 2011) dance (Tarr, Launay, Cohen, & Dunbar, 2015) and performing music (Dunbar, Kaskatis, MacDonald, & Barra, 2012). Increased pain threshold was not necessarily due to increased positive affect, as control conditions aimed to raise positive affect without social laughter enhanced mood yet did not alter pain tolerance (Dunbar et al., 2011), indicating the specific importance of socially-rewarding activities on the MOR system. The suggested purpose of these social activities in humans is to expand the ability to bond with more than one individual at the same time, as grooming only facilitates the bond between a pair and would be very time-costly to maintain many relationships. Human social networks are vast, and these socially rewarding group activities have allowed us to expand social ties using the same neurobiological pathway as grooming. Another study also reported that pain tolerance was positively correlated with social network size (Johnson & Dunbar, 2016), suggesting that MOR sensitivity may be involved in the ability to maintain social bonds and cohesion. However due to problems in inferring causality, it is equally possible

that more social ties could increase sensitivity of the MOR system. Although pain tolerance and threshold have been suggested as a cost-effective and easy method to probe the endogenous opioid system, this is still an indirect measure of endogenous opioid activity. Research using PET has confirmed that MOR receptor binding potential at resting state is positively related to pain threshold (but not tolerance) (Hagelberg et al., 2012), and activation of MOR is associated with reductions in sustained pain responses (Zubieta et al., 2001). However, pain responses are complex and affected by many external factors, therefore this method may not be the most sensitive measure of endogenous opioid activity; the link between social affiliative behaviours (such as social laughter, dance, and social network size) should be confirmed with a more powerful probe of the endogenous opioid system, such as using PET imaging. Nonetheless, these studies suggest the importance of endogenous opioid functioning in social bonding and reward in humans.

Blocking MOR activity with the antagonist naltrexone has shown to impair many aspects of interpersonal bonding; such as causing feelings of social disconnection (Inagaki, Ray, Irwin, Way, & Eisenberger, 2016), and reducing feelings social warmth, affection, and trust (Schweiger, Stemmler, Burgdorf, & Wacker, 2014). Conversely, by enhancing MOR activity using the opioid agonist morphine, social rewards are heightened: attractiveness ratings (used as an index of social reward) of the opposite sex are increased following morphine administration (Chelnokova et al., 2014). Another study has also suggested the role of MOR activity in gratitude, defined as a moral emotional feeling similar to empathy that mediates social cohesion and encourages prosocial behaviour, which is positively related to greater social functioning, interpersonal closeness, and personal wellbeing (see Henning, Fox, Kaplan, Damasio, & Damasio, 2017, for a review). The authors acknowledge research investigating the neurobiological underpinnings of gratitude is novel and sparse, but they relate this reciprocal social behaviour in humans to grooming in primates, which is affected by MOR activity.

Studies also suggest there are genetic differences in MOR that could be related to differences in affiliative behaviour. Genetic polymorphisms in the OPRM1 A118G MOR gene have shown that individuals carrying the G genotype are more affected by social rejection (Way et al., 2009), and also

engage in more affectionate and rewarding social interactions (Troisi et al., 2011). However, although such genetic evidence is interesting, it is not without flaws: there has been a recent move towards genome wide association studies (GWAS) as more a more reliable and explanatory avenue to elucidate complex social behaviours (Chabris et al., 2013). A genome may contain anything between 40-50 thousand single nucleotide polymorphisms (SNP), and studies investigating SNPs have been criticised for inflating the likelihood of obtaining a false positives (Finno, Aleman, Higgins, Madigan, & Bannasch, 2014). Hence, it is more likely that social behaviours arise from multiple interactions over the entire genome, opposed to a single polymorphism. In addition, more recent research has failed to replicate the link between the OPRM1 gene and sensitivity to social rejection, reporting no differences in A118G variation and sensitivity to social rejection (Persson et al., 2019). This study used a considerably larger sample size than Way and colleagues (2009) (490 participants vs 112), and weakens the argument that genetic predispositions play a major role in rejection sensitivity.

The MOR partial agonist, buprenorphine, has been shown to reduce perceived social rejection following social exclusion, and enhance receptiveness to social stimuli. Hence, opioid substances that act on MOR can attenuate the detection of negative social experiences (Bershad, Seiden, & de Wit, 2016). In this study, healthy participants were administered either 0.2mg of the drug (a small dose relative of that prescribed in opioid replacement therapy) or placebo, and were assessed on various social paradigms including the Cyberball Game, a reliable measure known to robustly simulate the experience of social exclusion and ostracism, and an Emotional Images Task, where positively or negatively valenced images either containing social or non-social content are rated. Buprenorphine increased participant's estimation of social inclusion after being excluded, as well as increasing positive ratings for socially-salient images. This suggested that buprenorphine buffered social distress caused by exclusion, similar to that reported in the animal literature following social isolation (Bershad, Seiden, & de Wit, 2016).

In addition to the above finding, evidence has shown that buprenorphine reduces the experience of social anxiety, potentially by reducing the cortisol response (Bershad, Seiden, & de Wit, 2015). During a social stressor paradigm

(the Trier Social Stress Test; TSST) that involves public speaking, both groups who received 0.2 and 0.4mg of the drug had a dampened cortisol response to stress compared to placebo. This study supports the involvement of the opioid system in social processing, but also importantly showing how the opioid system can mediate the stress response in socially demanding situations.

Cumulative evidence in both animals and humans indicates that MOR is involved in regulating interpersonal bonds, social rewards, and attachment behaviours, whilst reducing the experience of social pain. It is possible that these fundamental social processes may be negatively affected when the opioid system has been changed through chronic administration of opioid drugs.

1.4.3 Drug users

The BOTSA model (see section 1.4.1) highlights the importance of the endogenous opioid system in social affiliation and attachment behaviours, which has led researchers to investigate these behaviours in opioid use disorder (Herman & Panksepp, 1978; Panksepp et al., 1978). The separation distress observed in infant animals has been suggested to parallel that of opioid withdrawal. Similarly, opioid drug use is proposed to alleviate feelings of social isolation and therefore be used to substitute for socialisation in drug users (Herman & Panksepp, 1978). Therefore, if opioid drugs hijack this social affiliation system, they may be an appealing option in such cases where these needs are not fulfilled.

Repeated use of opioids may have negative consequences on social functioning, such as social distress. One study investigated this using individuals on an opioid substitution medication (OSM) with histories of heroin addiction by exposing them to a period of social inclusion and social exclusion using a computerised ball game (the Cyberball) (Bach et al., 2019). Participants were asked to rate their subjective distress and complete a physical pain threshold after social inclusion and exclusion, as well as rate how intensely they felt excluded. Those on an OSM reported feeling more excluded following social inclusion than controls, however both individuals on OSM and controls felt equally excluded following social exclusion. This contrasts with the findings reported by Bershad et al. (2016) in healthy non-opioid individuals, where buprenorphine acutely reduced perceived exclusion. The authors conclude that

the equivalent rates of reported feelings of exclusion after social exclusion could be due to a downregulation of opioid receptor availability in the OSM user group, thereby reducing the power of opioids to alleviate social distress (Bach et al., 2019). Those on an OSM also felt more excluded following social inclusion, where it was suggested that increased incidence of real-life ostracism in addicts could cause a suspicion of positive social interactions (Bach et al., 2019). Feelings of exclusion following social inclusion were also positively related to childhood trauma history, suggesting that pre-existing factors prior to drug abuse could result in an increased sensitivity to social distress.

Another similar study looked at responses to social exclusion in non-medically prescribed opioid users (NMPOUs) (Kroll et al., 2019). The study also used the Cyberball to emulate social inclusion and exclusion, and took additional physiological measures of social stress i.e. cortisol and adrenocorticotropic hormone (ACTH). They reported elevated cortisol and ACTH following social exclusion in the NMPOU group compared to opioid-naïve controls. However, NMPOUs were less subjectively affected by exclusion, as mood did not change between inclusion and exclusion. NMPOUs also reported smaller social network size than controls, which could support the use of opioids as a substitute for social bonding (Kroll et al., 2019). Both Bach et al. (2019) and Kroll et al. (2019) assessed social distress caused by exclusion in chronic opioid users; however, Bach and colleagues assessed individuals on OSM with histories of illicit heroin use, whilst Kroll and colleagues assessed NMPOUs who were abstinent at the time of testing and did not have histories of heroin abuse. The relationship between social distress and opioids is therefore complicated, and affected by multiple factors that predate opioid use (such as social cohesion and childhood adversity), and those that occur as a consequence of opioid use (such as downregulation of MOR following prolonged opioid use, as well as increased social ostracism and stigmatisation).

Another important social factor that may be affected by opioids is empathy. Empathy, the ability to understand that others have thoughts and feelings separate from our own, is fundamental for eliciting and catalysing human social interactions (Masten, Morelli, & Eisenberger, 2011). Accordingly, empathy has also shown to be a vital buffer against antisocial behaviours that involve afflicting another being (Martinez, Stuewig, & Tangney, 2014). Antisocial

behaviours are ubiquitous in opioid addiction, with high levels of acquisitive crime often reported from friends and loved ones (Copello, Templeton, & Powell, 2009) which could suggest difficulties in social functioning. The small amount of existing literature looking at empathy among opioid addicts thus far suggests that opioid-using populations exhibit a reduced level of empathy/concern for others (Gonzalez-Liencres, Shamay-Tsoory, & Brune, 2013; Stange et al., 2017; Tomei, Besson, Reber, Rougemont-Bücking, & Grivel, 2017). The opioid system is suggested to be involved in social cognition, yet little research has systematically investigated the influence of chronic opioid drug use on this fundamental prosocial process (Gonzalez-Liencres et al., 2013). Empathy is thought to be divided into two subtypes: cognitive and emotional empathy (Singer, 2006). Cognitive empathy refers to the ability to understand, or 'mentalise', the psychological states of others, which is commonly referred to in the literature as 'theory of mind' (Lawrence, Shaw, Baker, Baron-Cohen, & David, 2004). Emotional empathy, however, refers to the ability to *feel* the emotional experience of others, including both basic emotions such as joy, and complex emotions such as embarrassment, which occurs without the individual being subjected to that emotion directly (Davis, 1983). These subtypes are believed to operate independently, which are reflected by separate neurobiological systems. Emotional empathy is thought to be evolutionarily rooted in emotional contagion, where an individual spontaneously mimics the emotions and behaviour of another, which occurs across many species via the activation of mirror neurons (see Gonzalez-Liencres et al., 2013, for a review). Brain imaging studies link this emotional contagion to activation in multiple brain areas reflecting the mirror neuron system, including the supplementary motor area (Gonzalez-Liencres et al., 2013), as well as areas involved in emotion processing, including the insula and thalamus (Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). Cognitive empathy is suggested to develop later as a consequence of increasing social complexity, and recruits frontocortical systems (Gonzalez-Liencres et al., 2013; Nummenmaa et al., 2008).They are also suggested to be neurochemically distinct: mentalising emotions such as in cognitive empathy is thought to be modulated by DA and serotonin, whilst emotional empathy is thought to be modulated by the oxytocin, vasopressin, and opioids (see Gonzalez-Liencres et al., 2013, for a review). Hence, due to the neurobiological actions of opioid

drugs, it is possible that their chronic use could exert specific effects on emotional empathy and the corresponding neurobiological pathways.

In opioid users explicitly, one recent study investigated this in NMPOUs using a cognitive task called the Multifaceted Empathy Test (MET) (Dziobek et al., 2008), used to differentiate between cognitive and emotional empathy (Kroll et al., 2018). When compared to opioid-naïve controls, NMPOUs showed impairments in identifying others' emotions (cognitive empathy), with specific difficulties with positive emotions. The authors also calculated 'global cognitive empathy' across multiple measures of cognitive empathy by averaging the z-transformed scores, which was significantly lower in the NMPOUs and it was negatively correlated with hair concentrations of opioids. This suggests impairments in the ability to recognise the emotional states of others in NMPOUs who were not treated with opioids at the time of testing, which may be dose dependent. This does not rule out the possibility of pre-existing differences prior to opioid use, however the correlation does suggest at least some additive effects potentially caused by opioids.

Two more studies assessed empathy in opioid users via a subjective questionnaire - the Interpersonal Reactivity Index (IRI; Davis, 1983) - in diacetylmorphine-maintained (Stange et al., 2017) and methadone-maintained individuals (Tomei et al., 2017). Both studies investigated emotional and cognitive empathy. Emotional empathy subscales used in the IRI were: empathic concern, a measure of 'other-orientated' concern to others distress (e.g. "I often have tender, concerned feelings for people less fortunate than me"), and personal distress, a measure of 'self-orientated' feelings to others distress (e.g. "In emergency situations, I feel apprehensive and ill-at-ease"). Cognitive empathy subscales were: Perspective taking, a measure of the ability to take the perspective of others (e.g. "When I'm upset at someone, I usually try to put myself in their shoes for a while"), and fantasy, a measure of taking the perspective of fictional characters (e.g. "When I am reading an interesting story or novel, I imagine how I would feel if the events in the story were happening to me"). Both studies reported heightened personal distress in opioid users compared with opioid-naïve controls, and no differences in cognitive empathy (Stange et al., 2017; Tomei et al., 2017). The latter study also reported impairments in empathic concern (Tomei et al., 2017). This finding is at odds

with the study by Kroll et al. (2018), who did not report any differences using the IRI and observed impaired cognitive empathy. Potential reasons for these differences could be due to differences in the opioid users with histories of illicit use of heroin versus NMPOUs who have never used heroin. Ex-heroin users have high levels of polysubstance use, and may be from poorer socio-economic backgrounds with higher rates of social deprivation and poverty. In addition, the studies that only used the IRI did not have well-matched control groups. Nonetheless, these studies show impaired empathic abilities in opioid users, where the types of impairment may differ by how individuals transitioned to opioid addiction, their socio-economic background, and polysubstance abuse.

Other studies using addicted populations have yielded similar results. One study assessed both emotional and cognitive empathy using both the Empathy Quotient and the IRI in individuals with alcohol use disorder (Maurage et al., 2011). They likewise reported specific deficits with emotional empathy, whilst cognitive empathy remained intact. The above studies, however, relied on self-report measures of empathy, which require a high level of introspective insight. Although many studies have used self-report measures, such conclusions would be made stronger by exhibiting corresponding findings using a cognitive task.

One cognitive task used to assess the two different types of empathy is the Multifaceted Empathy Test (MET) (Dziobek et al., 2008). Performance on the MET among chronic cocaine users demonstrated impairments in emotional empathy specifically (Preller et al., 2014). Moreover, performance on the MET was associated with social network size, and emotional empathy was related to amount of criminal offences. The causation of these relationships, however, is not clear: it is possible that deficits in emotional empathy could lead to difficulties in social bonding and increased crime. Alternatively, smaller social networks could mean less social interactions and less social scenarios requiring empathy, as well as crime preceding empathy deficits.

Other complex social processes may also be impaired by chronic opioid use, such as compassion. Compassion has typically been conceptualised as the ability to feel warmth and kindness to oneself and others in the face of suffering, and making effort to alleviate or prevent it without judgement or

criticism (Gilbert, 2005). Currently, there are two major approaches to defining and understanding compassion: an evolutionary and attachment-based approach (Gilbert, 2014) or drawing from Buddhist perspectives (Neff, 2016). More recently, researchers have tried to synthesise these differing approaches and propose a new comprehensive definition based on the shared elements, suggesting that compassion contains five components: to recognise suffering in oneself and others; understand universality; feel sympathetic or empathetic for others who are suffering; tolerate difficult or uncomfortable feelings; and be motivated to alleviate suffering (Strauss et al., 2016). In line with this definition, compassion and empathy are intrinsically linked, as empathy for another's pain can elicit feelings of compassion for that individual (Wei, Liao, Ku, & Shaffer, 2011). Yet compassion also encompasses the ability to feel warmth and kindness, and the ability to be mindful of one's own negative emotions (Neff, Kirkpatrick, & Rude, 2007) as well as a commitment to alleviate suffering. High compassion has been shown as a protective barrier for negative health outcomes and relapse among those living with addictions: it is associated with better mental health outcomes, improved well-being, and reduced self-criticism (Rodrigues, 2014). In those with severe alcohol use disorder, increased self-compassion was associated with reductions in alcohol use, depression, anxiety and stress and increases in self-kindness and mindfulness (Brooks, Kay-Lambkin, Bowman, & Childs, 2012). In injecting drug users, higher levels of self-compassion were found to be associated with a lower risk of drug-related health issues; such as less risky sexual behaviour among those living with HIV/AIDs (Dawson Rose et al., 2014; de Cordova, Phibbs, Schmitt, & Stone, 2014). High self-criticism and low self-esteem is extremely characteristic of those living with addictions, particularly among chronic opioid users (Blatt, Rounsaville, Eyre, & Wilber, 1984; Manganiello, 1978).

Heightened social distress, difficulties in empathising and relating with others, and low levels of self-compassion, could all be important characteristics that maintain the use of opioids in addiction. Understanding the nature of these difficulties may be key to developing more efficacious treatments aimed at nurturing these social factors. Current treatments are limited and questionable in their efficacy, highlighting the need for novel interventions. The current

section will give an overview of current treatments for opioid use disorder, alongside their advantages and drawbacks.

1.5 Treating social impairments in opioid addiction

Current treatments for addiction have been heavily criticised for being only modest in their effects, and overly-relying on understanding addiction as a 'brain disease' whilst ignoring the wider psychosocial factors (Hall, Carter, & Forlini, 2015; Heilig et al., 2016). For illicit opioid addiction, the current guidelines suggest that both pharmacological and psychological therapies are advised concomitantly; however, a pharmacological treatment will often precede psychological help in order to stabilise individuals to maximise their engagement in psychotherapy (NICE, 2015). The following section will briefly cover the most widely used existing psychological and pharmacological treatments aimed at treating opioid use disorder.

1.5.1 Pharmacological interventions

At present, the NICE guidelines state pharmacological therapies are the first line of treatment for those with an illicit opioid addiction (National Institute for Health and Care Excellence, 2017). These treatments include opioid substitution medications (OSM) which exert long-acting effects, and include methadone (an opioid agonist), and buprenorphine (a partial agonist). Methadone was developed in 1963 as the first long-term treatment for people with an opioid addiction, and is still the most common treatment to date (see Kreek, 2000 for a review). Buprenorphine was developed later, in 1966, which was created in attempt to formulate a pharmacologically similar acting opioid to morphine but with less unwanted side-effects (see Campbell & Lovell, 2012 for a review). Buprenorphine was successful in producing similar effects to methadone, yet was also able to block the effects of using any additional opioid agonists (for example, heroin), hence enabling buprenorphine to have less abuse liability. Overall, OSMs have been suggested to be the most effective form of reducing the risk of death among individuals who use opioids (Advisory Council on the Misuse of Drugs, 2016). Their longer-acting effects allow the individual to live a stable life: permitting them to hold down a job, reduce their involvement in crime, and decrease their chances of premature death and disease. Another less commonly given treatment proposed in the NICE guidelines is naltrexone (an opioid antagonist), which blocks any euphoric

effects of opioid agonists if they are used (National Institute for Health and Care Excellence, 2007). This treatment is only prescribed following opioid detoxification for highly motivated individuals who are not currently using any opioid agonist drug and wishing to remain abstinent. More recently, supervised injectable heroin has been suggested as a potential treatment, with high effectiveness in chronic opioid users who have not responded to other treatments; however, this treatment is not yet widely implemented (see European Monitoring Centre for Drugs and Drug Addiction, 2012, for a review). Despite the benefits of these pharmacological treatments, they are also associated with a number of drawbacks.

Although OSMs can reduce the risk of premature death, paradoxically they have been heavily criticised for causing high rates of overdose when additional illicit drugs are used on top. One study reported methadone was present in 71% of overdose deaths, and 63.1% of these were on prescribed OSM (Tjagvad et al., 2016). One reason for this is because when using illicit opioids, individuals on OSM may not account for the methadone currently acting in their system, causing increased sedative effects. Furthermore, OSM are still related to high rates of relapse, and consequently many people remain on their substitution prescription indefinitely (see Bell, 2012 for a review), thus limiting full recovery and prognosis. There is also increasing concern for the diversion of OSM, such as illegally selling or sharing medical prescriptions, which still happens despite the presence of many clinical safeguards (European Monitoring Centre for Drugs and Drug Addiction, 2016). Methadone is the primary target for this form of diversion and misuse (Davis & Johnson, 2008). Due to these reasons, OSM has been criticised for not necessarily treating the addiction, but prolonging and replacing it, with potentially added dangers. As for naltrexone, this treatment has shown little efficacy and adherence in treating opioid use disorder (Johansson, Berglund, & Lindgren, 2006). Furthermore, this treatment can cause severe opioid-like precipitated withdrawal, with one study reporting 96% of patients expressing severe agitation, accompanied by other undesirable symptoms such as decreased levels of consciousness, nausea and vomiting (Hassanian-Moghaddam, Afzali, & Pooya, 2014). Thus, the current pharmacological treatments are questionable in their success for treating opioid use disorder.

1.5.2 Psychological interventions

OSM's are the first line of treatment for individuals with an opioid use disorder; however these individuals may also be offered psychological interventions. In substance abuse treatment, common therapies offered may be cognitive behavioural therapy (CBT), addiction counselling, and family therapy. The following section will briefly describe each of these treatments alongside the evidence for their effectiveness in treating opioid use disorder.

The role of CBT is to actively identify cognitive distortions and damaging behavioural patterns, and to challenge and replace them with more adaptive techniques for coping (Fenn & Byrne, 2013). CBT has been shown as an effective treatment for substance use disorders due to targeting the operant processes behind drugs, as well as cognitive and motivational obstacles that may maintain use (McHugh, Hearon, & Otto, 2010). In opioid users on OSM, CBT has been shown to improve psychological wellbeing and reduce illicit opioid use (Abrahms, 1979). A more recent study also found CBT to increase abstinence in opioid users on OSM with co-occurring chronic pain (Barry et al., 2019). However, another study with OSM patients failed to find any additive benefits of CBT on abstinence and treatment adherence when given alongside usual treatment (counselling and OSM) (Fiellin et al., 2013). There is thus evidence to suggest benefits of CBT used alongside an OSM, however other forms of psychological therapies – such as counselling – are also beneficial.

Counselling is often provided alongside an OSM, and can come in multiple forms. Motivational interviewing (MI) is commonly used for substance use disorders, where the counsellor tries to mobilise behaviour change through reducing ambivalence (Rollnick & Miller, 1995). It requires the patient to envisage and articulate their own goals and arguments for change, where the counsellor encourages them without imposing their own ideas or suggestions (Britt, Hudson, & Blampied, 2004). This low-cost and effective technique is widely implemented in substance abuse treatment, however multiple studies have shown it is most efficacious when used either alongside other treatments or as a pre-treatment before inpatient drug programmes (Madson, Schumacher, Baer, & Martino, 2016). Not only is MI effective at reducing drug use when used alongside other treatments, but it can also increase treatment retention (such as detoxification) (Rasekh et al., 2018), suggesting it as a useful adjunctive

technique that may facilitate treatment success. In opioid users specifically, MI has been shown to reduce opioid craving and increase treatment retention (Navidian, Kermansaravi, Tabas, & Saeedinezhad, 2016), as well as reduce heroin use up to 6 months following therapy (Bernstein et al., 2005). Improved psychological well-being in opioid users has also been reported when MI is used alongside CBT (Smyth, Ducray, & Cullen, 2018). The evidence highlights MI as a useful technique in the treatment of opioid use disorder when used in conjunction with OSM and other psychological therapies.

Family therapy involves discussion and development of appropriate boundaries with families or couples over multiple sessions (Yandoli, Eisler, Robbins, Mulleady, & Dare, 2002). Family members or partners are also asked to attend sessions, and the therapy encourages creating shared goals and ways to deal with problems encountered by both the patient and family (alongside discussion of the patients OSM treatment). Family therapy has been shown to increase abstinence from opioids at 6 and 12 month follow up, indicating its therapeutic potential, however it is suggested to be used as part of a larger treatment regime alongside OSM (Yandoli et al., 2002).

Psychological therapies are clearly important in the treatment of opioid use disorder. The use of psychological therapies not only improves psychological wellbeing, but also increases treatment retention. Treating opioid use disorder with an OSM in conjunction with psychological therapies such CBT, MI and family therapy significantly reduces treatment drop out, as well as reduces illicit opioid use during OSM treatment (Amato, Minozzi, Davoli, & Vecchi, 2011). Despite this, relapse rates in opioid use disorder are still considerably high and treatment adherence is modest, highlighting the importance for more efficacious treatments with longer-term improvements in well-being and reductions in relapse.

1.6 Summary

The role of social factors in the onset and maintenance of illicit opioid addiction have been overlooked in prevention and treatment interventions. Both animal and human research has clearly identified the endogenous opioid system in regulating a wide range of fundamental social processes. Pre-existing evidence suggests that addicted populations exhibit abnormalities in the social

domain, such as reduced empathy and compassion, which may have negative consequences on psychological wellbeing and interpersonal bonding. Disruptions in these social processes have not been well investigated among chronic opioid users. Given the importance of the endogenous opioid system in social cognition, and the long-term effects that use of opioid drugs may have on social functioning, research in this area seems crucial.

Understanding the mechanisms behind disruptions in social functioning among chronic opioid users would also be beneficial from a treatment perspective (Heilig et al., 2016). A number of mechanisms for these changes are plausible. Exogenous stimulation of the endogenous opioid system via opioid agonists may cause a hyposensitivity of receptors (due to cellular downregulation), resulting in a reduced ability to stimulate the opioid system. This may have negative repercussions for social functions, where individuals are not able to able to soothe socially distressing situations and do not experience socially positive situations as rewarding and enjoyable. Conversely, it is possible that problems in the social environment prior to opioid use, including childhood trauma, deprivation, isolation, or stigma, do not nurture a sensitive and responsive endogenous opioid system from a young age. In these circumstances, it is possible that opioid agonists are used to both compensate and regulate a pre-existing hyposensitive endogenous opioid system by producing positive and soothing feelings that are not otherwise experienced, consistent with a 'self-medication' approach. To visually illustrate how these mechanisms are connected, a model has been conceptualised and will be used as the basis for the research questions in this thesis (figure 1.3). Both this 'downregulation' and 'self-medication' suggestion are equally plausible, and may both interact in chronic opioid addiction; however, neither has been systematically investigated.

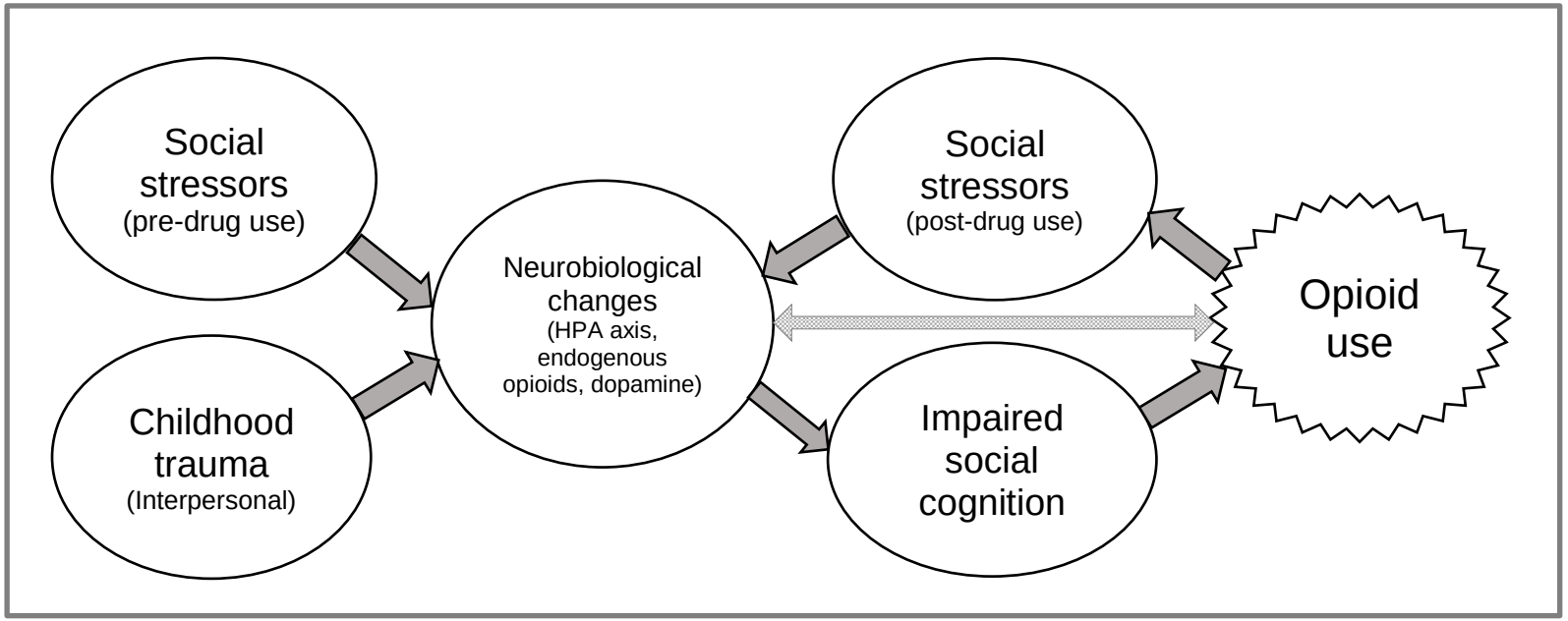


Figure 1.3. A social risk factor model proposed to illustrate how childhood trauma and social stressors may precede and maintain an opioid addiction. Both experiences of interpersonal childhood trauma (such as abuse and neglect) and social stressors (such as marginalisation, deprivation, and stigma) may independently cause alterations to the HPA axis, as well as the endogenous opioid and dopaminergic systems due to chronic exposure to stress. These may lead to impaired social functioning, causing difficulties in social integration and a hypersensitivity to negative social events, in turn leading to drug/opioid use as an exogenous form of emotion regulation and coping. Social stressors such as stigma and deprivation are also experienced as a consequence of drug use, which may perpetuate the neurobiological alterations due to stress exposure, therefore exacerbating problems in social functioning. There is also a direct bidirectional link between opioid use and neurobiological changes due to the chronic effects of these drugs on downregulating the endogenous opioid system, which in itself is a risk factor for opioid use via withdrawal symptoms.

Elucidating the exact mechanisms behind abnormalities in social cognition among opioid users would be useful in developing novel treatments, as well as for producing preventative measures for at-risk groups prior to addiction. It is possible that individuals early in their addiction may require treatment surrounding pre-existing problems in the social environment, whilst those further in their addiction may also be experiencing adverse effects via the biological consequences of chronic opioid use on neurons.

Finally, current treatments for treating opioid addiction have been criticised for showing little efficacy or understanding of how fundamental social processes impact addiction, which only are more recently being emphasised (see Heilig et al., 2016, for a review). It is thus important to investigate the value of novel treatments that focus on enhancing social cognition for opioid users.

1.7 Research questions and Hypotheses

As a result of the literature summarised in Chapter 1, and the formulation of the social risk model depicted in figure 1.3, the current thesis aims to answer the following questions via a series of empirical studies:

1. Do histories of childhood trauma affect the development of the endogenous opioid system, and does this have consequences on (a) social functioning, (b) pain processing, and (c) reward sensitivity to opioid drugs? (study 1)
2. Do chronic opioid users exhibit deficits in social cognition, and are these deficits due to problems (a) preceding illicit opioid use, (b) due to chronic opioid use, or (c) an interaction of both, whereby there are issues preceding drug use which are then perpetuated by it? (study 2)
3. What novel pharmacological and psychological approaches may be suitable for addressing problems of social functioning in opioid use disorder? (study 3 & 4)

Chapter 2: Greater subjective pleasure following an acute dose of morphine in those with histories of childhood trauma

2.1 Introduction

Childhood adversity is a key vulnerability factor for a myriad of mental health problems later in life. Evidence has shown interpersonal traumas in childhood are related to the onset of not only post-traumatic stress disorder (McLaughlin et al., 2017) but also bipolar disorder (Palmier-Claus, Berry, Bucci, Mansell, & Varese, 2016), schizophrenia (Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013), personality disorders (Cirasola, Hillman, Fonagy, & Chiesa, 2017; Velikonja et al., 2019), depression, and anxiety (Tracy, Salo, Slopen, Udo, & Appleton, 2019; Van Assche, Van de Ven, Vandenbulcke, & Luyten, 2019). There is also strong evidence that links childhood adversity with later development of addiction (Dube et al., 2003; Kristjansson et al., 2016), where rates of childhood abuse and neglect are disproportionately higher in opioid use disorder compared with non-addicted individuals (Naqavi et al., 2011). Greater severity of childhood adversity has been linked to earlier onset of opioid use (Taplin et al., 2014), increased rates of poly-drug use (Vogel et al., 2011) and poorer treatment retention (Kumar, Stowe, Han, & Mancino, 2016). Childhood adversity could cause this vulnerability via impaired development of appropriate emotion regulation abilities early in life (Garland, Reese, Bedford, & Baker, 2019), which has been shown to mediate the link between childhood trauma and later substance use disorders (Mandavia, Robinson, Bradley, Ressler, & Powers, 2016; Wolff et al., 2016). This may be due to individuals using substances to soothe symptoms of hyperarousal (Reed, Anthony, & Breslau, 2007) and to cope with internalised problems (Blake, Tung, Langley, & Waterman, 2018).

Experiences of childhood trauma may also affect the reinforcing and rewarding properties of opioid drugs. The primary target of opioid drugs is the endogenous opioid system, which is commonly known for its involvement in pain processing and pleasure (Basbaum & Fields, 1984). However, this neurobiological system is also involved in social and emotional functioning, where the release of opioid peptides when bonding with another individual can produce warm and soothing feelings which is important for initiating and maintaining relationships (Machin & Dunbar, 2011). Opioid drugs can acutely alleviate symptoms of physical pain as well as induce feelings of euphoria, however these effects may be altered following childhood trauma, potentially due to neuroadaptations to the endogenous opioid system. Pre-clinical research has shown maternal separation (a model of early trauma in animals)

can heighten pain sensitivity in rats (Vilela, Vieira, Giusti-Paiva, & Silva, 2017) and attenuate the analgesic effects of morphine, as well as intensify opioid-induced withdrawal due to permanent changes to the endogenous opioid system (Kalinichev, Easterling, & Holtzman, 2001). Maternal separation has also been shown to enhance the rewarding properties of opioids, where separated rats show vast increases in morphine self-administration when exposed to the drug in adulthood, as well as increased place-preference for morphine-paired areas and slower extinction of place-conditioning (Vazquez, Giros, & Dauge, 2006; Vazquez et al., 2005). Although greater self-administration of other rewards (including sucrose and amphetamines) are also observed in maternally separated individuals, self-administration was considerably greater for morphine, suggesting a specific vulnerability to opioid addiction (Vazquez et al., 2006; Vazquez et al., 2005). Basal opioid activity was lower in individuals with maternal separation, and has been potentially suggested as one mechanism underlying the heightened rewarding effects of opioids (Vazquez et al., 2005); however, this remains to be confirmed. In human studies, childhood trauma is associated with a hypersensitivity to physical pain in adulthood (Creech, Smith, Grimes, & Meagher, 2011; Pieritz, Rief, & Euteneuer, 2015; Scarinci, McDonald-Haile, Bradley, & Richter, 1994; Tesarz, Eich, Treede, & Gerhardt, 2016; You & Meagher, 2016), however it is not known if pain processing differs following opioid administration in people with histories of childhood trauma. In addition, it is also not known if childhood trauma alters endogenous opioid functioning in humans, and whether this is linked to a hypersensitivity to the rewarding effects of opioid drugs.

Alterations in endogenous opioid functioning as a consequence of childhood trauma may also affect the rewarding and adverse effects of opioids. In-vivo microdialysis studies have linked receptor tone with drug reinforcement, where greater endogenous dopamine activity is associated with more adverse effects of cocaine – a dopamine agonist (Glick, Raucci, Wang, Keller Jr, & Carlson, 1994). In a seminal positron emission tomography (PET) study, Volkow and colleagues (1999) reported significantly greater drug-induced pleasure, happiness and positive mood in individuals with lower D2 receptor density, whereas higher receptor density was associated with unpleasant drug effects, such as annoyance and distrust. More recently, another study similarly using PET linked childhood adversity to greater

mesolimbic dopamine responses to amphetamine (a dopamine agonist) (Oswald et al., 2014), thus supporting the notion that childhood trauma may have permanent effects on neurochemistry. Greater activity in the medial pre-frontal cortex was found when responding to aversive images in people with a history of childhood adversity after receiving naltrexone (Savulich et al., 2017), although this study was confined to those with histories of drug and/or alcohol abuse. The authors suggest this may reflect greater effort to exert emotion regulation. In addition, naltrexone reduced connectivity between the anterior cingulate cortex and the hippocampus, which may be related to therapeutic effects of naltrexone. This is because high connectivity between these areas in drug addicts has been linked to greater incidence of drug relapse and poor emotion processing (Adinoff et al., 2015; Dean, Kohno, Hellemann, & London, 2014). However, the absence of differences in behavioural responses to aversive images between groups or as a consequence of naltrexone can make this difficult to interpret. Nonetheless, this highlights a potential mechanism behind the therapeutic effects of naltrexone to remediate emotion regulation difficulties linked to changes in the opioid system caused by childhood adversity. To our knowledge, the link between childhood adversity and responses to opioid agonists has not been investigated in humans, despite the strong association between childhood trauma and opioid use disorder.

The current study aimed to assess the impact of childhood trauma on responses to morphine as well as pain processing. We set out to compare people with histories of severe childhood trauma to those without, and investigate the impact of a dose of morphine on the reinforcing, pleasurable, and adverse effects of the drug, along with analgesia and social processes. Social processes such as empathy and social distress were examined due to the overlap of the endogenous opioid system with affiliative bonding (Machin & Dunbar, 2011), where opioids have been shown to reduce social distress (Bershad et al., 2016), as well as reduce empathy for others' pain by attenuating the ability to feel pain in oneself (Rutgen et al., 2015). Based on the prior literature, we firstly hypothesised that individuals with childhood trauma would have a lower physical pain threshold and tolerance at baseline than individuals without trauma, as well as experiencing less analgesic effects of morphine, indicating lower opioid receptor density. We secondly hypothesised that those with childhood trauma history will report more pleasant drug effects, in line with

preclinical findings and potentially due to reduced endogenous opioid density, whilst the control group will report more unpleasant drug effects. We finally hypothesised that the trauma group will show poorer social functioning via heightened social distress to social exclusion, and poorer empathy for other's emotions (due to impaired emotion regulation), as well as greater empathy for other's pain (due to a heightened sensitivity to physical pain – in line with hypothesis 1) which would be reduced by morphine.

2.2 Methods

2.2.1 Participants and design

Two-hundred and eighty individuals were screened for the study, 152 were eligible, and of these 52 participants aged 18-65 with a mean age of 30.91 ± 14.89 years were randomised into the study (35 females; 17 males). Barriers from eligibility to randomisation included: inability to attend sessions on weekdays; the time commitment; and being required to drive vehicles following the study. Randomisation was calculated via a random number generator and was performed by the research supervisor who oversaw the study and was not in direct contact with participants. Participants were selected based on their score on the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998), and then allocated into either Trauma (n=27) or Control group (n=25). To fit the criteria for the Trauma group, individuals were required to score in the severe range for any CTQ subscale (score either ≥16 for emotional abuse, ≥13 for physical abuse, sexual abuse, or physical neglect, or ≥18 for emotional neglect). For the Control group, individuals should show no evidence of childhood trauma (score ≤5 for sexual abuse, ≤7 for physical abuse and neglect, ≤8 for emotional abuse, and ≤9 for emotional neglect on all subscales). Individuals were ineligible for the study if they scored between these ranges of the CTQ. The groups were matched for age and gender. Recruitment was completed using convenience and snowball sampling via participant databases, poster advertisements, and word of mouth.

The study was a double-blind, placebo-controlled cross-over design. Participants underwent two study sessions approximately 7 days apart (±1 day) where they either received a physiologically active dose of morphine (0.15mg/kg) or a very-low dose control condition (morphine 0.01mg/kg). Drug administration order

was randomised and counterbalanced between groups. Although both the participants and researchers conducting the study were blinded, the anaesthetists were not blinded to the drug randomisation. The control condition contained a very low dose of morphine; participants were told they would receive two morphine doses, and therefore better conceal the treatment allocation and reduce effects of expectations.

Other inclusion criteria were: aged 18-65 years; body mass index more than 18.5 but less than 35. Exclusion criteria were: any relevant physical health problems or taking medications known to be contraindicated with morphine (as listed in the summary of product characteristics in Appendix 2.1); past or current history of alcohol or drug use disorder; recent drug or alcohol use (confirmed by a negative urine drug test and breathalyser BAC level of 0.00); any severe mental health problems; known allergy to morphine; pregnancy (confirmed by negative pregnancy test) or breastfeeding. Participants were asked to fast for two hours prior to the study session, and abstain from alcohol or any pain medications for 24 hours prior to the session. The study was reviewed by the NHS Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki, and all participants gave written, witnessed, informed consent.

2.2.2 Drug administration, blood sampling and monitoring

In each session, participants received one intramuscular injection of morphine (0.15mg/kg or 0.01mg/kg) in saline in a counterbalanced order via a 2ml syringe to the antero-lateral thigh muscle. In the high dose morphine session, participants received one 0.15mg/kg dose of morphine with a maximum dose of 10mg. 22 individuals exceeded 67kg and therefore were given the maximum dose (n=13 in the Trauma group, n=9 in the Control group). In the control session, participants were given saline containing a negligible amount of morphine (0.01mg/kg). Blood pressure, heart rate and pulse oximetry were monitored and recorded every 5 minutes for the first 30 minutes, then every 10 minutes up until the hour. After 60 minutes they were only measured when deemed necessary by the anaesthetist. Participants were also cannulated prior to drug administration in the non-dominant arm and blood samples were taken from a cannula prior to drug administration, and again at 30 and 60 minutes post-drug administration to assess morphine levels in plasma. Further details of plasma analysis are in Appendix 2.2.

2.2.3 Assessments

Physical pain

Pain threshold was used as a proxy to assess endogenous opioid activity, in line with previous suggestions (Johnson & Dunbar, 2016). The cold water pressor method was used to assess physical pain. Participants were first asked to submerge their hand in a warm water bath controlled at 35±1°C for two minutes to ensure hand temperature equilibrium. Following this, they were asked to submerge the same hand into a cold water tank controlled at 5°C with their fingers spread apart and not touching the sides of the tank. The water tank was fitted with a thermostatically controlled water cooler and a pump, the latter used to continuously circulate the water in the tank to minimise any local warming from the hand. Pain threshold was then measured, which was time in seconds from onset until participants indicated when the sensation changed from cold to painful by raising their opposite hand, and pain tolerance, which was how long in seconds they could withstand the cold water before withdrawing their hand.

Reward sensitivity

Progressive ratio task (PRT). To assess morphine reward, participants were told they were able to work towards either the drug dose they received earlier in the session or for money (£3.50) in a forced choice task. Participants were given seven opportunities where they were required to button press for either 1/7th of the dose, or 50p. Button presses for each choice were on an independent progressive ratio schedule, where the number of button presses would increase in the following order: 10, 20, 40, 80, 160, 320, 640. Maximum number of button presses for either reinforcer were 1270. During the instructional phase, participants were told they will be button-pressing to hypothetically work for either the morphine dose they received, or for £3.50, and they would have seven opportunities to do this. They were told that for each choice they made, the number of button presses required for that choice would increase. This task was adapted from Babalonis and colleagues (Babalonis, Lofwall, Nuzzo, Siegel, & Walsh, 2013). Percentage of morphine and money choices were calculated, as well as the maximum number of button presses completed for either drug or money.

Effort reward task (Husain & Roiser, 2018; Treadway, Bossaller, Shelton, & Zald, 2012). To assess reward sensitivity for other reinforcers, participants completed a computer task where they were required to button press for points to go into a £30 lottery. Participants were presented with a series of offers for points which varied in quantity (low, medium, high), which they could either accept or reject. Each offer also gave a difficulty level (easy, medium, hard) associated with the speed at which they were required to press the space bar in order to win the points. When instructed to complete the task, participants were told that they were working to earn points to go into a £30 lottery, where they could either accept or reject given offers to button press for varying amounts of points. They were told that for each offer there would a specified difficulty level – how fast they would be required to button press – and it was suggested that they make their decisions to accept or reject the offers based on whether they think it is worth working for. However, they were also reminded that the more points they earned, the greater likelihood they had of winning. Participants were told to use the little finger of their non-dominant hand to button press in order to increase the difficulty. Number of accepted offers at each level of quantity and difficulty was recorded.

Social functioning

Multifaceted Empathy Test (Dziobek et al., 2008). This is a computerised task that measures and discriminates between both cognitive and emotional empathy (figure 2.1). The task involved showing participants 40 photographs of people with emotionally charged expressions, which were given in eight blocks each consisting of 10 pictures. In four of these blocks, participants were required to identify the correct mental state of the subject in each scene by picking one from a choice of four emotion labels (cognitive empathy). In the other four blocks, participants were asked to rate how much they empathise with the individual in each scene on a 9-point Likert scale (1 = not at all; 9 = very much) (emotional empathy) before being presented with the next trial. For the cognitive empathy blocks, participants were instructed to pick the emotion that best describes the individual presented on the screen, and that although sometimes multiple different emotions may apply, they should choose the one they feel is the best fit. For emotional empathy, participants were instructed to rate how much seeing the emotion of the person on the screen made them feel that emotion as a consequence (e.g. how much seeing someone

feeling sad made them feel sad). Participants were also instructed to answer the questions as quickly and accurately as possible. The task lasted approximately 15 minutes.

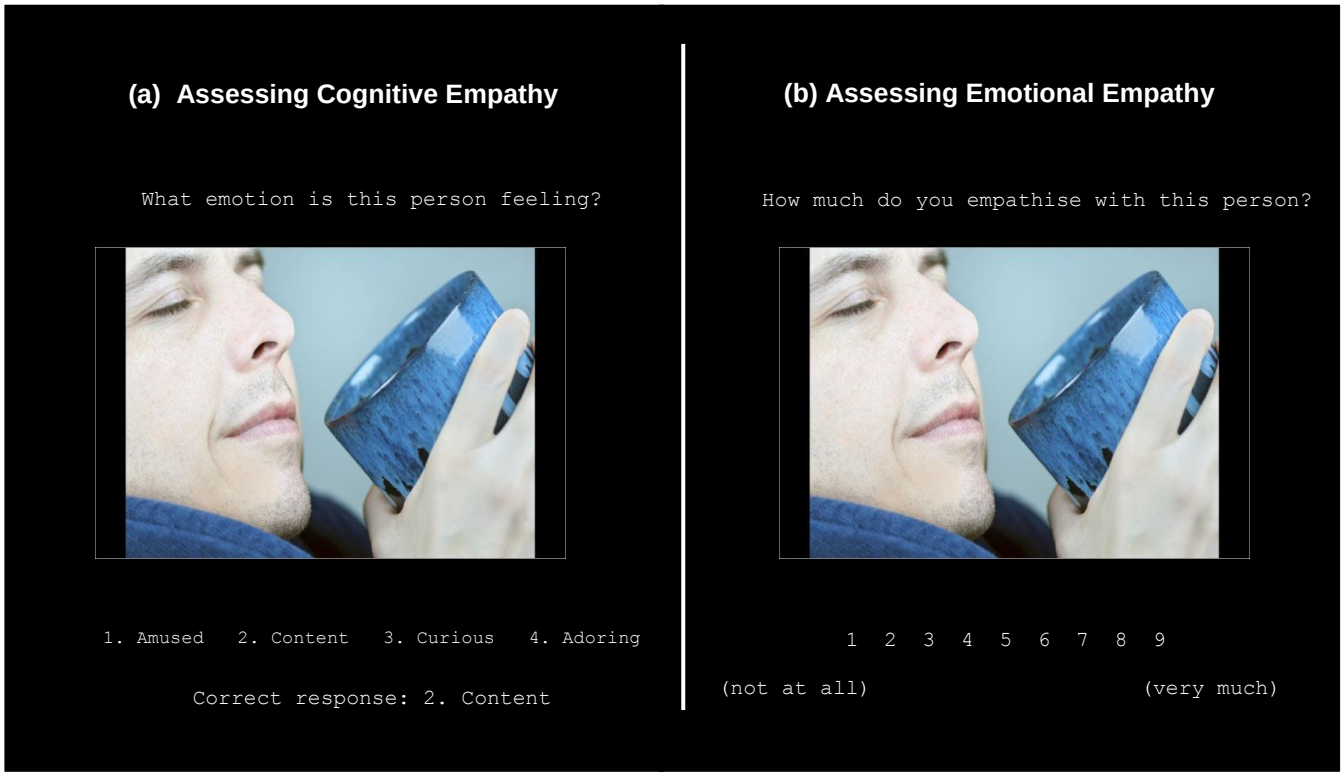


Figure 2.1. Differential blocks assessing cognitive and emotional empathy in the MET. (a) For cognitive empathy, participants were required to pick one of four emotion labels. (b) For emotional empathy, participants were asked to rate how much they empathised (which they were instructed means 'feel what they are feeling') with the subject in the photo using a 9-point Likert Scale (1=not at all; 9=very much). Image taken with permission from the task creator (Dziobek et al., 2008).

Empathy for pain task (Jackson, Meltzoff, & Decety, 2005). This computer task shows a series of painful and non-painful images of hands and feet. The images are displayed as a range of pain types (mechanical, thermal and pressure), with a matching non-painful image. 64 images were presented for 2 seconds following which participants were asked to rate 1) how much pain they think that person is in, and 2) how concerned they feel for that person. Both pictures and questions were presented in a randomised order, and participants responded using a 100-point sliding scale. Participants were instructed to answer as quickly as possible, and to try and imagine themselves in the given scenario and how painful they think it would be. Both sessions used a different set of images, which were counterbalanced between

participants. Responses for non-painful images were subtracted from painful images for both questions.

The Cyberball task (Williams & Jarvis, 2006). This is a computerised game that uses ball tosses between the participant and fictitious virtual players, and has been reliably shown to simulate the experience of social exclusion (Figure 2.2). Participants were told that they were playing with two other participants on a virtual network in a mental visualisation experiment, and were instructed to try and mentally visualise the experience by trying to imagine what kind of people they are playing with, what they look or sound like, and whether they would get on with them in real life. Unbeknown to them, the two other players were not real and were programmed to socially exclude them. There were two conditions ('inclusion status') that simulated either social inclusion or social exclusion. Conditions were counterbalanced between participants, and each condition included a block of two games that lasted approximately three minutes each. Participants received exactly one-third (10±1) of all ball throws from the other players during the inclusion condition, and only one-sixth (5±1) of all ball throws in the exclusion condition. The task took approximately 15 minutes to complete. Measures of mood and psychological needs via the Post-Cyberball Questionnaire (Williams et al., 2002) were assessed after each game, which includes 25 items to measure: positive and negative affect; self-esteem; sense of belonging; meaningful existence; control; hurt feelings; anger; and estimated percentage of ball throws (manipulation check).

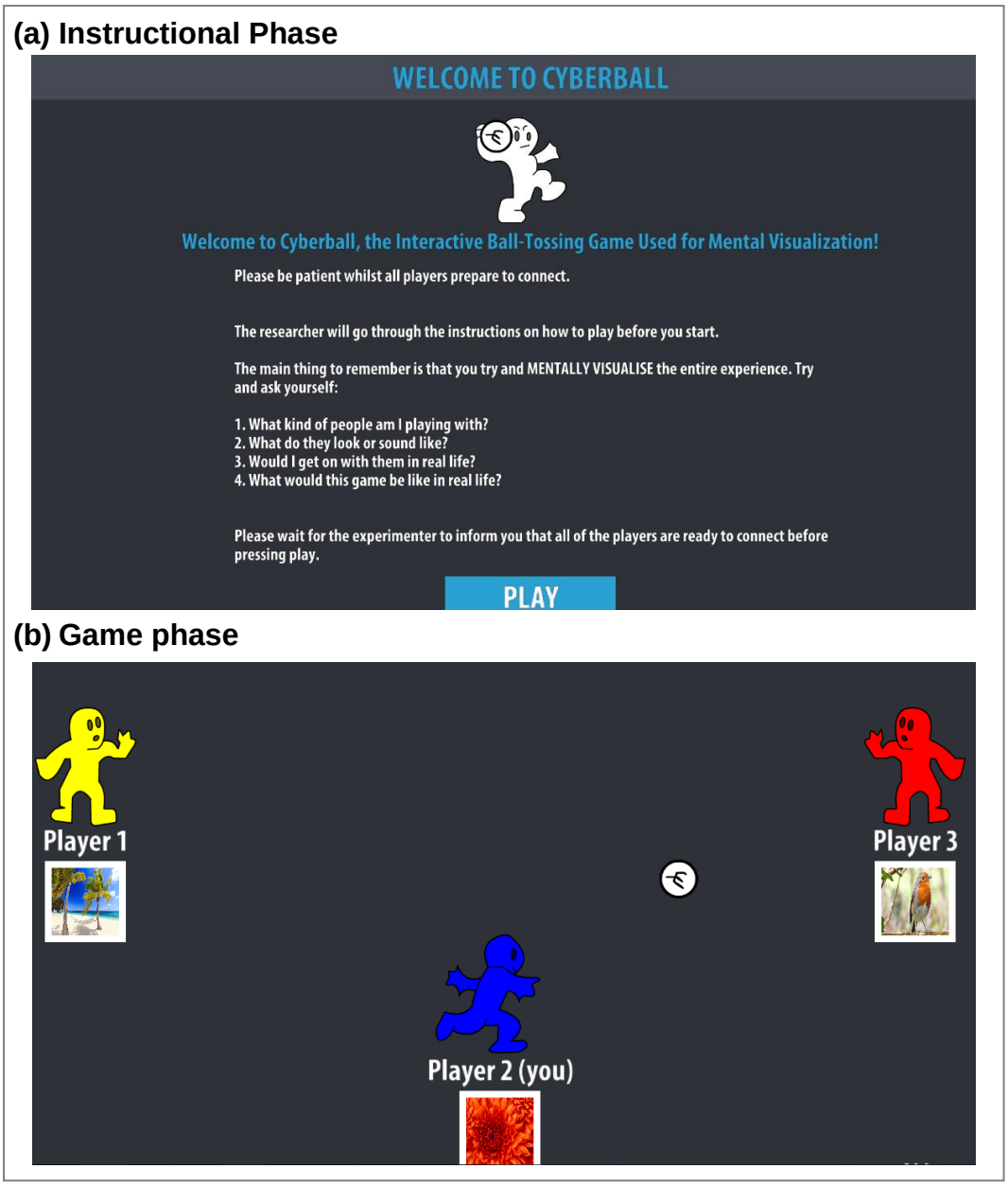


Figure 2.2. The Cyberball Game. (a) The instructional phase tells participants it is a mental visualisation task, and asks them to try and mentally visualise the entire experience, such as what kind of people they are playing with, what these people might look like, whether they would get on with them in real life, and what the game would be like in real life. (b) The game phase requires participants to throw the ball to the other players. During the exclusion game the participants receive one sixth of all ball throws, whilst during the inclusion game they receive one third of all ball throws. Prior to the game, participants choose a profile picture for their avatar.

Trauma

The Childhood Trauma Questionnaire (short form) (Bernstein et al., 2003) was 28 items which measured five types of childhood adversity – emotional, physical, and sexual abuse, and emotional and physical neglect, as well as

minimisation/denial – which was used to identify eligible participants prior to the study. All questions started with “when I was growing up…” and answers were given on a 5-point Likert scale (1 = never true, 5 = always true). These subscales of abuse and neglect were identified by the authors through the literature on childhood maltreatment (Bernstein & Fink, 1998), however this is more restricted than the general term childhood adversity, which also includes growing up in extreme poverty, disrupted family environments (parental severe mental health problems or substance addiction), or losing a parent. Therefore, we also measured childhood adversity using the Adverse Child Experience Questionnaire (ACE; Felitti et al., 1998), which includes 10 items requiring a yes or no response which assessed experiences of household dysfunction while growing up. This was included due to its predictive validity and to allow comparison with a large range of studies (Hughes, Hardcastle, & Bellis, 2016).

We also used the Potentially Traumatic Events scale (PTE; Forbes et al., 2012), which is a 14-item scale that asked about potentially traumatic events over a lifetime, which were either non-interpersonal events (e.g. motor vehicle accident), interpersonal but not intimate (e.g. mugged or kidnapped), or interpersonal and intimate (e.g. sexual assault). The questionnaire also asks which event caused the most severe reaction, as well as whether that event caused 1) feelings of fear, horror or helplessness, and 2) a dissociative experience. Participants were required to respond with ‘yes’ or ‘no’.

Subjective Drug Effects

Participants completed the Drug Effect Questionnaire (DEQ; Morean et al., 2013) at eight time points (pre-drug baseline, 15, 30, 45, 60, 90, 120, & 150 minutes post-drug). This uses a series of 100mm visual analogue scales (VAS) anchored from “Not at all” to “Extremely” and includes the following items: ‘feeling the effect of the drug’, ‘feeling high’, liking and disliking the drug effects, and wanting more of the drug. Opioid-specific items were also added to the questionnaire and included ratings of euphoria, nausea, dizziness, and sedation. When measured at pre-drug baseline, participants were aware they had not yet received the drug, however they were instructed to answer the questions to the best of their ability.

Other Questionnaires

The Pain Catastrophising Scale (PCS; Sullivan, Bishop, & Pivik, 1995). A 13-item scale that measured catastrophic thinking surrounding pain by asking participants to reflect on past painful experiences. There were three subscales: rumination, magnification and helplessness. Responses were on a 5-point Likert scale (0=not at all, 4=all of the time).

General Self-Efficacy Scale (GSES; Schwarzer & Jerusalem, 2010). A 10-item measure of optimistic self-beliefs for coping with life's demands, which is linked to the adaptation to stress and chronic illnesses. Responses were made on a 4-point Likert scale (1=not at all true, 4=exactly true).

The UCLA Loneliness Scale (UCLA LS; Peplau & Cutrona, 1980). A 20-item measure of feelings of social isolation and loneliness. Answers were made on a 4-point Likert scale (1=never, 4=always).

The Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, & Farley, 1988). A 12-item measure of reported support from family, friends and significant others. Answers were made on a 7-point Likert scale (1=very strongly disagree, 7=very strongly agree).

Depression, Anxiety, and Stress Scale (DASS; Lovibond & Lovibond, 1995). A 21-item measure of depression, anxiety and stress over the past two weeks. Answers were on a 4-point Likert scale (0=did not apply to me at all, 4=applied to me very much or most of the time).

Self-Compassion Scale - short form (SCS-SF; Raes, Pommier, Neff, & Van Gucht, 2011). A 12-item measure of self-compassion towards oneself. Answers are made using a 5-point Likert scale (1=almost never, 5=almost always).

2.2.4 Procedure

Prior to the study sessions individuals who expressed an interest in taking part were screened over the phone or via a secure online link. If they met initial eligibility criteria and were still interested, they were then allocated a unique study ID and provided written consent before completing the CTQ. If they then met criteria for taking part in the main study (in that they scored in the "none" or "severe" categories of childhood trauma on the CTQ), they were invited to the Clinical Research Facility

(CRF) at the Royal Devon & Exeter (RD&E) hospital for medical screening and then the two testing sessions, both of which lasted approximately 3.5-4.5 hours and were separated by 7 days. In the first session, participants underwent a screening with a medical professional to ensure they were fit to take part. Once screened, participants gave written, witnessed informed consent and then completed a demographics questionnaire and a substance use interview, followed by their first pain threshold assessment. They then completed the Cyberball Game. Following this, participants completed a baseline DEQ, were cannulated and gave their first blood sample before being administered the drug dose. Following their dose, participants completed eight further DEQ over 2.5 hours. Participants completed two computer tasks measuring empathy 30 minutes post-administration. At 60 minutes post-administration they completed their second pain threshold assessment, following which they performed two computer tasks assessing reward sensitivity. Participants also completed a series of questionnaires towards the end of their first session. Session two followed the same procedure as session one but excluded the medical screening, demographics, substance use interview and the Cyberball Game. An overview of the procedures over both sessions alongside approximate timings is visually illustrated in figure 2.3.

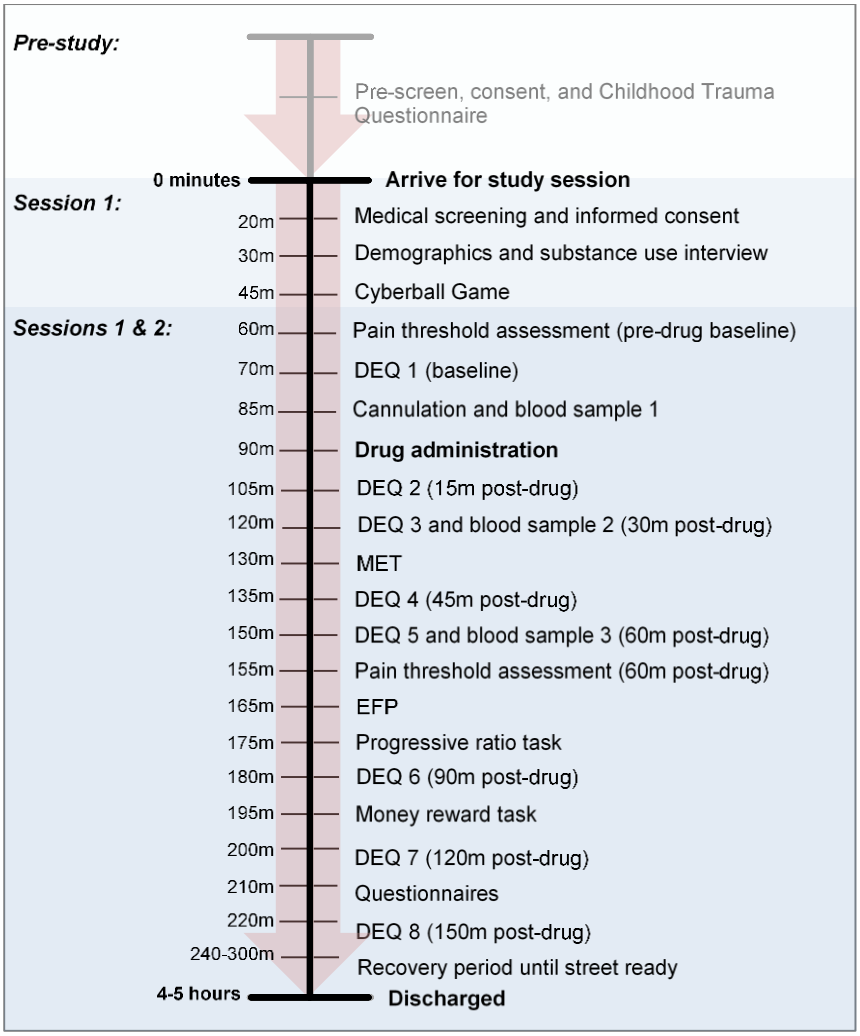


Figure 2.3. Study procedure alongside approximate timings (in cumulative order). Procedure for session two identical to session one from DEQ 1 onwards. m= minutes, DEQ= Drug Effects Questionnaire, MET= multifaceted empathy test, EFP= empathy for pain test).

2.2.5 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 23 and Stata version 15.

Assumptions of parametric tests were checked, including normality and homogeneity of variance. Group differences in demographic information and questionnaires were analysed using t-tests, Chi-square tests where data was categorical, or Mann Whitney U test where data was non-parametric. Post-hoc tests were controlled for multiple comparisons by using the Holm-Bonferroni correction.

To assess pain threshold and tolerance, 2×2×2 mixed measures ANOVA's were used with Group (trauma, control) as the between subject variable, and both Drug (morphine, placebo) and Time (pre-, post-administration) as a within subjects variables. A series of 2×2 repeated measures (RM) ANOVA's assessed differences between Group and Drug on the outcomes for the PRT, MET, and EFP. A series of 2×2×3 RM ANOVAs were used for the different levels of effort expended for rewards during the effort reward task by assessing the difference between Group, Drug and reward quantity (low, medium, high). The different levels of effort were analysed using separate ANOVA's because including effort level together in a single analysis (e.g. a 4-way design) made the outcomes difficult to interpret. The Cyberball Game was only assessed at baseline, and not investigated under the influence of morphine, therefore a series of 2×2 mixed measures ANOVA's assessed the difference between group and the within subject variable Inclusion Status (inclusion, exclusion) on subjective reports of mood and psychological needs. Blood plasma was analysed using enzyme-linked immunoassay kits (collection and analysis procedure can be found in Appendix 2.2), and differences were statistically analysed using a 3×2×2 ANOVA comparing session and group with the within-subjects variable of measurement time (baseline, 30mins, 60mins).

Mixed effect models

As the drug effect data was measured over many time points, linear mixed effect random intercept models were developed to analyse the drug effect for each primary/secondary outcome variables. Randomised Groups, Time (baseline, 15, 30, 45, 60, 90 120, and 150 minutes post-drug) and Sessions (i.e. 'Drug': morphine or low dose control) were added as categorical variables in the models and Group×Time×Session interaction effects were estimated to compare the time-related change in outcome variables. Mixed models are based on Maximum Likelihood method which accounts for missing data, as wellas data dependency from multi-level data structure. Primary outcomes assessed were from the DEQ and included: Feeling drug effects, feeling high, disliking effects, liking effects, and wanting more of the drug. Secondary outcomes assessed were opioid-specific and included feeling: nauseous, euphoric, dizzy, and sedated. All models were initially developed as variance component model to test whether there are enough variances at subject level. Log likelihood ratio (LR) test were used to test the variance component models

with single level models assuming no variance at subject level. No other variables were used in the model as the study had balanced randomisation. Since the model contained only categorical variables (group, time, session) no random slopes were assumed for them. Identity matrix was used as the covariance structure as the models were assumed to have random intercepts only.

2.3 Results

2.3.1 Demographics

Groups were matched on age, gender, BMI, familial histories of chronic pain, mental health and substance abuse problems (Table 2.1). The trauma group rated significantly higher in history of interpersonal trauma, but the groups were matched in non-interpersonal trauma history. The trauma group also reported greater loneliness, depression, anxiety and stress, and significantly lower perceived social support and self-compassion.

Table 2.1. *Demographic differences (M and SD) between the trauma and control group.*

	Trauma (n=27)	**Control (n=25)**	**t, χ^2 or U**	***p*-value**
Age	28.92 (13.38)	33.04 (16.39)	1.00	.325
Gender (male, female)	10, 17	7, 18	0.48	.488
BMI	24.62 (4.62)	23.30 (2.71)	1.27	.211
Physical health problems	4	3	0.09	.766
History of mild to moderate anxiety or depression	14	4	6.10	.014*
Received morphine in the past	9	7	0.17	.677
Been under general anaesthetic	15	11	0.96	.328
Regular use of over-the-counter painkillers	8	4	1.36	.244
Familial history of chronic pain	1	2	0.40	.529
Familial history of mental health problems	9	9	0.01	.918
Familial history of substance abuse problems	5	3	0.50	.478

Inter- and intrapersonal characteristics				
Childhood trauma questionnaire (total score)	64.37 (13.58)	28.20 (2.61)	12.08	<.001***
Physical abuse	11.56 (5.45)	5.08 (0.28)		
Emotional abuse	16.44 (4.80)	6.00 (1.04)		
Sexual abuse	9.82 (5.86)	5.08 (0.40)		
Physical neglect	9.85 (3.81)	5.32 (0.63)		
Emotional neglect	16.70 (4.05)	6.72 (1.60)		
PTE Non-interpersonal trauma [a]	0.00 (1.00)	0.00 (1.00)	284.0	.268
PTE Non-intimate interpersonal trauma [a]	1.00 (1.00)	0.00 (0.00)	194.0	.001**
PTE Intimate interpersonal trauma [a]	2.00 (2.00)	0.00 (0.50)	94.00	<.001***
ACE score [a]	4.00 (3.00)	0.00 (1.00)	12.00	<.001***
Perceived social support	2.22 (1.21)	3.74 (0.65)	5.70	<.001***
Loneliness	50.33 (9.15)	37.16 (7.38)	5.73	<.001***
Self-compassion	2.83 (0.75)	3.39 (0.73)	2.70	.010*
Depression [a]	10.00 (9.00)	7.00 (2.00)	170.50	.005**
Anxiety [a]	9.00 (6.00)	7.00 (2.00)	189.00	.014*
Stress [a]	12.00 (9.00)	8.00 (3.00)	155.50	.002**
Drug use history, (n=ever used)			χ^2	***p***
Alcohol (n=yes)	27	25	-	-
Tobacco	20	15	1.17	.280
Ecstasy/MDMA	9	6	0.55	.458
Cannabis	23	16	3.11	.078
Cocaine	7	3	1.62	.203
Illicit opioids	2	1	0.28	.599

Note. [a] Non-parametric test used where data is non-normal (median and interquartile range are reported). No chi squared data is presented for 'Alcohol' in drug use history as all participants from both groups have used alcohol.

* p<.05, ** p<.01, *** p<.001

2.3.2 Pain measures

Pain threshold

Due to negative skew, both threshold and tolerance were log-transformed prior to analyses. When assessing pain threshold, there was a significant interaction between Time and Drug ($F(1,47)=21.81$, $p<.001$, $\eta^2=0.10$), where Holm Bonferroni-corrected t-tests revealed a significant increase in pain threshold following morphine ($t(50)=4.29$, $p<.001$, $\eta^2=0.27$) but no significant difference in pain threshold following the very low dose control ($t(49)=0.75$, $p=.455$, $\eta^2=0.01$) (figure 2.4a). There was also main effect of Drug ($F(1,47)=10.76$, $p=.002$), yet no main effects of Group ($F(1,47)=0.03$, $p=.857$) or Time ($F(1,47)=1.99$, $p=.165$), and no interactions between Group and Time ($F(1,47)=1.41$, $p=.242$) or Drug ($F(1,47)=0.36$, $p=.550$), or between Time, Group and Drug ($F(1,47)=1.11$, $p=.298$). For the morphine session, pain threshold had a range of 59.29 seconds prior to drug administration, and a range of 62.37 seconds post-drug administration (for the non-transformed, raw data). In the low-dose control session, the range was 175.98 seconds and 55.10 seconds for pre- and post-drug administration, respectively.

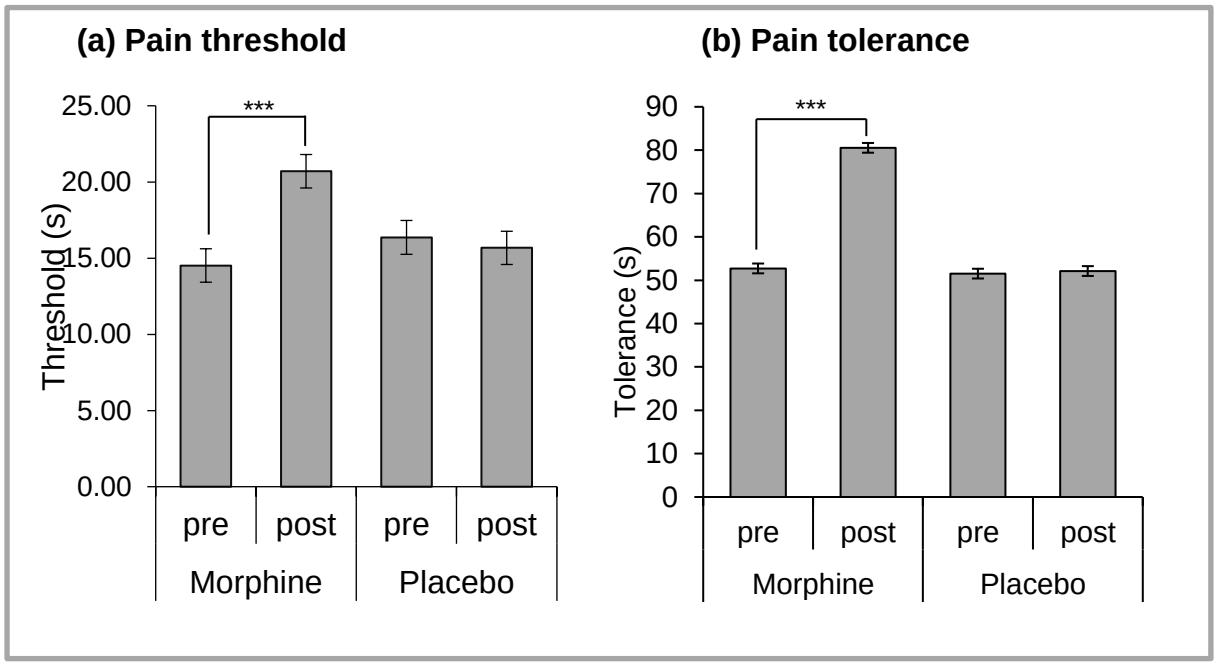


Figure 2.4. Pain threshold and tolerance pre- and post-drug administration collapsed across trauma and control groups. (a) There was a significant increase in pain threshold post-drug administration in the morphine session ($p<.001$) but not in the placebo session ($p=.455$). (b) There was a significant increase in pain tolerance post-drug administration in the morphine session ($p<.001$) but not in the placebo session ($p<.999$). (s= seconds). Data presented are back-transformed means and

standard errors bars, where the standard error bars presented are proportional to the y-axis. Error bars represent ± 1 SEM.

Pain tolerance

When assessing pain tolerance, there was a significant interaction between Tiime and Drug (F(1,47)=35.30, *p*<.001), where Holm Bonferroni-corrected t-tests revealed a significant increase in threshold in the morphine session (t(50)=5.07, *p*<.001) but no significant difference in the placebo session (t(49)=0.92, *p*>.999) (figure 2b). There was also a main effect of Time (F(1,47)=19.49, *p*<.001) and Drug (F(1,47)=14.99, *p*<.001). There were no main effects of Group (F(1,47)=0.84, *p*=.364), and no interaction between Group and Drug (F(1,47)<0.01, *p*=.957) or Time (F(1,47)=1.52, *p*=.224), or interaction between Drug, Group and Time (F(1,47)=1.50, *p*=.227). For the morphine session, pain tolerance had a range of 173.78 seconds prior to drug administration, and a range of 173.18 seconds post-drug administration (for the non-transformed, raw data). In the low-dose control session, the range was 163.70 seconds and 166.93 seconds for pre- and post-drug administration, respectively.

Pain Catastrophising

Subjective pain catastrophising was significantly higher in the childhood trauma group (*M*=32.30, *SD*=8.74) than the controls (*M*=23.26, *SD*=6.90) (t(48)=4.01, *p*<.001, η^2=0.25). Self-efficacy was not significantly different between the trauma group (*M*=3.09, *SD*=0.09) or controls (*M*=3.30, *SD*=0.09) (t(50)=1.66, *p*=.102, η^2=0.05).

2.3.3 Drug effects (Figure 2.5 and 2.6)

For all outcomes (primary/secondary), the χ^2 values for the variance component models were highly significant (p<0.0001) compared to the single-level models indicating there were significant variances at the subject level (to see ratio test tables, see Appendix 2.3). The between-group effects are reported within the text below, however for all outcomes (between-session and between-group comparisons), mean differences, 95% confidence intervals, and statistical significance levels are presented in Appendix 2.3. As the mixed models for primary and secondary outcomes did not test group differences directly, the mixed models table for all outcomes are provided in Appendix 2.4.

Feel effects. When assessing primary outcomes using the DEQ, both groups rated significantly higher in feeling the drug effects in the morphine session after every time point (figure 2.5a) (p<.001 for all time points). There were no significant group differences in feeling the effects in the morphine or placebo session (all p-values were >.284).

Feeling high. Feeling high was significantly greater for the childhood trauma group in the morphine session at 30 minutes than the controls (figure 2.5b) (MD=10.42, 95% CI [0.16, 20.69], p=.047), alongside a trend at 15 and 45 minutes in the same direction (15 minutes: MD=10.07, 95% CI [-0.20, 20.33], p=.055; 45 minutes: MD=9.82, 95% CI [-0.45, 20.08], p=.061). Both groups rated feeling significantly more "high" after morphine than placebo between 15-90 minutes (all p-values were <.001 for the trauma group, and <.026 for the controls).

Disliking drug effects. Disliking the drug effects were significantly higher in the control group at 90 minutes (MD=16.65, 95% CI [5.40, 27.91], p=.004) and 150 minutes (MD=18.86, 95% CI [7.55, 30.81], p<.001) compared with the trauma group after morphine, alongside a trend at 120 minutes (MD=11.05, 95% CI [0.20, 22.31], p=.047) (figure 2.5c). The control rated greater for disliking the effects in the morphine session over the placebo session between 90-150 minutes (90 minutes: MD=24.19, 95% CI [15.24, 33.14], p<.001; 120 minutes: MD=16.78, 95% CI [7.82, 25.73], p<.001; 150 minutes: MD=24.11, 95% CI [15.16, 33.06], p<.001), and at 15, 120 and 150 minutes for the trauma group (15 minutes: MD=10.42, 95% CI [2.00, 18.84], p=.015; 90 minutes: MD=10.00, 95% CI [1.58, 18.42], p=.020; 120 minutes: MD=10.00, 95% CI [1.58, 18.42], p=.020) (figure 2.5c).

Liking drug effects. The trauma group rated liking the drug effects significantly more in the morphine session than placebo at all time points (all p-values <.010), whilst liking the drug effects were not statistically different between sessions at any time point for the controls (all p-values >.125) (figure 2.5d). In addition, the trauma group rated liking the drug effects significantly more than controls after morphine at the following time points: 30 minutes (MD=14.67, 95% CI [0.48, 28.87], p=.043), 45 minutes (MD=20.02, 95% CI [5.82, 34.21], p=.006), 90 minutes (MD=18.20, 95% CI [4.00, 32.39], p=.012), 120 minutes (MD=20.14, 95% CI [5.94, 34.33], p=.005), and 150 minutes (MD=20.97, 95% CI [6.71, 35.24], p=.004).

Wanting more of the drug. The trauma group wanted more of the drug significantly greater after morphine compared with placebo at all time points (all p-values <.001) (figure 2.5e), whereas the control group did not rate significantly differently in wanting more between the two sessions (all p-values >.307). In addition, wanting more of the drug was significantly higher in the trauma group compared with controls after morphine at all time points (15 minutes: MD=23.42, 95% CI [10.55, 36.29], p<.001; 30 minutes: MD=24.53, 95% CI [11.66, 37.40], p<.001; 45 minutes: MD=29.90, 95% CI [17.03, 42.77], p<.001; 60 minutes: MD=38.05, 95% CI [25.10, 51.01], p<.001; 90 minutes: MD=35.51, 95% CI [22.65, 48.38], p<.001; 120 minutes: MD=31.09, 95% CI [18.23, 43.96], p<.001; 150 minutes: MD=25.25, 95% CI [12.31, 38.19], p<.001). There was also a trend to suggest greater wanting more between 30-150 minutes in the trauma group after placebo (30 minutes: MD=12.87, 95% CI [0.00, 25.74], p=.050; 45 minutes: MD=12.61, 95% CI [-0.26, 25.47], p=.055; 60 minutes: MD=11.35, 95% CI [-1.52, 24.21], p=.084; 90 minutes: MD=12.06, 95% CI [-0.81, 24.92], p=.066; 120 minutes: MD=12.81, 95% CI [-0.06, 25.67], p=.051).

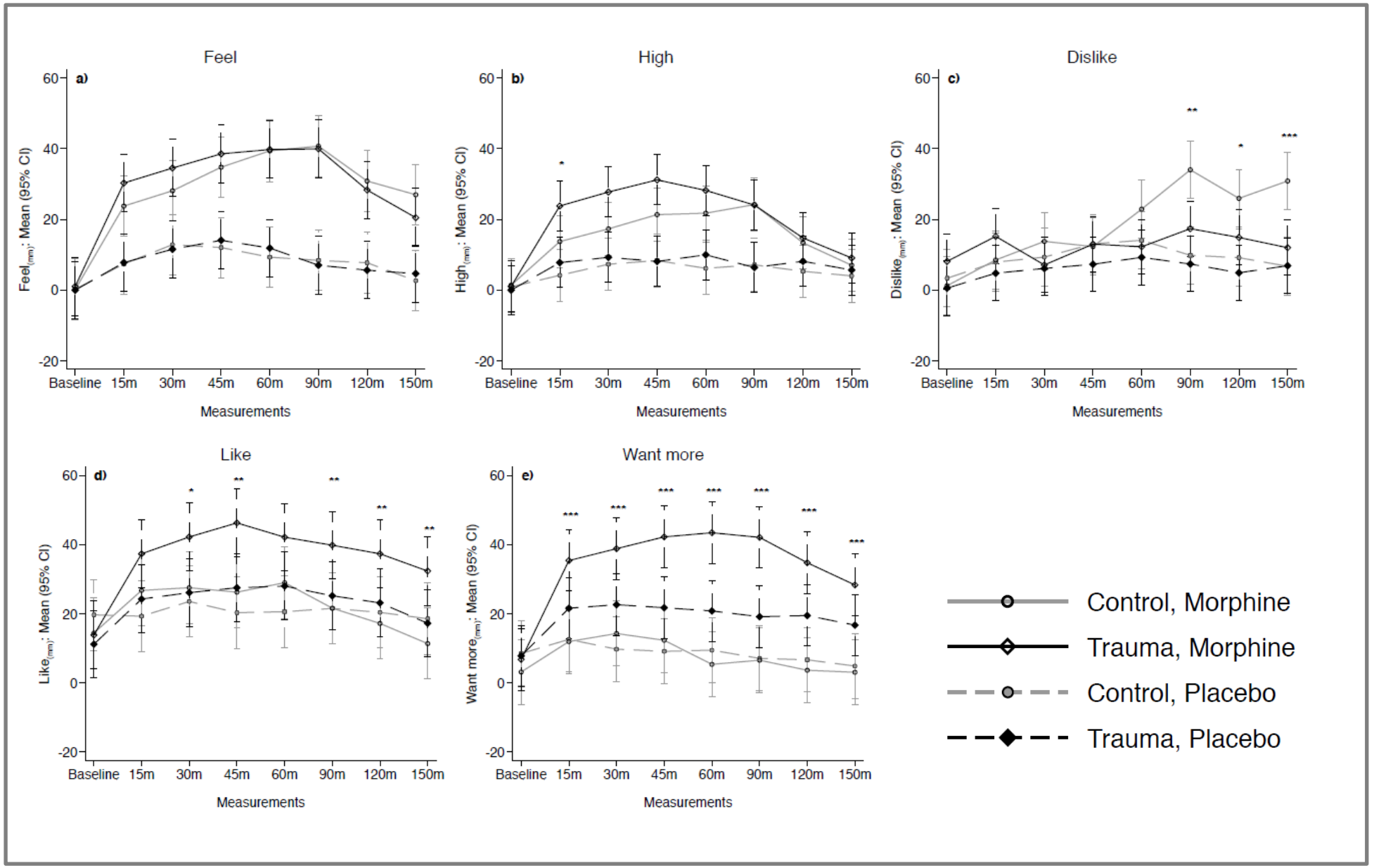

Feel
a)
Feel(mm); Mean (95% CI)
60
40
20
0
-20
Baseline
15m
30m
45m
60m
90m
120m
150m
Measurements
High
b)
High(mm); Mean (95% CI)
Measurements
Dislike
c)
Dislike(mm); Mean (95% CI)
Measurements
Like
d)
Like(mm); Mean (95% CI)
Measurements
Want more
e)
Want more(mm); Mean (95% CI)
Measurements
Control, Morphine
Trauma, Morphine
Control, Placebo
Trauma, Placebo

Figure 2.5. Subjective responses to morphine and placebo using the Drug Effects Questionnaire between the trauma and control groups over eight time points (baseline, 15m, 30m, 45m, 60m, 90m, 120m & 150m post-drug administration). (a) Feeling effects, (b) Feeling high, (c) Dislike effects, (d) Like effects, (e) Want more. (X-axis: m = minutes; y-axis: mm = millimetres). Graphs reflect predicted means and 95% confidence intervals. Significant differences between trauma and control group in the morphine session are indicated by * p<.05, ** p<.01, *** p<.001.

For opioid-specific outcomes, the control group felt significantly more nauseous after morphine than the trauma group between 120-150 minutes (figure 2.6a) (120 minutes: MD=9.27, 95% CI [1.56, 16.98], p=.018; 150 minutes: MD=10.24, 95% CI [2.47, 18.01], p=.010). Nausea was significantly greater following morphine compared with placebo between 60-150 minutes for controls (all p-values were <.005) and 90-150 minutes for the trauma group (all p-values were <.041). The trauma group were significantly more euphoric than controls between 15-60 minutes (figure 2.6b) (15 mins: MD=17.99, 95% CI [6.69, 29.30], p=.002; 30 mins: MD=13.69, 95% CI [2.39, 25.00], p=0.18; 45 mins: MD=14.20, 95% CI [2.89, 25.50], p=.014; 60 mins: MD=14.84, 95%CI [3.45, 26.22], p=.011). The trauma group also reported feeling more euphoric after morphine compared with placebo between 15-90 minutes (all p's<0.18), whereas the controls did not feel any difference in euphoria between the morphine or placebo sessions (all p's>.195). Controls reported feeling more dizzy than the trauma group after morphine between 90 (MD=12.81, 95% CI [4.69, 20.92], p=.002) and 120 minutes (MD=10.64, 95% CI [2.52, 18.75], p=.010), alongside a trend in the same direction at 60 and 150 minutes (figure 2.6c). Both groups reported feeling more dizzy after morphine compared with placebo between 45-150 minutes (all p's<.030. For reported sedation, both groups reported feeling more sedated after morphine compared with placebo at every time point (all p's<.012) (figure 2.6d), however there were no significant differences between the two groups after morphine or placebo.

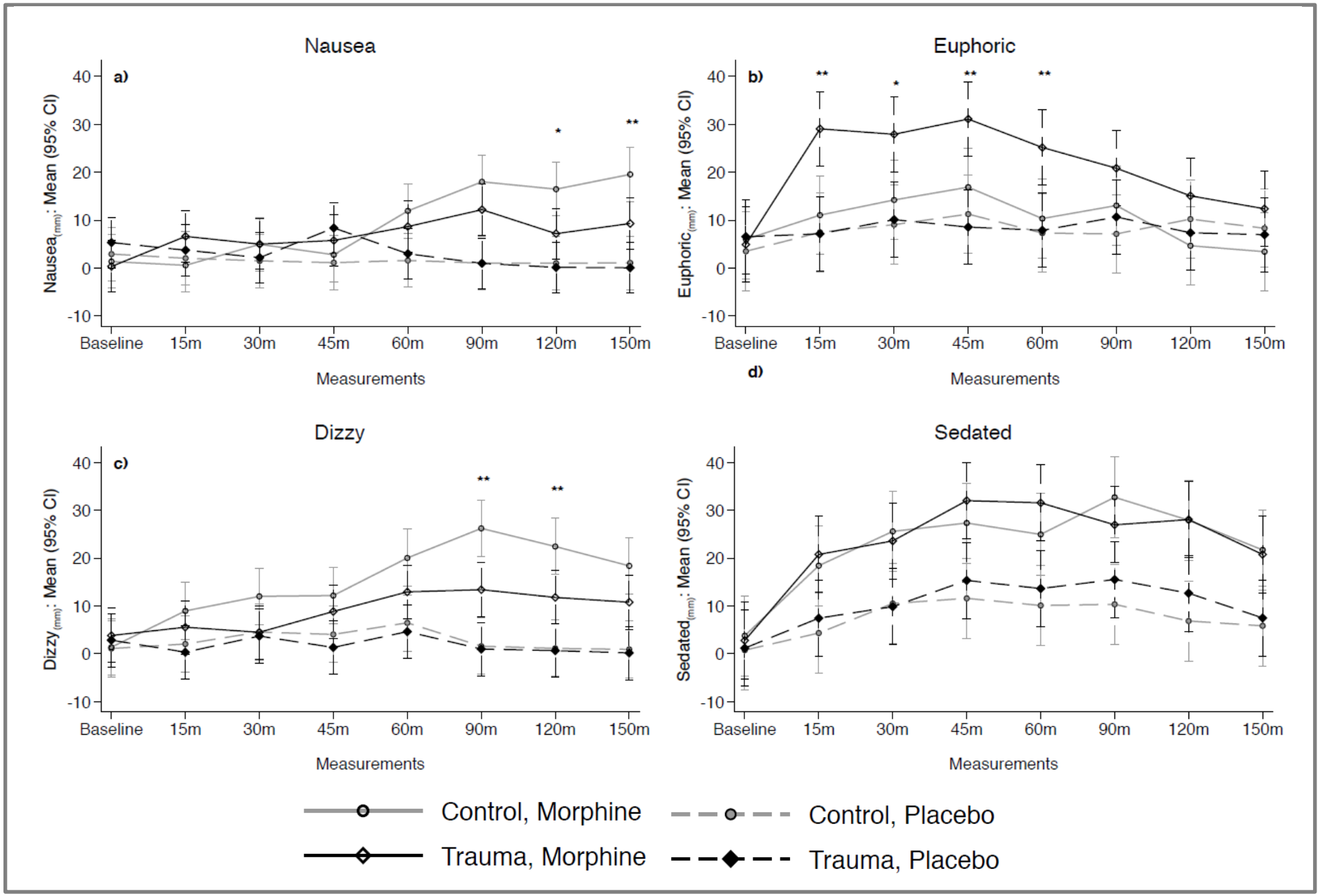

Nausea
a)
Nausea(mm): Mean (95% CI)
40
30
20
10
0
-10
Baseline
15m
30m
45m
60m
90m
120m
150m
Measurements
*
**
Euphoric
b)
Euphoric(mm): Mean (95% CI)
**
*
**
**
Measurements
d)
Dizzy
c)
Dizzy(mm): Mean (95% CI)
**
**
Measurements
Sedated
Sedated(mm): Mean (95% CI)
Measurements
Control, Morphine
Control, Placebo
Trauma, Morphine
Trauma, Placebo

Figure 2.6. Subjective responses to opioid-specific effects in the morphine and placebo sessions between the trauma and control groups over eight time points (baseline, 15m, 30m, 45m, 60m, 90m, 120m & 150m post-drug administration). (a) Feeling nauseous, (b) Feeling euphoric, (c) Feeling dizzy, (d) feeling sedated. (X-axis: m = minutes; y-axis: mm = millimetres). Graphs reflect predicted means and 95% confidence intervals. Significant differences between trauma and control group in the morphine session are indicated by * p<.05, ** p<.01, *** p<.001.

2.3.4 Reward sensitivity

PRT: when analysing the percentage of morphine choices made, there was no main effect of Group ($F(1,46)=0.55$, $p=.461$, $\eta^2=0.01$), or Drug ($F(1,46)=1.22$, $p=.276$, $\eta^2=0.03$), or interaction between Group and Drug ($F(1,46=0.30$, $p=.588$, $\eta^2=0.01$) (morphine session: trauma $M=31.32$, $SD=20.61$, controls $M=28.57$, $SD=18.70$; low dose control session: trauma $M=30.21$, $SD=18.66$, controls $M=25.33$, $SD=17.60$). When assessing the maximum button presses for morphine, there was no main effect of Group ($F(1,46)=1.84$, $p=.182$, $\eta^2=0.04$), or Drug ($F(1,46)=2.53$, $p=.119$, $\eta^2=0.05$), or interaction between Group and Drug ($F(1,46=0.04$, $p=.837$, $\eta^2<0.01$) (morphine session: trauma $M=34.62$, $SD=29.43$, controls $M=$,26.36 $SD=20.60$; low dose control session: trauma $M=30.77$, $SD=27.41$, controls $M=21.36$, $SD=16.42$).

Effort reward task: For rewards that required high effort (difficult), there was a significant interaction between Group and Drug ($F(1,43)=8.64$, $p=.005$, $\eta^2=0.01$), however Holm-Bonferroni t-tests did not reveal any differences between groups after morphine ($t(45)=1.96$, $p=.448$, $\eta^2=0.01$) or placebo ($t(47)=0.09$, $p>.999$, $\eta^2<0.01$) (figure 2.7). There was also a main effect of Reward Quantity ($F(2,86)=59.31$, $p<.001$, $\eta^2=0.47$), where high reward was picked more than medium ($p<.001$) and low ($p<.001$), and medium reward was picked more than low ($p<.001$). There were no main effects of Drug ($F(1,43)=0.21$, $p=.684$, $\eta^2<0.01$) or Group ($F(1,43)=1.76$, $p=.192$), or interactions between Reward Quantity with Group ($F(2,86)=2.54$, $p=.090$, $\eta^2=0.02$) or Drug ($F(2,86)=0.44$, $p=.627$, $\eta^2<0.01$) or Group and Drug ($F(2,86)=1.04$), $p=.354$, $\eta^2<0.01$). There were no significant Group differences for acceptances that required medium or low effort (Appendix 2.5)

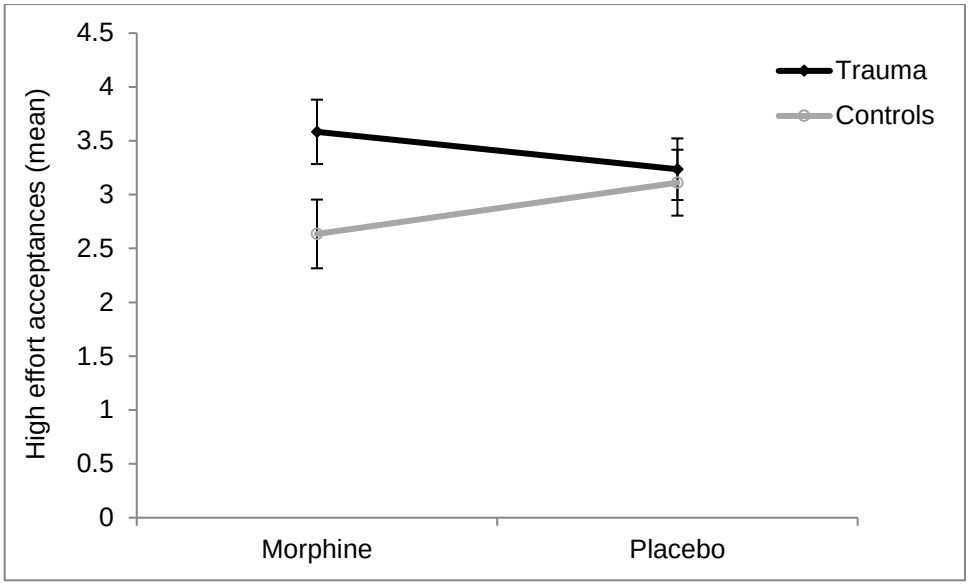


Figure 2.7. Number of accepted offers that required high effort between the trauma and control group after receiving morphine or placebo during the effort reward task. There is a significant interaction between session and group (p=.005), however there were no differences between groups or sessions (Holm-Bonferroni corrected). Error bars represent ± 1 SEM.

2.3.5 Social functioning

MET. For cognitive empathy, there were no main effects of Trauma history ($F(1,46)=0.65$, $p=.423$, $\eta^2=0.01$), Drug ($F(1,46)=2.38$, $p=.130$, $\eta^2=0.05$), or interaction ($F(1,46)=0.22$, $p=.640$, $\eta^2=0.01$). For emotional empathy, there were similarly no main effects of Group ($F(1,46)=1.84$, $p=.181$, $\eta^2=0.04$), Drug ($F(1,46)<0.01$, $p=.990$, $\eta^2<0.01$), or interaction between Drug and Group ($F(1,46)<0.01$, $p=.975$, $\eta^2<0.01$) (means and standard deviations are in Table 2.2)

Table 2.2 *Means and Standard Deviations for the MET and EFP between the Trauma and Control Groups.*

Task		**Session**	**Trauma (n=27)**	**Controls (n=25)**
Multifaceted Empathy Test	Cognitive empathy	Morphine	27.22 (4.04)	28.29 (3.39)
		Placebo	26.74 (4.07)	27.38 (4.13)
	Emotional empathy	Morphine	4.53 (1.57)	5.07 (1.53)
		Placebo	4.54 (1.41)	5.07 (1.20)
Empathy for Pain Task	Rated pain	Morphine	49.26 (17.40)	51.89 (17.11)
		Placebo	46.91 (14.75)	56.72 (14.90)
	Rated concern	Morphine	43.14 (17.34)	45.81 (18.33)
		Placebo	41.02 (15.63)	52.70 (14.60)

EFP. When assessing how much pain participants perceived the person in the image felt, there were no main effects of Group ($F(1,47)=2.29$, $p=.137$, $\eta^2=0.05$) or Drug ($F(1,47)=0.35$, $p=.558$, $\eta^2=0.01$), and no interaction between Group and Drug ($F(1,46)=2.88$, $p=.096$, $\eta^2=0.06$) (Table 2.2). When assessing how *concerned* participants felt for the person in the image, there was a significant interaction between Group and Drug ($F(1,47)=5.46$, $p=.024$, $\eta^2=0.10$), where Holm-Bonferroni corrected t-tests revealed the trauma group scored significantly lower than the control group in the placebo session ($t(49)=2.75$, $p=.040$, $\eta^2=0.13$) but with no significant group differences in the morphine session ($t(47)=0.52$, $p=.605$, $\eta^2=0.01$) (figure 2.8). There were no main effects of Group ($F(1,47)=2.74$, $p=.105$, $\eta^2=0.06$) or Drug ($F(1,47)=1.52$, $p=.223$, $\eta^2=0.03$).

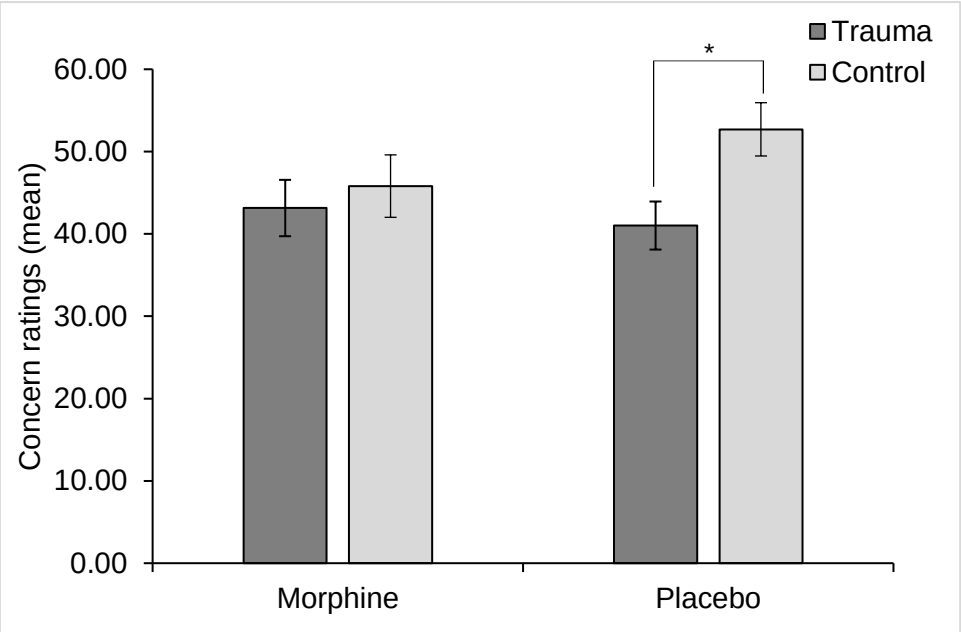


Figure 2.8. Rated concern for individuals in painful scenarios between the trauma and control groups after morphine and placebo sessions. There is a significant interaction between group and session (p=.024) where the trauma group score significantly lower than controls in the placebo session. Error bars represent ± 1 SEM.

Cyberball Game (baseline only). There were significant reductions in mood, self-esteem, sense of belonging, meaningful existence, control, hurt feelings, and perceived percentage of ball throws following social exclusion (Table 2.3). However, there were no interactions with Trauma history on any of these indices.

Table 2.3 *Statistical outcomes for the Cyberball between groups and inclusion status, alongside means and standard deviations.*

	Inclusion status	**Trauma (n=27)**	**Controls (n=25)**	**F-Statistic**		***p* value**	**η^2**
Mood	Inclusion	2.30 (1.23)	2.40 (0.97)	Group	<0.01	.992	<0.01
	Exclusion	0.91 (1.82)	0.80 (1.75)	Inclusion status	46.56	<.001***	0.48
				Group*inclusion status	0.24	.627	<0.01
Self-esteem	Inclusion	3.42 (1.00)	3.28 (0.83)	Group	0.02	.883	<0.01
	Exclusion	2.40 (0.93)	2.47 (0.80)	Inclusion status	45.38	<.001***	0.48
				Group*inclusion status	0.64	.426	0.01
Sense of belonging	Inclusion	1.75 (0.94)	1.57 (0.66)	Group	0.75	.390	0.02
	Exclusion	3.61 (0.95)	3.40 (1.26)	Inclusion status	140.92	<.001***	0.74
				Group*inclusion status	0.01	.936	<0.01
Meaningful existence	Inclusion	1.51 (0.71)	1.37 (0.47)	Group	0.78	.382	0.02
	Exclusion	2.51 (1.00)	2.95 (1.07)	Inclusion status	70.50	<.001***	0.57
				Group*inclusion status	3.56	.065	0.03
Control	Inclusion	2.37 (0.94)	2.49 (0.77)	Group	0.24	.629	0.01
	Exclusion	1.50 (0.49)	1.52 (0.74)	Inclusion status	60.91	<.001***	0.55
				Group*inclusion status	0.08	.786	<0.01
Hurt feelings [c]	Inclusion	1.29 (1.57)	1.11 (1.33)	Group	0.09	.768	<0.01
	Exclusion	1.57 (1.66)	1.73 (1.73)	Inclusion status	14.01	<.001***	0.21
				Group*inclusion status	2.05	.158	0.03
Anger [c]	Inclusion	1.27 (1.53)	1.20 (1.48)	Group	0.22	.638	0.01

	Exclusion	1.68 (1.77)	1.61 (1.73)	Inclusion status	9.55	.003	0.16
				Group*inclusion status	0.01	.916	<0.01
% of perceived ball throws	Inclusion	40.41 (17.49)	41.13 (17.52)	Group	0.04	.849	<0.01
	Exclusion	12.11 (7.09)	12.52 (8.46)	Inclusion status	147.73	<.001***	0.75
				Group*inclusion status	<0.01	.948	<0.01

Note. 'Mood' was calculated by subtracting negative affect scores from positive affect scores.
[c] Non-normal and log transformed. Means and standard deviations have been back transformed
* p<.05, ** p<.01, *** p<.001

2.3.6 Plasma morphine levels

When assessing blood plasma levels of morphine (ng/ml), there was a significant interaction between Drug and Time ($F(2,100)=104.58$, $p<.001$, $\eta^2=0.16$), confirming significantly greater levels of morphine present at 30 ($M=22.63$ ng/ml, $SD=1.93$) ($t(51)=11.09$, $p<.001$, $\eta^2=0.71$) and 60 minutes post-morphine ($M=21.53$ ng/ml, $SD=1.84$) ($t(51)=10.95$, $p<.001$, $\eta^2=0.70$), compared with placebo (30m: $M=2.40$ ng/ml, $SD=0.32$; 60m: $M=2.46$, $SD=0.27$). There were no significant differences in baseline measurements between morphine and placebo sessions ($t(51)=0.62$, $p=.538$, $\eta^2=0.10$). There was main effects of Drug and Time, and no differences with Group or any other interactions (see Appendix 2.6 for analyses)

2.3.7 Exploratory analyses

There was a large effect size for the correlation between ACE score with liking the effects of morphine at peak effects (30 minutes) ($r=0.47$, $n=27$, $p=.154$) (Holm-Bonferroni corrected) within the childhood trauma group (figure 2.9). There was no significant relationship with ACE score and wanting more morphine at peak effects ($r=.23$, $n=27$, $p=.400$). In addition, there was no significant relationship between self-compassion and liking or wanting at peak effects within the childhood trauma group ($r=-0.22$, $n=27$, $p=.281$, and $r=-0.27$, $n=27$, $p=.175$).

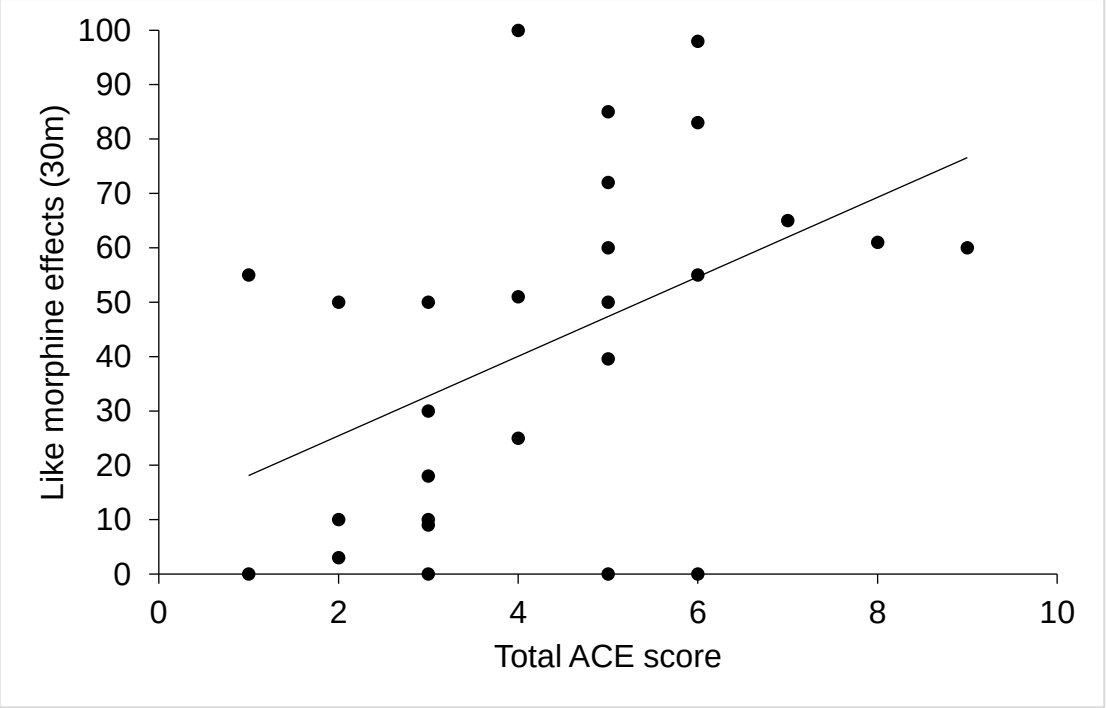


Figure 2.9. Correlation between ACE score and liking the effects of morphine at peak effects (30 minutes post-drug administration) within the childhood trauma group.

2.4 Discussion

In the current study, we aimed to investigate the impact of childhood trauma on acute response to morphine, pain threshold and tolerance, and social functioning. We found that individuals with childhood trauma consistently reported liking the effects of morphine more than those without a history of childhood trauma, as well as reported wanting more of the drug compared with the controls over the duration of the session. The control group disliked the effects of morphine greater than those with childhood trauma histories towards the end of the session, and controls experienced more nausea and dizziness than the trauma group. Rated euphoria was also significantly greater in the trauma group, as well as feeling 'high' at peak effects, whilst euphoria in the controls was low and did not differ between the active and very low dose morphine sessions. We found increased pain threshold and tolerance following morphine administration, in line with its known analgesic effects; however this did not differ between the trauma and control group, although pain catastrophising was greater in the childhood trauma group. We also reported lower ratings of concern for others in pain in the trauma group when not acutely treated

with morphine, yet there were no other group differences in cognitive or emotional empathy, or responses to social exclusion between the groups. We also found an indication of greater effort to work for other rewards (money) after morphine in the trauma group, however there were no differences in the effort made to choose morphine over money between the groups. The two groups were well matched on gender, age, BMI alcohol and drug use. However those who had experienced childhood trauma showed greater levels of depression, anxiety, stress, loneliness and lower perceived social support and self-compassion.

Liking the effects of morphine, feeling more euphoric and wanting more of the drug was greater in those with histories of childhood trauma. This supports our hypotheses that those with histories of childhood abuse and neglect would find the drug more pleasurable and rewarding. This is in line with the pre-clinical research in maternally separated rats, where early trauma (maternal separation) is associated with greater reinforcing effects of morphine – shown by more rapid rates of morphine self-administration and stronger conditioned place-preference (Vazquez et al., 2006; Vazquez et al., 2005). In addition to this, the non-traumatised control group reported disliking the effects more than the childhood trauma group, as well as increased rates of aversive effects such as nausea and dizziness. We also found a large effect that failed to reach statistical significance which suggested severity of childhood adversity in the trauma group may be positively associated with how much they liked the morphine at the time of peak blood concentration (tMax). To our knowledge, this is the first study to link history of childhood trauma with the experiential effects of opioids in non-addicted individuals, suggesting that childhood trauma may actually produce a greater sensitivity to the positive and pleasurable effects of opioids.

In the current study, childhood adversity increased both the pleasurable effects of morphine (via greater liking and euphoria), intensified the motivational qualities of morphine (via wanting more), and reduced the likelihood of experiencing negative effects such as nausea and dizziness. One potential explanation for these differences may be via alterations in the endogenous opioid system through childhood adversity. Prior research has linked childhood trauma to altered neural responses to naltrexone, potentially via existing differences in endogenous opioids (Savulich et al., 2017). Preclinical research has also reported that maternal separation in rats results in hyposensitive endogenous opioid functioning, which is

suggested as responsible for the heightened sensitivity to the rewarding effects of opioid drugs (Vazquez et al., 2005). A hyposensitive endogenous opioid system via lower receptor density could therefore potentially underlie the increased pleasurable effects and reduced aversive effects of morphine in the trauma group in the current study. This combination of not only increased pleasurable effects but also blunted adverse effects provides a compelling case for enhanced risk of susceptibility to the addictive properties of the drug, providing evidence for individual differences in opioid reward sensitivity that could be a major vulnerability factor for addiction.

However, contrary to the idea of disrupted endogenous opioids and our hypotheses, the current study found no significant group differences in pain threshold using the cold pressor test, unlike previous studies (Creech et al., 2011; Pieritz et al., 2015; Scarinci et al., 1994; Tesarz et al., 2016; You & Meagher, 2016). Neither did we report a reduced analgesic effect of morphine in those with childhood trauma, unlike reports by preclinical studies (Kalinichev et al., 2001). The observed increases in threshold and tolerance following morphine administration suggests that our pain threshold assessment was a sensitive measure of opioid activity. There was also a large range in responses to the cold water pressor, highlighting large differences between different people in the experience and reporting of pain. Potential explanations for the lack of difference between groups in the current study could be due to the type of pain measurement used: prior studies have reported increased pain sensitisation (increases in pain following repeated exposure of identical painful events) and slower decay (time taken for pain to subside following painful event) following childhood trauma (You & Meagher, 2016). Where threshold has been assessed, prior research have used different forms of pain, such as thermal or pressure (Scarinci et al., 1994), whilst other studies have only reported differences in pain threshold after specific forms of abuse (such as emotional abuse) (Pieritz et al., 2015). We did find higher levels of pain catastrophising in the trauma group suggesting some differences in pain interpretation, as well as greater depression and anxiety. These highlight the importance of psychological interpretations to physical and emotional pain that could be altered as a consequence of childhood trauma. This is relevant not only for addiction but also for chronic pain, where there are similarly high rates of childhood trauma (You, Albu, Lisenbardt, & Meagher, 2018). High self-efficacy has been shown as a resilience

factor protecting against chronic pain in the presence of childhood trauma, reduced social support, pain catastrophising, and depression (Edwards, Dworkin, Sullivan, Turk, & Wasan, 2016). Whilst pain catastrophising, depression, anxiety, and stress were high and perceived social support was low in the current trauma group, self-efficacy was equivalent to the controls, potentially suggesting it as a resilience factor for not only chronic pain but also for addiction.

Given the absence of differences in pain threshold, the findings of the current study may not support the notion that greater opioid-induced pleasure and wanting of morphine is due to impaired endogenous opioid functioning, as suggested by preclinical studies (Vazquez et al., 2006; Vazquez et al., 2005). However other explanations may be that increased liking of opioids is not specific to this drug, as a similar pattern has been observed with amphetamines in men (Oswald et al., 2014). One potential reason could be due to permanent alterations in the hypothalamic–pituitary–adrenal (HPA) axis caused by chronic stress in childhood (see van Bodegom, Homberg, & Henckens, 2017, for a review), which could affect the response to drugs. We also observed greater stress in adulthood in the form of lower social support and higher loneliness in the trauma group. The stress hormone corticosterone has been linked with reward and sensation-seeking, where higher levels of this hormone have been shown to potentiate the rewarding effects of substances (Piazza et al., 1993). Pre-clinical research has shown that plasma corticosterone is greater in rats exposed to early life stress (Zhang et al., 2013), and mice exposed to social stress that show greater corticosterone have higher alcohol consumption, where it is suggested that corticosterone interacts with dopamine to promote alcohol intake (Norman et al., 2015). It is possible that neurobiological differences in HPA functioning, as well as its effects on other neurotransmitters such as dopamine, could underlie the heightened pleasurable effects in the childhood trauma group. However, there may also be psychological explanations: Childhood trauma is related to heightened vigilance and preparedness for threats in both childhood (Shackman, Shackman, & Pollak, 2007) and adulthood (Repetti, Robles, & Reynolds, 2011), where opioids may be pleasurable and rewarding because they offer relief from a chronic hypervigilant state.

Dissociable aspects of reward are associated with different neurochemical systems: drug ‘liking’ (pleasure) has been shown to involve opioid, endocannabinoid,

and GABA neurotransmitter systems, whilst drug 'wanting' (the motivational component to seek a reward) is related to dopaminergic and glutamate transmission (Berridge, Robinson, & Aldridge, 2009). It is possible that childhood trauma increases sensitivity to both the hedonic and motivational qualities through alterations to the connectivity between these systems. However, although we reported greater subjective wanting and liking of morphine in the trauma group, we did not find evidence of implicit wanting of morphine as we did not observe any differences in effort to work for morphine using the progressive-ratio computerised task. This may be because the study did not use addicted individuals, and although ratings of 'wanting more' were higher in the trauma group, willingness to expend effort for more was not greater than controls. Another potential explanation that links with dysregulated reward processing may be that histories of childhood trauma could foster impulsivity and greater sensation seeking. One study has reported negative urgency (the tendency to act recklessly when experiencing negative emotions) to be greater in those with childhood trauma and to predict substance abuse, as well as greater sensation seeking (Oshri et al., 2018). It may also have been that this task presented choices between morphine and money, however it may have been better to assess effort to work for just money with no comparator.

The current study reported lower concern for others in pain in the trauma group when not intoxicated with morphine. This was a surprising finding, as we predicted that the trauma group would have greater empathy for pain at baseline, in line with research suggesting that empathy for others' pain depends on whether you are able to feel pain in yourself (Rutgen et al., 2015). We also predicted reduced empathy following morphine (as morphine produces analgesia therefore reducing pain) which was not supported by these data. This tentatively conflicts with the 'shared-representations' theory of empathy, as the analgesic morphine altered pain thresholds yet did not impact on empathy for pain. Alternatively, prior work has reported reduced empathic concern and greater personal distress in those with childhood trauma, which is thought to be due to a preoccupation with one's own pain and negative thought patterns, as well as reduced ability to mentalise due to a state of hyperarousal (Parlar et al., 2014). This could be one potential explanation for reduced concern in the trauma group in the current study, who also reported greater pain catastrophizing, depression, anxiety and stress, all of which could be associated

with a preoccupation with one's own suffering. However we also did not find any differences in emotional or cognitive empathy between the groups, or social distress caused by exclusion. Prior work looking at empathy is conflicting, where some researchers have linked childhood trauma with reduced emotional and cognitive empathy using a subjective questionnaire (Parlar et al., 2014) whilst others have reported the converse (Greenberg, Baron-Cohen, Rosenberg, Fonagy, & Rentfrow, 2018). These studies have not measured empathy using the MET, however, which could operationalise empathy differently.

Clinical implications of this study are wide-ranging. The suggestion that people who have experienced childhood trauma feel more positive and less negative effects of morphine may go some way towards starting to reduce the stigma associated with opioid use disorder. Evidence suggests that it is still widely believed that addiction is a choice, which is a major barrier for seeking help (Wakeman & Rich, 2018). This attitude also actively reduces the public's willingness to support policies for helping addicts, and increases willingness to accept discriminatory practices towards them (Barry et al., 2014). Another implication is regarding the prescribing of opioids medically. Chronic pain is one condition that has been linked to childhood trauma (Davis, Luecken, & Zautra, 2005; You et al., 2018), and prior work has reported childhood adversity is associated with greater cue-induced opioid craving in chronic pain patients on opioid pain management (Garland et al., 2019). The current study suggests that this subset of patients may benefit from alternative forms of pain management, and that history of childhood trauma should be assessed and considered when prescribing opioids for pain. This is especially timely in light of the recent opioid epidemic, where these drugs have been over-prescribed and led to vast increases in addiction and overdoses (deShazo et al., 2018), emphasising the importance of more careful prescribing. This also highlights the potential to investigate whether novel, trauma-focused treatments for chronic pain may be beneficial for this group and reduce the risk of addiction to opioids. This should be specifically related to interpersonal trauma, as we did not report any differences between groups in history of non-interpersonal trauma (e.g. traffic accident, fire). The findings of this study also highlight the importance of introducing preventative measures aimed at high-risk children and adolescents to reduce the initiation of opioid use. Such preventative measures could include introducing these individuals

to other rewarding activities in order to reduce the motivational strength of opioids. Examples may include sports or creative arts introduced within school. In addition to this, training in emotion regulation in dealing with stressors may regulate changes in HPA stress reactivity, providing individuals with the psychological tools to deal with difficult emotional states. Attempts to reduce hyperarousal may also have positive repercussions on dealing with psychological difficulties such as pain catastrophising, as well as improve social functioning.

The current study has several strengths and limitations. One strength is that the pain threshold assessment maintained strictly controlled conditions, however it may have been interesting to rate pain intensity continuously or over multiple time points to assess how pain changed over time. In addition we may have chosen an inappropriate pain index for this group, in one related to acute pain, and it may have been more helpful to look at variables related to chronic pain such as sensitisation and wind-up. Furthermore, a more sophisticated technique such as positron-emission tomography may be more sensitive than pain to probe the endogenous opioid system. Another potential limitation is that the exclusion of severe mental health problems or addiction history which could indicate trauma group as particularly resilient, therefore potentially reducing ecological validity. Yet there were greater rates of social stressors such as loneliness and reduced social support, and greater depression and anxiety in those with childhood trauma, thus it is difficult to disentangle the influence of trauma and these other factors on the current findings. However, the positive relationship between severity of childhood trauma and liking morphine does indicate trauma as directly influencing responses to opioids. Furthermore, in the progressive ratio task we assessed behavioural responses to wanting more morphine via asking them to work towards another dose hypothetically, yet future studies could build on this by assessing self-administration of morphine using patient-controlled analgesia pumps. Finally, the placebo was not a ‘pure’ placebo in order to better conceal the sessions. Including a pure placebo session in addition would have been preferable, however this was not possible due to constraints on time and costs.

In summary, the current findings suggest that experiences of childhood trauma can sensitise individuals to opioid-induced pleasure and are associated with greater motivation to work for opioids. Although there was greater explicit wanting of

morphine in people who had experienced childhood adversity, this was not fully supported by implicit measures. The trauma group reported greater catastrophising of pain, but did not respond differently to a painful stimulus in terms of threshold or tolerance. Concern for other's in pain was reduced in the trauma group, which may be due to preoccupation with one's own pain, however there were no differences in other social behaviours (social distress from exclusion and empathy for other's emotions). The findings of this study are a stepping stone in highlighting the role of childhood trauma in opioid use disorder, emphasising the need to address trauma symptoms in this vulnerable group, along with targeting early intervention at traumatised young people. These findings have many clinical and social implications including reducing the guilt and shame common amongst opioid addicts about the reasons behind the development of this damaging addiction.

Chapter 3: Impaired empathy and increased anger following social exclusion in opioid users

3.1 Introduction

The misuse of opioids is a growing global concern, with approximately 34 million users worldwide and recent reports of a dramatic increase in overdose rates (United Nations of Office on Drugs and Crime, 2018). As well as high rates of mortality, opioid misuse has other health-related consequences, such as increased rates of HIV, hepatitis C, and neonatal abstinence syndrome (National Institute on Drug Abuse, 2018). Understanding the factors that initiate and maintain opioid use disorder is thus imperative from a public health perspective. Much work has focused on the biological and behavioural mechanisms of opioid addiction, however research into the role of psychosocial factors is comparatively sparse (Heilig et al., 2016). It is well understood that social factors including social deprivation and interpersonal trauma can predict and maintain addiction (Gerra et al., 2014; Heffernan et al., 2000; Kendler et al., 2014; Lake et al., 2015; MacGregor & Thickett, 2011; Naqavi et al., 2011). Opioids may be used in part to compensate for difficulties in emotion regulation (Moustafa et al., 2018; Wolff et al., 2016). Additionally, high rates of social marginalisation, ostracism, and discrimination towards addicted individuals (Barry et al., 2014) may perpetuate deficits in social functioning, and could contribute to the maintenance of opioid use.

Neurobiologically, the endogenous opioid system plays a role in social functioning (see Machin & Dunbar, 2011, for a review) and is involved in empathy (Rutgen et al., 2015), which has a uniquely social purpose (Panksepp & Panksepp, 2013; Pearce, Wlodarski, Machin, & Dunbar, 2017). Empathy is crucial for interpersonal relationships and bonding: impairments in the ability to empathise are observed in disorders such as autism spectrum disorder (Baron-Cohen & Wheelwright, 2004) and schizophrenia (Green, Horan, & Lee, 2015), and are related to difficulties in social functioning (Baron-Cohen & Wheelwright, 2004). Impaired empathy in people with substance use disorders have also been reported (Ferrari, Smeraldi, Bottero, & Politi, 2014) (as discussed in Chapter 1 Section 4.3). Two pivotal aspects of empathy are ‘emotional empathy’, referring to the ability to vicariously feel the emotional state of others, and ‘cognitive empathy’, which refers to the ability to identify and understand the emotional state of others (sometimes referred to as ‘theory of mind’) (Baron-Cohen & Wheelwright, 2004; Blair, 2005). Impairments in emotional empathy have been observed in a heterogenous group of

drug users (Ferrari et al., 2014), alcohol users (Maurage et al., 2011), and stimulant users (Kroll et al, 2018; Preller et al., 2014). Two studies with chronic opioid users have similarly reported impairments in emotional empathy using a subjective questionnaire among methadone- and diacetylmorphine-maintained individuals (Stange et al., 2017; Tomei et al., 2017) but a further study with a different group of opioid users not maintained on OSM failed to replicate these findings (Kroll et al., 2018). The ability to empathise can be affected by situational factors including psychosocial stress, affective state, and socioeconomic status (Kanske, Böckler, & Singer, 2017), and acute opioid intoxication state may also be important to understand impairments in empathy within the context of wider social stress.

Opioid drugs may also affect social functioning by altering responses to difficult social events. Acutely, exogenous opioids have shown to alleviate the experience of both physical pain and social distress (Bershad et al., 2016; Inturrisi, 2002; Stein, van Honk, Ipser, Solms, & Panksepp, 2007). The latter is termed 'emotional analgesia' and is thought to be a protective mechanism associated with reductions in subjective distress and cortisol following social exclusion (Bass, Stednitz, Simonson, Shen, & Gahtan, 2014). 'Social' pain is used to refer to a specific form of social distress, such as the painful feelings following an unpleasant social event like bullying, social rejection or exclusion (Eisenberger, 2015). Further evidence supports the opioid-induced reductions in cortisol following a social stressor (the Trier Social Stress Test [TSST] known to robustly induce social anxiety) following buprenorphine administration, supporting the involvement of the opioid system in mediating social distress (Bershad et al., 2015). However, although there were reductions in anticipatory anxiety prior to the task, buprenorphine did not reduce subjective ratings of anxiety or heart rate in response to social stress; This could be correspond with increased nausea caused by the drug, or possibly that the TSST is a powerful anxiety induction and the small dose of buprenorphine was not enough to reduce feelings of anxiety. Nonetheless, both social and physical pain have been suggested to have some overlapping neural mechanisms (however see Iannetti et al., 2013, for a review of the differences). Similar to physical pain, the brain responds to social pain (exclusion) by releasing endorphins to buffer against the unpleasant emotional experience (Hsu et al., 2013).

Pain perception is altered following chronic use of opioid drugs. Studies have consistently reported a heightened sensitivity to physical pain in chronic opioid users (Compton, Charuvastra, & Ling, 2001; Higgins, Smith, & Matthews, 2018; Lee, Silverman, Hansen, Patel, & Manchikanti, 2011; Mao, 2002; Pud, Cohen, Lawental, & Eisenberg, 2006). Increased opioid tolerance via the downregulation of endogenous opioid receptors has been suggested to underpin opioid-induced hyperalgesia (Higgins et al., 2018; Mao, 2002). As physical and social pain share some similar neural mechanisms (Eisenberger, 2015; Hsu et al., 2013), it is plausible to suggest that alterations in opioid receptor function could similarly cause a heightened sensitivity to social, as well as physical, pain. To our knowledge, only one study has investigated the link between chronic opioid use and the experience of social pain in non-intoxicated opioid users, and found a heightened cortisol response to social exclusion (Kroll et al., 2019). They also reported lower heart rate variability in opioid users, which is linked to poorer emotion regulation and is also observed in other psychological disorders, alongside lower positive affect that did not alter as a consequence of social exclusion. We do not yet know how the acute use of opioids affects response to social exclusion and empathy in opioid users, which may be a powerful factor in maintaining problematic substance use.

Therefore, the current study aimed to investigate alterations in social functioning by measuring empathy and responses to social exclusion among individuals with histories of chronic opioid use. We aimed to examine both the acute and long-term effects of opioids in people prescribed an opioid substitution medication (OSM), by testing people who have recently taken their OSM at the time of testing (‘treated’), and people who had not taken their medication for at least 12 hours (‘non-treated’). For methadone, plasma concentrations peak after four hours, and the half-life of methadone is approximately 25 hours in those who receive regular, repeated doses (Electronic Medicines Compendium, 2019b). For buprenorphine, peak plasma concentrations occur 90 minutes after administration and there is a half-life of 32 hours (Electronic Medicines Compendium, 2019a). For both methadone and buprenorphine, subjective effects are suggested to decline after 9 hours of administration, and in high dose cases may not return to baseline until 48 hours post-drug administration in healthy volunteer studies (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994). The same study reported physiological effects such as

restricted pupil diameter caused by these drugs are still present at 24 hours, however this returns to normal by 96 hours; they did not report changes in heart rate or blood pressure. In those on an OSM, mood disturbances (anger depression, fatigue, and tension) have been shown to be lowest at the peak drug effects (4 hours), and increase over 24 hours until the next dosing time (Kuhlman Jr, Levine, Johnson, Fudala, & Cone, 1998).

Based on previous research showing deficits in empathy in opioid users, we hypothesised that both of the opioid user groups would show impairments in empathy; however, given evidence that acute opioid use is associated with impaired emotional empathy (Stange et al., 2017; Tomei et al., 2017), we predicted that emotional empathy would be most impaired in the treated opioid user group. Secondly, we hypothesised that the treated user group would have a dampened response to social exclusion - based on the analgesic effects of opioids and the assertion that physical and social pain are related. Specifically for cortisol, we hypothesised that both the non-treated and control group would show an increase in cortisol in response to social exclusion, however this would be greater for the non-treated group and would not reduce as quickly as the controls over time, whilst the treated group would show no change in cortisol as a response to social exclusion. We further predicted that the non-treated user group would be more subjectively affected by social exclusion given the hyperalgesia to physical pain seen in non-intoxicated opioid users.

3.2 Methods

3.2.1 Design and participants

Sixty-four participants (39 males; 24 females; 1 non-binary) aged 22-67 (*M*=42.69, *SD*=11.54) were recruited into the study. Forty were opioid users currently stabilised on OSM (methadone or buprenorphine), and all had histories of illicit heroin use. Of these, 20 individuals took their opioid prescription in the morning of the study (intoxicated group), and 20 individuals had taken their prescription >12 hours ago (non-treated group). Group membership was validated with tests of salivary opioid levels. The remaining 24 individuals were opioid-naïve controls with no history of opioid use. Groups were matched in age, gender, and verbal IQ.

Participants were recruited via word of mouth and advertisements in drug services and employment/training agencies.

The study was a mixed design. Inclusion criteria for the opioid groups were: a prolonged history of opioid use and currently taking daily OSM. General inclusion criteria were: being a minimum of 18 years old and a fluent English speaker. Exclusion criteria were: neurological conditions; history of severe mental health issues; diagnosis of a physical illness that directly influences cortisol activity (i.e. Cushing or Addison disease); taking oral steroid medication; pregnancy. Individuals were excluded from the control group if they had any history of opioid use. Participants were asked to abstain from alcohol and drugs 24 hours prior to their study session, and abstain from smoking or eating for 45 minutes prior to their session. The study was reviewed by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki, all participants gave written, witnessed, informed consent.

3.2.2 Measures

Multifaceted Empathy Test (MET) (Dziobek et al., 2008). This computerised task indexes cognitive and emotional empathy (see also Chapter 2 Section 2.3 for figure). Forty photographs of people with emotionally charged expressions are given in eight blocks consisting of ten pictures each. In half of these blocks, participants are asked to identify the correct emotion of the subject in each scene (cognitive empathy). In the other half, participants were asked to rate how much they empathise with the individual in each scene (emotional empathy). Each image was presented until the participant gave a response, and participants were asked to respond as quickly as possible. The task lasted approximately 15 minutes. Responses for cognitive empathy were the total count of correctly identified emotions, while responses for emotional empathy were the mean empathy score.

The Cyberball Game (Williams, Yeager, Cheung, & Choi, 2012). This is a computerised ball-tossing game shown to simulate social exclusion (see also Chapter 2 Section 2.3 for figure). Participants are told that they are playing real people on a virtual network in a mental visualisation experiment, yet unbeknown to them the other players are fictitious and were set up to socially exclude them. In the present study, the Cyberball Game contained four players, and had two conditions

that simulated either social inclusion or exclusion. There were two games: inclusion followed by exclusion, and each game lasted between two to four minutes. Each condition had approximately 60 ball throws between the four players. In the social inclusion condition, participants were over-included and received 20±1 (~33.3%) of 60 ball throws. In the exclusion game, participants received exactly 6±1 (~10%) of 60 ball throws.

Affective and physiological responses to social inclusion and exclusion were recorded after each game with the Post-ostracism Cyberball Questionnaire (POCQ) (POCQ; Williams et al., 2002), which assessed mood and basic psychological needs (see Chapter 2 Section 2.3 for more details).

Physiological Measures. Seven saliva samples were collected by passive drool method. Participants were required to provide approximately 2ml of saliva, which was immediately stored at -80°C until analysis using enzyme-linked immunosorbent assay (ELISA) kits to assess cortisol levels, as well as levels of methadone, buprenorphine, and opiates (baseline sample only). Heart rate was also assessed alongside each saliva sample (see Appendix 3.1 for more details).

3.2.3 Questionnaires

Interpersonal Reactivity Index (IRI; Davis, 1980). This 28-item scale assesses trait empathy, and differentiates between self-reported cognitive and emotional empathy. It consists of four different subscales, two of which characterise emotional empathy (empathic concern; personal distress), and the subsequent two characterise cognitive empathy (perspective taking; fantasy scale). Responses were recorded on a 5-point Likert scale (A = does not describe me well; E = describes me very well).

The Life Events Checklist Version 5 (LEC-5; Weathers et al., 2013). This 17-item questionnaire assesses whether participants have been previously exposed to any stressful or traumatic life events, and how proximal these events were to the participant (‘happened to me’; ‘witnessed it’; ‘learned about it’; ‘part of my job’; ‘not sure’; ‘doesn’t apply’). This questionnaire was adapted in the current study to include age when event occurred so that responses could be categorised into childhood, pre- to mid-adolescence, and adult trauma. Responses were further categorised into

interpersonal (e.g. physical or sexual abuse) and non-interpersonal (e.g. transportation accident, or fire).

UCLA Loneliness Scale (Russell, 1996). This 20-item scale assesses feelings of social isolation and loneliness. Responses were recorded on a 4-point scale (1 = never; 4 = often).

Craving. A 100mm visual analogue scale (VAS) was used to assess craving for opioid drugs following each Cyberball game. It included three, single items that assessed drug liking, wanting, and motivation to obtain opioid drugs – a method of which has been frequently used in the past with high validity (Pool, Sennwald, Delplanque, Brosch, & Sander, 2016). The term 'opioid drugs' was used to cover craving for any opioid-acting drug; such as methadone, buprenorphine, and heroin.

Spot-the-Word Test (Baddeley, Emslie, & Nimmo-Smith, 1993). This test was used to assess verbal IQ by presenting participants with 60 word-pairs. In each pair, one word was real and one word was made up, and participants were asked to identify the real word in each pair.

Positive and Negative Affect Schedule (Watson, Clark, & Tellegen, 1988). A 10-item questionnaire measuring positive and negative affect recorded on a 5-point Likert scale (1 = not at all; 5 = very much).

3.2.4 Procedure

Participants arrived in the afternoon between the times of 1-1.30pm to control for diurnal variation in cortisol, and testing lasted for approximately two hours. All procedures and approximate timings are depicted in figure 3.1.

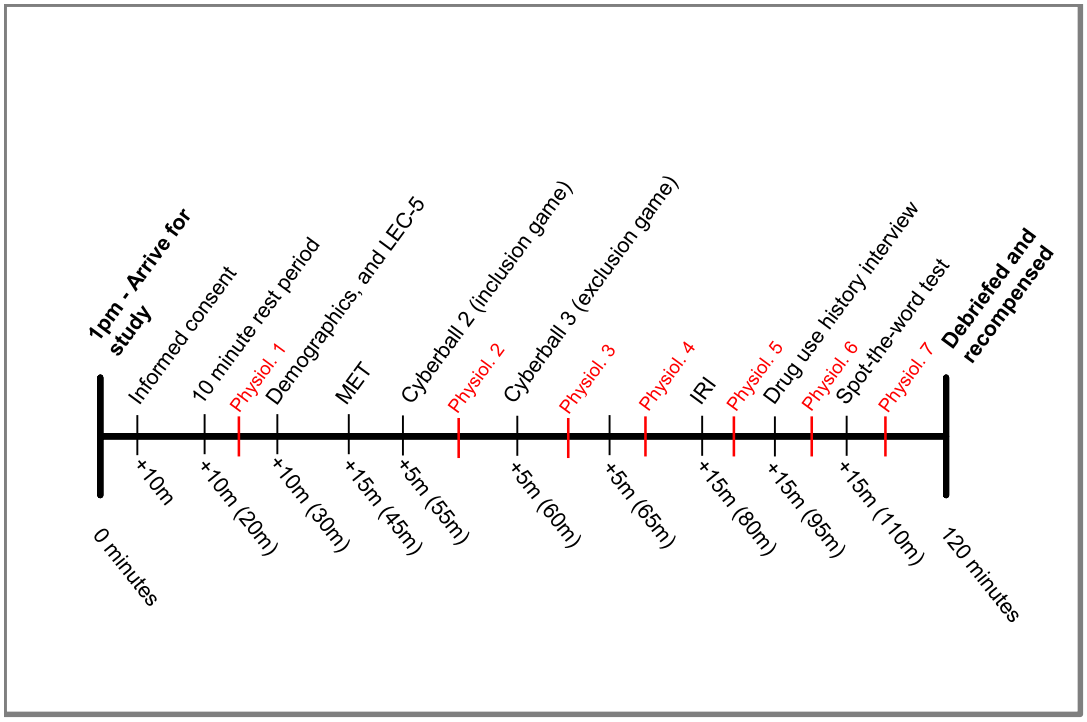


Figure 3.1. Study procedures in sequential order and accompanied by approximate timings. There were seven time points where physiological measures (salivary cortisol and blood pressure) were collected, and are labelled 'Physiol.' in red. (IRI = Interpersonal Reactivity Index, MET = Multifaceted Empathy Test, LEC-5 = Life Events Checklist version 5).

Upon completion of all procedures, participants were fully debriefed on the true nature of the study, and given an opportunity to ask any questions. Participants were remunerated for their participation with a voucher.

3.2.5 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 23 and Mplus version 8. Assumptions of parametric tests including normality were checked, extreme outliers were winsorized (Wilcox, 2005) and random missing values were imputed by group mean substitution.

A series of one-way, between-subjects ANOVA's were used to assess the effect of Group on both emotional and cognitive empathy. For the Cyberball Games, subjective responses to social exclusion were analysed using a series of 3x2 mixed measures ANOVA's assessed the effects of Group and Inclusion Status on subjective measures (the POCQ and craving). For the cortisol and heart rate, latent

growth curve models (LGCM) were used to understand the between-person difference in the trajectory of responses over time in respect to the average trend (Muthén & Curran, 1997; Willett & Sayer, 1994), and encompasses features of both structural equation modelling and repeated measures ANOVA (Duncan, Duncan, & Strycker, 2013) (described in Appendix 3.2). This statistical approach was taken because the data had multiple time points, and we were aiming to investigate differences in the overall trend over time in response to social exclusion between the groups over specific time points.

Any significant interactions were investigated further using post-hoc t-tests, which were adjusted using the Holm-Bonferroni correction. Differences between groups in demographic information was analysed using t-tests, Chi-square tests where data was categorical, and the Kruskal-Wallis test (groups$\geq$3) or Mann Whitney U (groups$\leq$2) test where data was non-parametric. Pearson's correlations were used to assess statistical relationships, and Spearman's correlations were used when normality was violated.

Latent Growth Curve Modelling (LGCM). To investigate if the levels of opioid exposure ('Group') were associated with different physiological response trajectories throughout the tasks, we applied LGCM using Mplus (Muthén & Muthén, 2000) (the growth model procedure is described in more detail in Appendix 3.2). Model fit was assessed using the comparative fit index (CFI), the Tucker-Lewis index (TLI), the root mean squared error of approximation (RMSEA), and the standardized root mean square residual (SRMR). Improvements in the model were assessed using both the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC). The Robust Maximum Likelihood Estimation (MLR) was used for each model.

3.3 Results

3.3.1 Demographics and drug use (Table 3.1)

Groups were matched in age, gender, ethnicity, alcohol use, verbal IQ, baseline positive affect, and familial history of substance abuse problems and mental health problems. There were differences in the number of diagnosed mental health problems, with increased incidence of mental health problems in the non-treated

opioid users compared to controls (χ^2=11.13, *p*=.004), but no other significant differences (Holm-Bonferroni corrected). Although there was an overall group difference in age individuals left education and baseline negative affect, after correction for multiple comparisons there were no significant group differences.

There was a significant difference in the number of months taking an OSM between the two opioid user groups, with a greater number of months on OSM in the treated users (see Table 3.1). There was no significant differences in OSM dose, but there was a significantly greater number of hours since taking OSM in the non-treated group (as expected). There were significant group differences in substance use for opioids, tobacco, cannabis, and cocaine use between both the opioid groups compared with the controls (χ^2=15.02, *p*=.012; χ^2=14.53, *p*=.012; χ^2=7.44, *p*=.042; and χ^2=9.79, *p*=.016, respectively); however, there were no significant differences in illicit substance use between the two opioid user groups (χ^2<0.001, *p*>.999, χ^2=1.29, *p*>.999; χ^2=0.00, *p*>.999; and χ^2=0.11, *p*>.999, respectively) (Holm-Bonferroni corrected). Further details on drug use history can be found in Appendix 3.3.

Table 3.1 *Demographic Information and Drug Use between Groups (Means and Standard Deviations)*

		Treated (n=20)	**Non-treated (n=20)**	**Controls (n=24)**	**Test statistic**	**P-value**
Age		44.45 (11.51)	40.40 (10.04)	43.13 (12.83)	F = 0.64	.533
Gender (male,female,other)		12,8,0	14,6,0	13,10,1	χ^2 = 2.56	.663
Ethnicity (Caucasian, Hispanic, Mixed)		20,0,0	18,1,1	21,0,3	χ^2 = 5.20	.267
Age left education		16.25 (1.55)	15.32 (3.79)	17.65 (3.25)	F = 3.26	.045*
Verbal IQ		47.35 (10.82)	44.89 (8.91)	48.83 (5.76)	F = 1.09	.342
Mental health problems (n=yes)		11	16	8	χ^2 = 11.12	.004**
Diagnosis (n)	Depression	10	14	6		
	Anxiety	5	2	1		
	Other	0	2	1		
Physical health problems (n=yes)		6	4	3	χ^2 = 2.04	.360
Antidepressants (n=yes)		7	10	5	χ^2 = 4.72	.095
Oral contraceptives (n=yes)		1	1	0	χ^2 = 1.71	.426
Familial mental health problems (n=yes)		4	6	9	χ^2 = 1.61	.447

Familial substance use disorder (n=yes)	7	4	6	$\chi^2 = 1.04$	.595
Baseline positive affect	28.33 (7.50)	29.72 (8.17)	29.92 (7.13)	F = 0.25	.779
Baseline negative affect	14.16 (5.56)	15.45 (6.20)	11.71 (2.94)	F = 3.23	.046*
Opioid substitution medications (OSM)					
Medication, n (methadone, buprenorphine, other)	16,1,3	12,6,2		$\chi^2 = 4.34$	.114
Dose (standardised to oral morphine[b], mg)	28.78 (17.24)	36.43 (19.32)		F = 1.75	.194
Months taken OSM	60.00 (173.25)[a]	12.00 (31.00)[a]		U =106.0	.011*
Hours since taken OSM	3.92 (2.01)	23.41 (7.65)		F =114.19	<.001***
Current regular drug use (n)					
Illicit opioids	9	9	0	$\chi^2 = 15.03$	.001
Alcohol	11	12	13	$\chi^2 = 0.17$	.919
Tobacco	14	17	7	$\chi^2 = 15.46$	<.001***
Cannabis	8	8	2	$\chi^2 = 7.44$	.024*
Benzodiazepines	3	3	0	$\chi^2 = 3.97$	.137
Cocaine	7	6	0	$\chi^2 = 9.94$	.007**
Salivary opioid screens	**n=20**	**n=20**			
Methadone, n=positive, % due to opioid prescription	16, 100%	13, 83.3%			
Buprenorphine, n=positive	0	1, 100%			
Opiates, n=positive	6, 33.3%	1, 0%			
Urine drug screens	**n=20**	**n=15**	**n=24**		
Methadone, n=positive	14	10	0		
Opiates, n=positive	9	8	0		
Cannabis/THC, n=positive	6	5	3		
Cocaine, n=positive	5	5	2		
Amphetamine, n=positive	1	1	2		
Benzodiazepines, n=positive	3	7	0		
MDMA, n=positive	0	1	0		

Note. [a] non-parametric data: median and IQR are reported
[b] the equivalent doses are an approximation and calculated from the following sources (Foley, 1985; Royal College of Anaesthetists, 2018).
Current regular use of MDMA, amphetamines, and hallucinogens were excluded from the table due to minimal numbers.
* $p<.05$, ** $p<.01$, *** $p<.001$.

3.3.2 Empathy

The Multifaceted Empathy Test (MET). For emotional empathy, there was a significant difference in Group ($F(2,61)=3.52$, $p=.036$, $\eta^2=.10$). Holm-Bonferroni t-tests indicated the non-treated user group scored significantly lower than the controls ($t(42)=2.64$, $p=.048$, $\eta^2=.14$) (figure 3.2), however there were no significant differences between the non-treated users and the treated users ($t(38)=1.91$, $p=.128$, $\eta^2=.09$) or the treated users and controls ($t(42)=0.40$, $p=.688$, $\eta^2<.01$). Emotional empathy to either positive or negative affect was also explored (all analyses were Holm-Bonferroni corrected). For emotional empathy for positively valenced emotions, there was an effect of group ($F(2,61)=6.39$, $p=.024$, $\eta^2=.17$), where the non-treated group rated significantly lower than controls ($t(42)=4.03$, $p=.002$, $\eta^2=.28$). There were no significant differences between the treated and non-treated users ($t(38)=1.53$, $p=.512$, $\eta^2=.06$) or treated users and controls ($t(42)=1.78$, $p=.415$, $\eta^2=.07$) (Fig. 3). For negative affect, there were no significant differences between groups ($F(2,61)=1.99$, $p=.512$, $\eta^2=.06$).

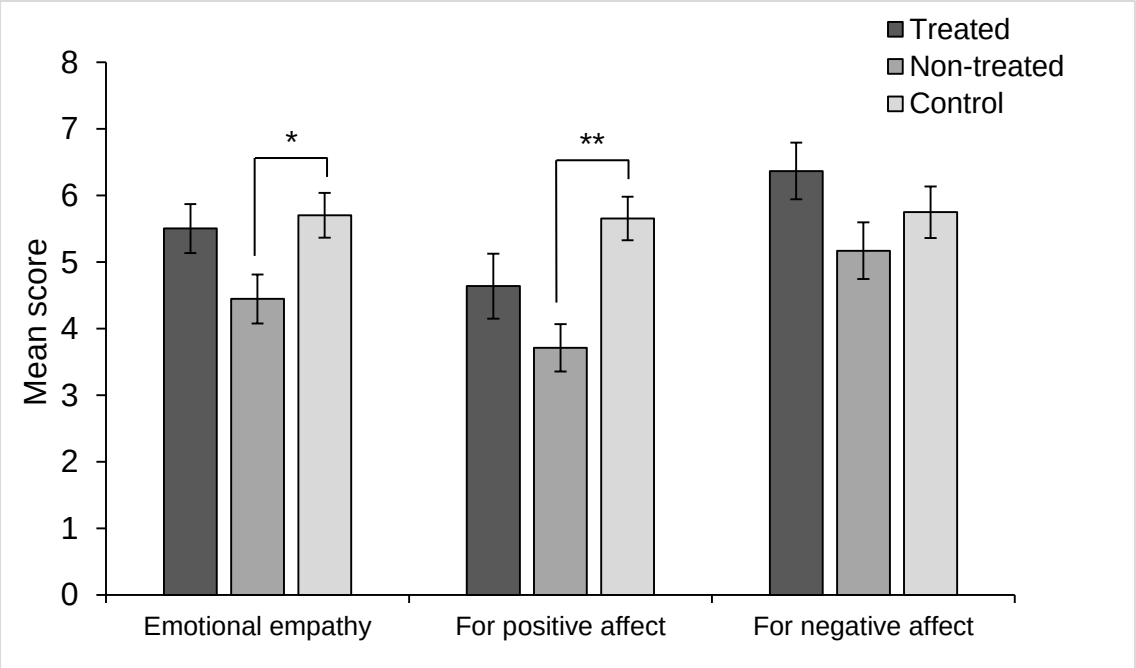


Figure 3.2. Emotional empathy on the MET between the three groups. There were significantly lower emotional empathy overall in the non-treated opioid user group compared with the controls (*p<.05). When broken down into positive and negative affect, there were significant lower levels of emotional empathy for positive emotions in the non-treated user group compared with controls (**p<.01), however there were no differences between the treated users and controls, or any group differences in negative affect. Error bars represent ± 1 SEM.

When assessing cognitive empathy, there were no significant differences between the three groups (F(2,56)=1.76, *p*=.182, η^2=.04). Number of words known in the MET was included as a covariate in this analysis due to being correlated with cognitive empathy (r=.55, n=60, *p*<.001). There were no significant group differences in cognitive empathy for positive or negative affect (F(2,61)=1.07, *p*=.696, η^2=.03 ,and F(2,61)=1.03, *p*=.696, η^2=.03, respectively) (Holm-Bonferroni corrected). (Table 3.2).

Table 3.2. *Means and Standard Deviations for the Empathy Measures between the Groups.*

		Treated	Non-treated	Controls
Multifaceted Empathy Test (MET)				
EE	Total	5.50 (1.80)	4.45 (1.70)	5.70 (1.46)
	Positive affect	4.64 (2.19)	3.71 (1.59)	5.65 (1.60)
	Negative affect	6.37 (1.83)	5.17 (2.15)	5.75 (1.71
CE	Total	26.50 (3.19)	24.60 (4.48)	24.83 (3.56)
	Positive affect	15.85 (1.73)	14.80 (2.78)	14.96 (2.69)
	Negative affect	10.65 (2.25)	9.80 (2.61)	9.88 (1.36)
Interpersonal Reactivity Index (IRI)				
EE	Empathic concern	4.02 (0.68)	3.91 (0.73)	3.97 (0.68)
	Personal distress	2.66 (0.80)	2.61 (0.67)	2.58 (0.76)
CE	Perspective taking	3.67 (0.71)	3.36 (0.81)	3.44 (0.71)
	Fantasy	3.28 (0.95)	2.81 (0.62)	3.16 (0.99)

Note. EE denotes 'emotional empathy' and CE denotes 'cognitive empathy'

The Interpersonal Reactivity Index (IRI). For emotional empathy subscales, there were no significant group differences in 'empathic concern' (F(2,61)=0.14, *p*=.871, η^2=.01) or 'personal distress' (F(2,61)=0.05, *p*=.950, η^2<.01). For cognitive empathy subscales, there were no significant group differences in 'perspective

taking' ($F(2,61)=0.95$, $p=.394$, $\eta^2=.03$) or 'fantasy' ($F(2,61)=1.62$, $p=.206$, $\eta^2=.05$) (Table 3.2).

3.3.3 Social distress after exclusion

For the Cyberball Task, there were significant main effects of Inclusion status which reflected decreases in mood, self-esteem, control, meaningful existence, and sense of belonging following exclusion, as well as increases in hurt feelings. However, there were no significant effects of Group, or interaction between Inclusion status and Group (Table 3.3).

Table 3.3. *Statistical Outcomes for the Cyberball Subscales and Opioid Craving.*

	Inclusion status	**Treated**	**Non-treated**	**Control**	**F-Statistic**		***p* value**	**η^2**
ΔMood	Inclusion	2.49 (1.04)	2.27 (1.35)	2.62 (0.83)	Group	1.95	.151	.03
	Exclusion	1.65 (1.92)	0.36 (2.03)	0.95 (1.74)	Inclusion status	39.00	<.001***	.18
					Group*inclusion status	1.79	.176	.02
Self-esteem	Inclusion	3.02 (1.33)	2.80 (1.23)	3.44 (0.95)	Group	1.63	.205	.09
	Exclusion	2.41 (1.31)	1.87 (0.85)	2.25 (0.89)	Inclusion status	47.28	<.001***	.39
					Group*inclusion status	1.68	.196	.03
Sense of belonging [c]	Inclusion	1.35 (0.48)	1.32 (0.71)	1.14 (0.28)	Group	0.77	.466	.02
	Exclusion	2.45 (1.43)	2.92 (1.48)	2.53 (1.13)	Inclusion status	69.46	<.001***	.52
					Group*inclusion status	0.74	.480	.01
Meaningful existence [c]	Inclusion	0.09 (1.78)	0.11 (0.16)	0.03 (0.08)	Group	2.23	.116	.03
	Exclusion	0.34 (0.22)	0.35 (0.26)	0.26 (0.21)	Inclusion status	52.13	<.001***	.28
					Group*inclusion status	<.01	.996	<.01
Control [c]	Inclusion	0.30 (0.20)	0.31 (0.20)	0.38 (0.17)	Group	1.06	.352	.02
	Exclusion	0.18 (0.22)	0.09 (0.16)	0.16 (0.20)	Inclusion status	68.12	<.001***	.20
					Group*inclusion status	1.97	.148	.01
Hurt feelings [c]	Inclusion	0.02 (0.07)	0.02 (0.11)	0.02 (0.08)	Group	0.20	.822	<.01
	Exclusion	0.19 (0.27)	0.23 (0.27)	0.19 (0.25)	Inclusion status	32.25	<.001***	.19
					Group*inclusion status	0.09	.910	<.01
% of perceived ball throws	Inclusion	32.93 (10.75)	38.62 (23.12)	41.47 (19.81)	Group	0.91	.409	.01
	Exclusion	15.27 (9.87)	11.14 (6.24)	16.03 (11.18)	Inclusion status	62.61	<.001***	.39

					Group*inclusion status	0.97	.386	.01
ΔMood [d] (baseline to exclusion)	Baseline	14.35 (8.91)	13.83 (11.05)	18.21 (9.52)	Group	0.68	.508	.02
	Exclusion	7.22 (14.06)	6.44 (12.09)	8.58 (12.41)	Inclusion status	32.06	<.001***	.11
					Group*inclusion status	0.43	.652	<.01

Note. ΔMood was calculated by subtracting negative affect scores from overall positive affect scores. The adjectives used to compute positive mood in the POCQ were: good; happy; friendly; relaxed, whilst negative mood were: bad; sad; unfriendly; tense.

[c] Log transformation was applied. Mean values are adjusted for the log transformation

[d] ΔMood (baseline to exclusion) is a manipulation check that Cyberball exclusion condition caused reductions in mood from baseline (using responses on the PANAS rather than mood assessed by the POCQ).

For Anger, there was a significant interaction between Inclusion Status and Group ($F(2,61)=5.42$, $p=.007$, $\eta^2=.10$). Holm-Bonferroni corrected pairwise comparisons indicated that there was a significant difference in anger between the non-treated user group with the treated group ($p<.001$) and controls ($p<.001$), however there were no significant differences between the treated group with controls ($p=.561$) (figure 3.3). There was also a main effect of Inclusion status ($F(1,61)=14.11$, $p<.001$, $\eta^2=.13$), alongside a main effect of Group ($F(2,61)=12.12$, $p<.001$, $\eta^2=.24$). There were no effects of Group or Inclusion status on opioid craving (Appendix 3.4).

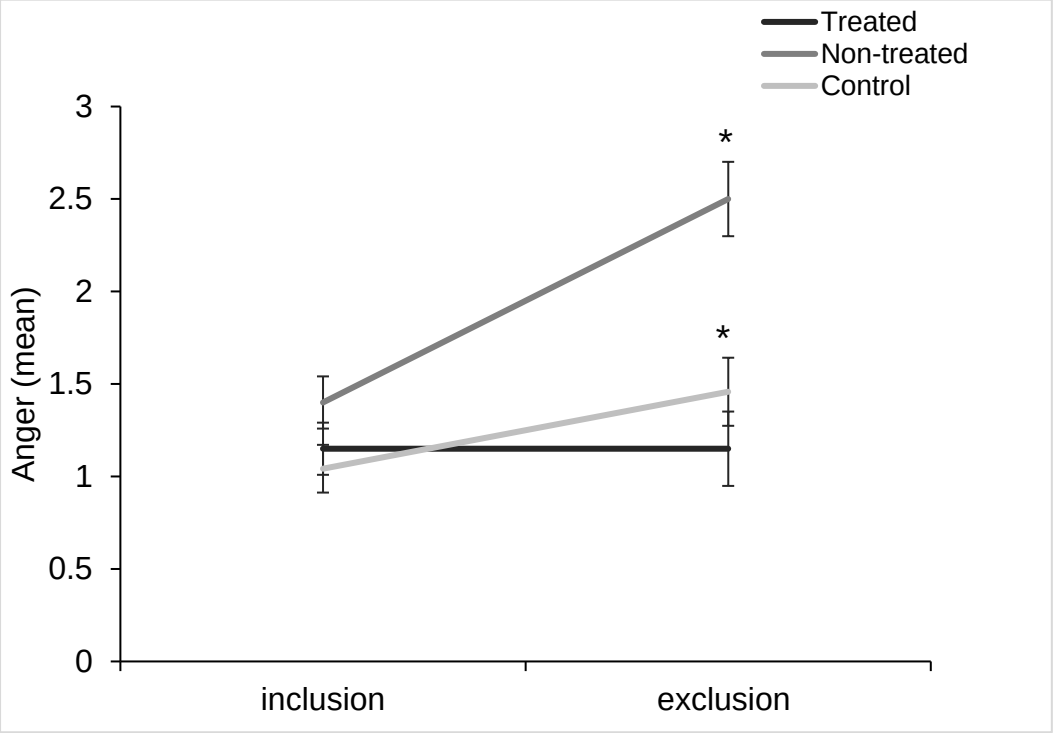


Figure 3.3. Anger following the inclusion and exclusion games between the three groups. Both the non-treated opioid user group and the controls significantly increase in anger from inclusion to exclusion, whilst the treated opioid user group remain the same. There was also a significant main effect of inclusion status, and a significant main effect of group. (*$p<.05$). Error bars represent ± 1 SEM.

3.3.4 Physiological responses

Salivary Cortisol. The LGCM with continuous latent variables of intercept for cortisol at minute 0 (baseline) and a quadratic slope as outcome between minutes 0-119 including dummy-coded Group as the covariate revealed a good fit $\chi^2(22)=34.54$, $p=.043$, CFI=.94; TLI=.93; SRMR=.07; RMSEA=.09, 90%CI

[0.02,0.15]; AIC=-1064.34; aBIC=-1027.66. Being treated by opioids was negatively related with the intercept at 0 minutes (*b*=-0.07, SE=0.03, *p*=.016), suggesting treated users had lower cortisol levels at baseline compared to the controls, but there were no effects for the non-treated group (*b*=-0.01, SE=0.04, *p*=.759) who showed similar cortisol levels as the controls (figure 3.4a). In addition, there were significant effects of the treated group when the intercept was set at minutes 46 (post-inclusion), 60 (post-exclusion), 85 (recovery period), and 101 (recovery period) (see Appendix 3.5 for the data) indicating that treated users had lower cortisol responses throughout social exclusion and recovery in comparison to the non-treated and controls. Neither being treated (*b*=0.01, SE=0.01, *p*=.326) nor being non-treated (*b*<0.01, SE=0.01, *p*=.690) was associated with the slope, suggesting that the trajectory of cortisol over time was not associated with acute opioid state.

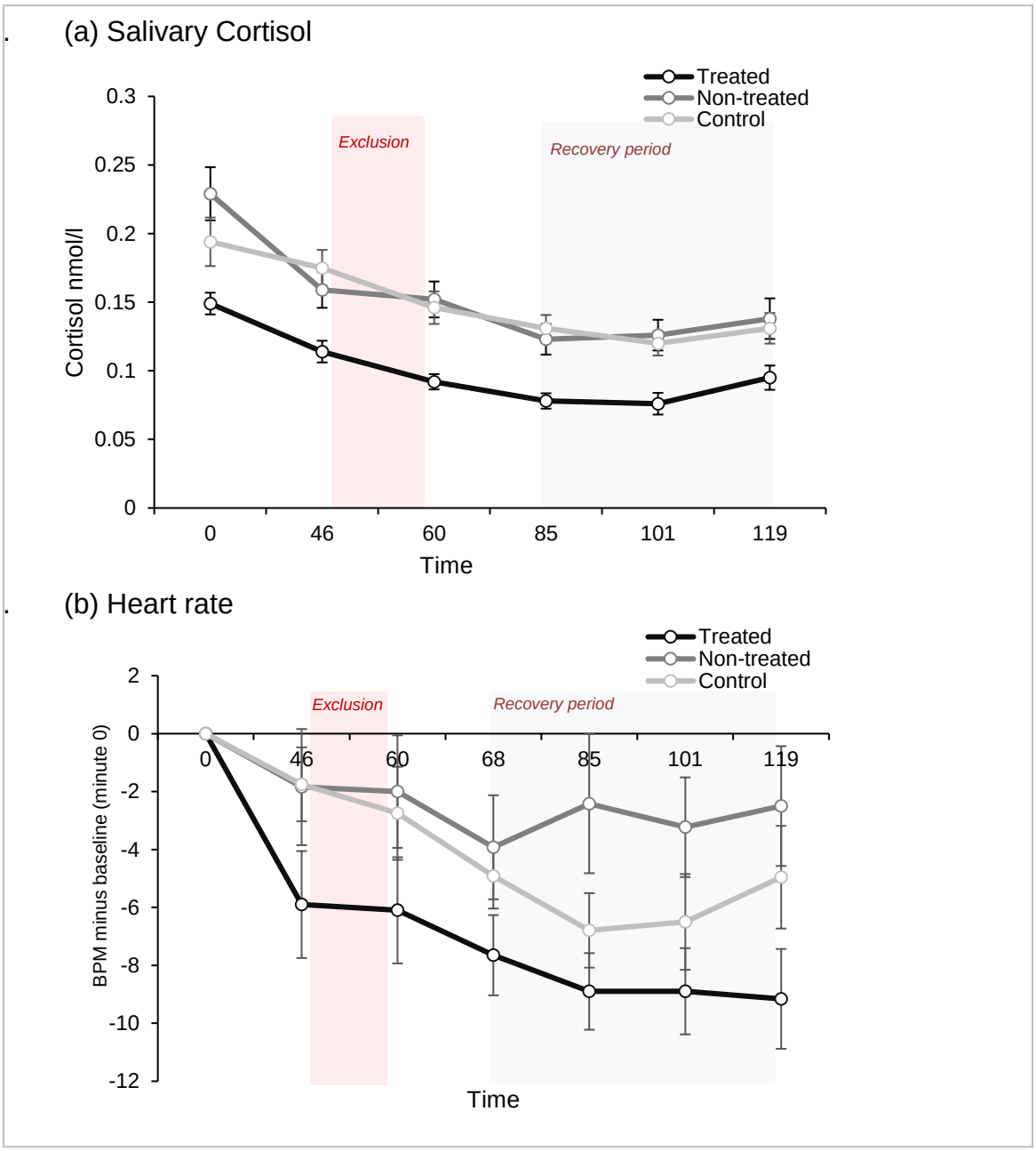


Figure 3.4. Physiological responses between the three groups over the seven time points for (a) cortisol and (b) heart rate. Error bars represent ± 1 SEM.

Heart rate. A piecewise LGCM with continuous latent variables of intercept, with one linear slope from 46-68 minutes (the Cyberball paradigm) and the second linear slope from 85-119 minutes (post-exclusion recovery period) in heart rate change, including Group and interpersonal trauma as a covariate revealed the best and an overall acceptable fit $\chi^2(21)=36.73$, $p=.018$, CFI=.95; TLI=.92; SRMR=.04; RMSEA=.12, 90%CI [0.05,0.18]; AIC=2008.64; aBIC=2056.81. Being treated had a

significant negative effect on the intercept at 46 minutes (*b*=-4.77, SE=2.17, *p*=.028) (figure 3.4b), suggesting lower heart rate at baseline. In addition, there were significant effects of the treated group when the intercept was set at minutes 60 & 101, and minutes 68 & 119 (see Appendix 3.5) indicating that treated users had less change in heart rate throughout social exclusion and recovery in comparison to the non-treated and controls. There were no significant slope effects but the treated user group had a near-significant effect on the linear slope between 46-68 minutes (*b*=1.04, SE=0.55, *p*=.057), and a similar trend was observed in the non-treated user group (*b*=1.26, SE=0.71, *p*=.075) suggesting a gentler downward slope compared with the control condition. There was also a trend to suggest the effect of the treated user group on the linear slope between 85-119 minutes (*b*=-1.46, SE=0.84, *p*=.081), suggesting smaller change during the recovery period compared with the controls. Rates of interpersonal trauma did not exert any significant effects on the intercept or slopes although adding it improved overall model fit.

3.3.5 Social risk factors

When assessing trauma history, there was a trend to suggest a Group difference in interpersonal trauma during early childhood and adulthood, however this did not reach the statistical threshold for significance (Table 3.4). There was an effect that approached significance to suggest a group difference in loneliness, with the treated user group scoring the highest, followed by the non-treated users and controls. There were no significant group differences in rates of non-interpersonal trauma.

Table 3.4 *Differences between Groups in Trauma History and Loneliness.*

	Treated users	Non-treated	Controls	Test statistic	*p*-value
Interpersonal trauma (n=yes)					
Childhood (ages 0-9)	3	6	1	χ^2=5.53	.063
Pre-mid adolescence (10-17)	8	9	8	χ^2=0.64	.728
Adulthood (18+)	12	14	9	χ^2=4.98	.083
Non-interpersonal trauma (n=yes)					
Childhood (ages 0-9)	1	5	5	χ^2=3.17	.205
Pre-mid adolescence (10-17)	9	6	5	χ^2=2.99	.225
Adulthood (18+)	11	15	13	χ^2=2.42	.298
Loneliness score	53.33 (10.31)	48.16 (9.36)	46.18 (10.35)	F=2.78	.070

Note. Interpersonal trauma consisted of: Physical assault; sexual assault; unwanted sexual experiences; held captive; caused harm to others.
Non-interpersonal trauma consisted of: natural disasters; fire; transportation accident; serious accident; exposure to toxic chemicals; in combat; serious illness; observing human suffering; violent death; accidental death.
Age groups were based on: Wolitzky-Taylor, K., Sewart, A., Vrshek-Schallhorn, S., Zinbarg, R., Mineka, S., Hammen, C., ... & Craske, M. G. (2017). The effects of childhood and adolescent adversity on substance use disorders and poor health in early adulthood. *Journal of Youth and Adolescence, 46*(1), 15-27.

3.3.6 Exploratory analyses

Emotional empathy was not correlated with the total months taking an OSM (r^S=-.372, n=20, *p*=.424) or hours since the OSM was taken (r=-.159, n=15, *p*>.999) within the non-treated group, nor was it correlated with rates of mental health problems over the sample (r=.03 n=63, *p*>.999) (alpha criterion is Holm-Bonferroni corrected for multiple comparisons). There was a medium effect size for the association between emotional empathy deficits and OSM dose within the non-treated user group, however it failed to reach significance (r=-.49, n=20, *p*=.203).

Negative affect at baseline was not significantly related to emotional empathy for positive emotions (r=-0.04, n=63, *p*=.773) or change in anger from inclusion to exclusion (r=-0.07. n=63, *p*=.606).

3.4 Discussion

The current study aimed to assess empathy and responses to social exclusion among individuals with opioid use disorder. We found lower emotional empathy (i.e. the ability to vicariously experience the emotional state of others) specifically for

positively-valenced emotions among non-treated opioid users compared with opioid-naïve controls. Non-treated opioid users also expressed significantly greater anger after being socially excluded compared to the treated user group and controls. On the other hand, treated opioid users showed lower salivary cortisol and heart rate across the testing session; however, they did not differ in the level at which cortisol and heart rate particularly increased or decreased in response to social exclusion.

The finding of lower emotional empathy in the non-treated users partially replicates previous research suggesting impaired empathy among drug users (Ferrari et al., 2014; Kroll et al., 2018; Maurage et al., 2011; Preller et al., 2014) and opioid users specifically (Kroll et al., 2018; Stange et al., 2017; Tomei et al., 2017), but crucially highlighted that acutely treated opioid users show intact emotional empathy compared to controls. This was contrary to our initial prediction that empathy would be lowest within the treated user group. Previous work in healthy participants has connected higher levels of endogenous opioids with decreased empathy for pain, possibly due to a decreased sensitivity in the ability to feel pain in oneself (Rutgen et al., 2015); therefore it has been suggested that the use of analgesic drugs like opioids could also reduce empathy more broadly. Our results suggest that this is not the case in this group of chronic opioid users and, in fact, the on-board opioids appear to repair their empathy to the level of controls, whereas non-treated users showed impairments – specifically for positive emotions. There was a medium to large effect size for the correlation between opioid substitution medication (OSM) dose and emotional empathy deficits, potentially indicating a dose-dependent reduction in emotional empathy within the non-treated group that was not driven by outliers. However, this should be interpreted with caution, as this relationship was using a small sample size and was non-significant after adjusting the α for multiple comparisons. Further work should investigate whether there is a dose dependent relationship between opioid use and the extent of empathy impaired when not intoxicated with opioids.

The specific impairment in empathy for positive emotions was demonstrated previously in a similar study with opioid users (Kroll et al., 2018). This suggests a possible negative bias where relating to positive emotions is more difficult for opioid users not currently experiencing the acute effects of opioids. Prior research has suggested that abstinent opioid addicts are biased when attending to negative

emotions, where they show enhanced detection of negative expressions during a visual search paradigm (Zhou et al., 2012). This bias is potentially due to greater exposure to negative expressions and reactions from society in everyday life, as well as impaired emotion processing that could predate addiction (Zhou et al., 2012). Additional to this, distress intolerance – the inability to endure difficult emotional states – is associated with greater attentional bias towards negative emotions and decreased attention toward positive emotions (Macatee, McDermott, Albanese, Schmidt, & Cougle, 2018). Opioid users on an OSM show greater trait distress intolerance (Kathryn McHugh & Otto, 2012), where opioids may heighten the threshold to cope with difficult emotional states. The empathy deficit for positive emotions in the non-treated users may therefore be due to reduced exposure to positive emotions in everyday life and reduced attention towards them. Opioid intoxication may serve to remediate emotion difficulties by increasing distress tolerance and enhancing their ability to relate to positive emotions.

The study also reported a novel finding of increased rates of anger following social exclusion in the non-treated opioid users, compared to the treated user group and controls. Past research has linked anger expression with endogenous opioid functioning, suggesting that increased anger expression may be related to an impaired endogenous opioid response to stress (Bruehl, Chung, Burns, & Diedrich, 2007). Preclinical evidence supports this assumption, finding that opioid blockade using naltrexone has shown to increase rates of anger and pain (Bruehl, Burns, Chung, & Quartana, 2008; Burns et al., 2009). As the non-treated user group in the current study may have a dampened endogenous opioid response, this could possibly account for the large increase in anger after being socially excluded. The treated user group may experience no change in anger as the acute effects of opioids buffer them from this unpleasant emotional state. Higher rates of hostility and anger are related to poor emotion regulation in drug users (Handelsman et al., 2000; Shabanloo, Alimoradi, & Moazedian, 2018). This finding of greater anger, together with impaired empathy, potentially suggests an overall impairment in both understanding and expressing one's own emotions in individuals who have chronically used opioids but are not acutely under the influence of them. It could suggest that opioids are used to alleviate difficult emotional states such as anger, and heighten users' ability to tolerate social exclusion.

Cortisol and heart rate change were lower in the treated user group, which is to be expected given cardiac depression following opioids (Vargish, Beamer, Daly, & Riggs, 1987) and evidence that opioids can reduce cortisol responses to psychosocial stress (Bershad et al., 2015). Heart rate did not recover (reduce) over the duration of the experiment for the non-treated user group; prior work has indicated the role of the endogenous opioid system in the recovery of the cardiovascular response to stress by reducing heart rate and cortisol (Morris et al., 1990). Heart rate has been linked with emotional and cognitive functions, where lower heart rate variability is related with poorer emotion regulation, higher alcohol craving (Ingjaldsson, Laberg, & Thayer, 2003), and lower empathy (Lischke et al., 2018). Moreover, the groups did not differ in physiological responses to social exclusion and over the recovery period as we expected, which is dissimilar to prior reports of a greater cortisol response to social exclusion in non-treated, non-medically prescribed opioid users (Kroll et al., 2019). A potential difference between the current study and the study by Kroll and colleagues could be that non-medically prescribed opioid users may not encounter stigma and social ostracism as frequently as the illicit opioid users in the current study, and therefore the Cyberball is not extreme enough to induce physiological changes. A psychosocial stressor such as the Trier Social Stress Test (Kirschbaum, Pirke, & Hellhammer, 1993) may produce more robust changes in cortisol and heartrate.

The current findings on empathy broadly concur with impairments observed in a previous study of opioid users by Kroll and colleagues (2018) who also implemented the Multifaceted Empathy Test (MET); however they reported impairments in *cognitive* empathy (i.e. the ability to understand and identify the emotional states of others) among non-medically prescribed opioid users. The discrepancy between the two studies could be due to various differences between our samples: the sample tested by Kroll et al. excluded those with history of heroin abuse, and consequently may have experienced much lower levels of deprivation, poly-drug use and social adversity than our sample. One similarity between the two studies is specific impairment to positive emotions, which could suggest an overall negativity bias across the samples irrespective of socioeconomic or drug use background.

The study had limitations. Firstly, the treated group had been prescribed OSM for more months than the non-treated group; however, the months on OSM were not

correlated with empathy, and the impairment in empathy was within the non-treated group which suggests that this does not account for the key findings of the study. Secondly, the study did not measure symptoms of opioid withdrawal, however this could have been linked with increased distress and anger following rejection in the non-treated group. In addition, high rates of polysubstance and antidepressant use were reported in the opioid user groups, which could have biased the results. Nonetheless, the two opioid groups are well matched in drug use history which indicates a specific effect of opioid intoxication on emotional empathy and post-exclusion anger. The three groups were well matched in other variables, including loneliness and history of childhood adversity. A within-subjects design comparing acute opioid use on empathy and social distress would have reduced the influence of pre-existing group differences, and increased the statistical power. However, this design would have been problematic for a number of reasons: firstly, there would be a high rate of drop out between the sessions within this population; secondly, many individuals prescribed an OSM are only able to take their medication supervised at a pharmacy in the morning; and finally there would not be an opioid-naïve control group. A within-subjects design could be investigated more effectively within a residential treatment, where the study is easily accessible for patients and access to OSM is not restricted to a given time slot. In addition, urinalysis did not test positive for all participants who were using methadone, which potentially suggests the accuracy of this method is limited. A more sophisticated confirmatory method (e.g. liquid chromatography) could have been useful in confirming exact levels of opioids in urine or saliva at the time of testing.

In summary, the current study provides both novel findings and supporting evidence for altered social functioning among opioid users. Blunted subjective anger in response to stress and lower cortisol and heart rate was observed in treated users, which partially supports the notion that opioids could cause hyperalgesia to social pain. Impaired emotional empathy and increased rates of anger among opioid users who are not currently treated with opioids may be due to an attentional bias toward negative expressions and poorer ability to tolerate difficult emotions, which is repaired by the use of opioids. With this knowledge, potential treatments for opioid use disorder should focus on heightening one’s ability to tolerate difficult social

situations in a wider attempt to improve social skills, alongside emotion regulation training specifically aimed at reducing anger.

Chapter 4: A pilot intervention of brief compassion-focused therapy in chronic opioid users

4.1 Introduction

Opioid use disorder (OUD) is responsible for the majority of illicit drug-related deaths worldwide (United Nations Office on Drugs and Crime, 2016), which have recently reached epidemic levels (Seth, Rudd, Noonan, & Haegerich, 2018; Zibbell et al., 2018). The first line of treatment for these individuals is opioid substitution therapy; involving the prescription of medications such as methadone and buprenorphine (NICE, 2015). However, these medications are only modest in their long-term effectiveness (see Bell, 2012 for a review). Although opioid substitution medications can stabilise the lives of people struggling with opioid addiction, they are also associated with a heightened risk of overdose (Tjagvad et al., 2016), illegally diverting prescriptions (European Monitoring Centre for Drugs and Drug Addiction, 2016), and severe symptoms of withdrawal when not used (Hassanian-Moghaddam et al., 2014). Due to the limited long-term success of these current treatment options, it is of paramount importance that we find more efficacious treatments to help those living with OUD.

As discussed in Chapter 1 section 3.1, rates of psychological trauma, particularly those that have occurred in childhood, are often disproportionately high among those living with substance use disorders (Heffernan et al., 2000; Naqavi et al., 2011). Such experiences include inconsistent parental responsiveness, lack of affection, neglect, bullying and abuse (Ravndal, Lauritzen, Frank, Jansson, & Larsson, 2001), all of which are vulnerability factors to later developing a substance use disorder (Felitti et al., 1998). Such adverse experiences can interfere with the adaptive development of emotion regulation which is typically acquired in childhood and adolescence (Hien, Cohen, & Campbell, 2005). It has been suggested that individuals may use analgesic drugs such as opioids as a form of 'emotional numbing' to deal with unpleasant emotional states when the ability to self-regulate emotions has not been nurtured in childhood (Hien et al., 2005). Unpleasant emotional states that persist following experiences of early adversity can include high levels of self-criticism, guilt, and shame (Feiring & Taska, 2005; Lassri, Luyten, Fonagy, & Shahar, 2017; Street, Gibson, & Holohan, 2005), all of which are frequently reported among those living with addictions (Blatt et al., 1984; Manganiello, 1978). Shame, described as a negative evaluation of oneself, has been shown to predict substance abuse-related problems, and has been linked to

substance use (see Luoma, Chwyl, & Kaplan, 2019, for a review); however, the relationship between shame and substance consumption is complex, and may vary based on one's self-image and shame proneness. Nonetheless, shame has shown to mediate the relationship between depressive symptoms and problematic alcohol use, where alcohol use may be used to attenuate this negative emotional state (Bilevicius et al., 2018). Increasing compassion has been shown to reduce feelings of shame (Johnson & O'Brien, 2013), and therefore fostering feelings of compassion has been suggested as therapeutically beneficial for the treatment of substance use disorders (Bilevicius et al., 2018).

Compassion has been conceptualised as the ability to feel warmth and affection towards oneself and others in times of hardship or distress (Gilbert, 2005; Neff, 2003). Self-compassion has been shown as protective for mental health and wellbeing (MacBeth & Gumley, 2012): it is positively associated with improved emotion regulation abilities, and mediates the relationship between childhood trauma and later emotional dysregulation (Vettese, Dyer, Li, & Wekerle, 2011). It is also related to reduced drug and alcohol use: People with severe alcohol use disorder who rate higher in self-compassion have better mental health, longer abstinence, and lower levels of negative emotional states such as stress, depression, anxiety (Brooks et al., 2012), and self-criticism (Rodrigues, 2014). Importantly, self-compassion was recently shown as inversely related to the risk of developing a substance use disorder, potentially indicating its protective involvement in reducing problematic drug use and demonstrating its therapeutic value (Phelps, Paniagua, Willcockson, & Potter, 2018). Treatments aimed at fostering self-compassion have already proven highly successful in the treatment of mental health problems, particularly in people that express high levels of shame and guilt (Au et al., 2017), and have histories of trauma (Hoffart, Øktedalen, & Langkaas, 2015). Thus, it seems plausible that an intervention focused on compassion may also help those living with OUD. One issue with such treatments, however, is a resistance to engage in self-compassion from individuals for whom such experiences are alien and often aversive (Gilbert, McEwan, Matos, & Rivis, 2011). Therefore, the current study set out to examine the feasibility and acceptability of a brief, three-session intervention developed to foster compassion in opioid users on opioid substitution medication (OSM).

Third-wave psychological therapies are being increasingly used for treatment-resistant conditions, such as Acceptance and Commitment Therapy (ACT), or mindfulness-based Cognitive Therapy (MBCT). However, what is missing from these therapies is an element that fosters the fundamental ability to self-soothe. Such self-compassion in those with OUD may be particularly beneficial, as external substances may be used as a compensatory mechanism to the absence of this process (Aldao, Nolen-Hoeksema, & Schweizer, 2010). The current intervention was brief in order to investigate whether it could exert a high impact and cost-effective means of treating OUD. The intervention drew on the principles of Compassion-Focused Therapy (CFT): a novel treatment formulated to increase levels of self-compassion (Gilbert, 2014; Neff & Germer, 2013). In development of the therapeutic protocol, the current study merged principles from two leading models of compassion in the literature: One of which is rooted in evolution and attachment (Gilbert, 2014), whilst the other is informed by Buddhism (Neff, 2003).

4.2 Methods

4.2.1 Participants and design

This study used a mixed design. Participants were allocated to one of the following groups: compassion-focused therapy (CFT), active comparison (relaxation training), or waitlist control. CFT and the active comparison group were randomised, and participants were blind to whether they were in the active treatment or active comparison group. Randomisation codes were calculated using a random number generator, which was performed by a member of the research team. The waitlist control group were not randomised for pragmatic reasons and were not blind to treatment allocation.

The final sample were 38 participants (24 male; 14 female) between the ages of 22 and 62 (M = 39.95, SD = 10.44) with a history of opioid drug misuse and/or currently taking an OSM (methadone; buprenorphine). All participants were previously illicit opioid users and did not transition to addiction through prescription opioids. The study was advertised as a ‘stress reduction skills course’ to reduce any pre-existing expectations from participants about what the groups involved. Participants were allocated to the different treatment types. The wait-list control group’s data were collected subsequent to the first two groups and this group were

offered the relaxation treatment following their participation. Inclusion criteria were that participants were: over 18 years of age; fluent English speakers; currently using opioid drugs (illicitly and/or in the form of OSM). Participants were excluded if they had learning difficulties or neurological impairment, or were currently intoxicated or illiterate. Participants were reimbursed for their time, and travel expenses. The study was approved by the institutional ethics committee.

4.2.2 Intervention Development

The CFT sessions involved a mixture of psychoeducation with experiential exercises, and were developed from the work of two researchers in the field, Dr Paul Gilbert and Dr Kristen Neff (Table 4.1.). The intervention was co-created by a team of psychologists with backgrounds in compassion and drug addiction, alongside key-workers from the local drug service and service users in recovery. The brief format was judged as most acceptable by users and key workers, and as having a good chance of treatment adherence in order to maximise retention and engagement. All interventions were delivered in groups by a CFT-trained psychologist and drug specialist councillor from the local drug service.

The relaxation training group was developed to emulate the experience of those in the active treatment group as closely as possible by containing a similar weighting of psychoeducation and exercises, but was focused on the physical effects of stress and relaxation (Table 4.1.).

Table 4.1 *Content of Sessions for Active Treatment (Compassion) and Comparison (Relaxation) Groups.*

		CFT treatment	**Relaxation training**
Session one	**Psychoeducation**	Building the foundations for understanding compassion: **'Tricky Brain Loops'[a]:** Understanding the brain as a product of evolution, and that human cognitive capacities for imagination, planning, and ruminating (this 'newer brain') can become easily hijacked by our 'emotional brain', where our capacity to reflect on negative events can activate negative and fearful emotions. **The Social Brain[a]**: Understanding that the development of social relationships is important for functioning, and we require socially safe connections with others to thrive. **The Three System Model**: Understanding behaviour is driven by three emotion regulation systems: (1) a threat-focused protection system (such as the fight or flight), (2) a motivational drive system for rewards and achieving goals, and (3) an affiliative system for feeling safe and self-soothed. If the affiliative system is not nurtured through attachment and care from others, the two other systems can dominate. Attempts to highlight that these brain loops are not our fault, but it is us that suffer if we do not take responsibility for them. **'Two Worlds'**: Human brains & bodies respond to both an external world and an internal world of thoughts/self-talk. The role of self-compassion and self-criticism in responding to difficulties and distress, and human suffering.	**Fight or flight response**: Understanding that the brain has evolved to respond to stress automatically, but this response can be problematic in modern day society. **Using relaxation to combat stress:** Discussing the benefits of relaxation in reducing the negative outcomes caused by stress. **Introducing relaxation with breathing:** Discuss how controlling breathing can help us relax. **Combating stress with visualisation:** Discuss the power and benefits of visualisations.
	Exercises	**Mindful eating:** Mindfulness is fundamental for compassion and thus was practiced within the sessions. This exercise involved eating food with more sensory awareness; taking care to notice the smell, feel, taste and texture. **Monitoring the three channels (thoughts, feelings, body, and behaviours):** This was a written/discussion exercise aimed at fostering awareness. Participants were asked to imagine a situation, and the thoughts, feelings, and behaviours associated with it. **Compassionate body scan**: A guided imagery exercise where you consider each part of your body and show gratitude to it, and was the first exercise that explicitly focused on compassion.	**Belly breathing:** A simple exercise that uses a deeper and slower form of breathing. **Rectangular breathing:** The use of an external, rectangular object to guide our breathing pace (shorter inhales, longer exhales). **Guided beach visualisation:** As well as using slow breathing, we are guided through a relaxing beach scene, with eyes closed.

Session two	**Psychoeducation**	Learning compassion: **Defining compassion[ab]:** Understanding and defining what compassion is, with reference to the evolutionary-attachment approach[a], as well as from a Buddhist perspective in understanding suffering as part of the human condition[b]. **Common misconceptions:** Understanding that compassion is not an overindulgence, a weakness, or demotivating[ab].,Compassion can be misinterpreted in these ways, but it is a strength that promotes motivation and health. **Different components of compassion:** Discussing that compassion is made up of three components: 1) self-kindness, 2) common humanity, and 3) mindfulness[b] that can all be fostered to develop a compassionate mind.	**Combining breathing techniques and visualisation** **How muscles hold tension:** muscles can hold a lot tension due to stress, which can be painful and unhealthy.
	Exercises	**Considering 'how do I treat a friend versus myself?'**: This was a written exercise where participants were asked to imagine the misfortune of a friend, and write what they would say to them. This exercise was used to highlight the disparity between the compassion we show for others versus the compassion we show to ourselves, and that we can be highly critical to ourselves in times of distress. **Write a compassionate letter to the self**: This was a written exercise where participants were then asked to imagine a time of their own misfortune and suffering, and to write a compassionate letter to themselves.	**Colour breathing** (breathing colours that make us feel relaxed) **Progressive muscle relaxation** (deliberately tensing and relaxing each muscle group)
Session three	**Psychoeducation**	Difficulties with training compassion: **Discussing fears surrounding compassion ('compassion blockers'):** Understand why compassion could be difficult, and how it can bring up painful past memories where compassion has been sought but unfulfilled. Fears of compassion fear of feeling safe can arise due to trauma in childhood, possibly via classical conditioning between abuse and family members or the home (people and a place that are supposed to feel safe)[a]. **Undoing these 'blockers':** comparing compassion as an under practiced skill that is difficult at first but can be trained by using techniques and exercises that were practiced within the sessions	**Combining techniques that were learned in past sessions:** breathing, visualisations, and muscle relaxation can be used together.
	Exercises	**Building a compassionate self**: This was an auditory exercise aimed at developing the ability for participants to feel and behave compassionately to others and themselves. **An ideal compassionate self:** This was another auditory exercise where participants were asked to imagine warm, supporting and caring emotions. This was done to try and enhance recognising these emotions.	**Autogenic relaxation** (imagining muscles as feeling heavy or warm)

		Soothing rhythm breathing: A breathing exercise aimed at nurturing compassion by soothing the mind
Between session resources	**Mp3**	Recordings of the exercises given in each session were recorded on an Mp3 and given to participants to practice in their own time, and were advised to use between sessions and in times of distress
	Keychain booklets	An attractively designed summary of the psychoeducation from each session in the form of a booklet was given to participants to take home. This enabled them to cover any information from the sessions in their own time.

[a] Informed by Paul Gilbert's model of compassion (Gilbert, 2014)
[b] Informed by Kristin Neff's model of self-compassion (Neff, 2016)

4.2.3 Measures

***Feasibility*.** Feasibility was assessed by assessing the percentage of: individuals agreeing to take part the study (success criteria: 60%); those completing the baseline measures (success criteria: 70%); those completing follow up measures (success criteria: 50%).

Obsessive-Compulsive Drug Use Scale (OCDUS) (Franken, Hendriks, & van den Brink, 2002). This 13-item scale assessed opioid drug craving, with three subscales: thoughts and interference; desire and control; resistance to thoughts and intention. Responses were on a 5-point Likert scale.

Visual Analogue Scales (VAS): Feelings surrounding their opioid prescription. Three questions developed to identify participant's current ratings of coping, motivation, and optimism surrounding their opioid prescription. Answers were given on a visual analogue scale, to 1) whether they felt they would cope if they reduced/continued to reduce their opioid prescription, 2) whether they felt motivated to reduce/continue reducing their opioid prescription, and 3) whether they felt they would need an opioid prescription forever. Responses were on a 100mm VAS.

Depression, Anxiety & Stress Scale (DASS) (Lovibond & Lovibond, 1995). A shortened, 21-item measurement of depression, anxiety and stress over the past week. Responses were on a 4-point Likert scale (0 = did not apply to me at all, 3 applied to me very much).

The Forms of Self-Criticising/Attacking & Self-Reassuring Scale (FSCRS) (Gilbert, Clarke, Hempel, Miles, & Irons, 2004). A 22-item scale of self-relating used to measure self-criticism and self-reassurance/compassion. Subscales include feelings of self-inadequacy, ability to self-reassure, and feelings of self-hate. Responses were on a 5-point Likert scale (0 = not at all like me, 4 = extremely like me).

4.2.4 Procedure

Both the experimental and active control group (CFT and relaxation, respectively) attended three two-hour sessions held over three consecutive weeks. The waitlist control group filled out the baseline measures, and repeated these on

the third week for follow up. Procedures for all groups at each session can be observed in figure 4.1.

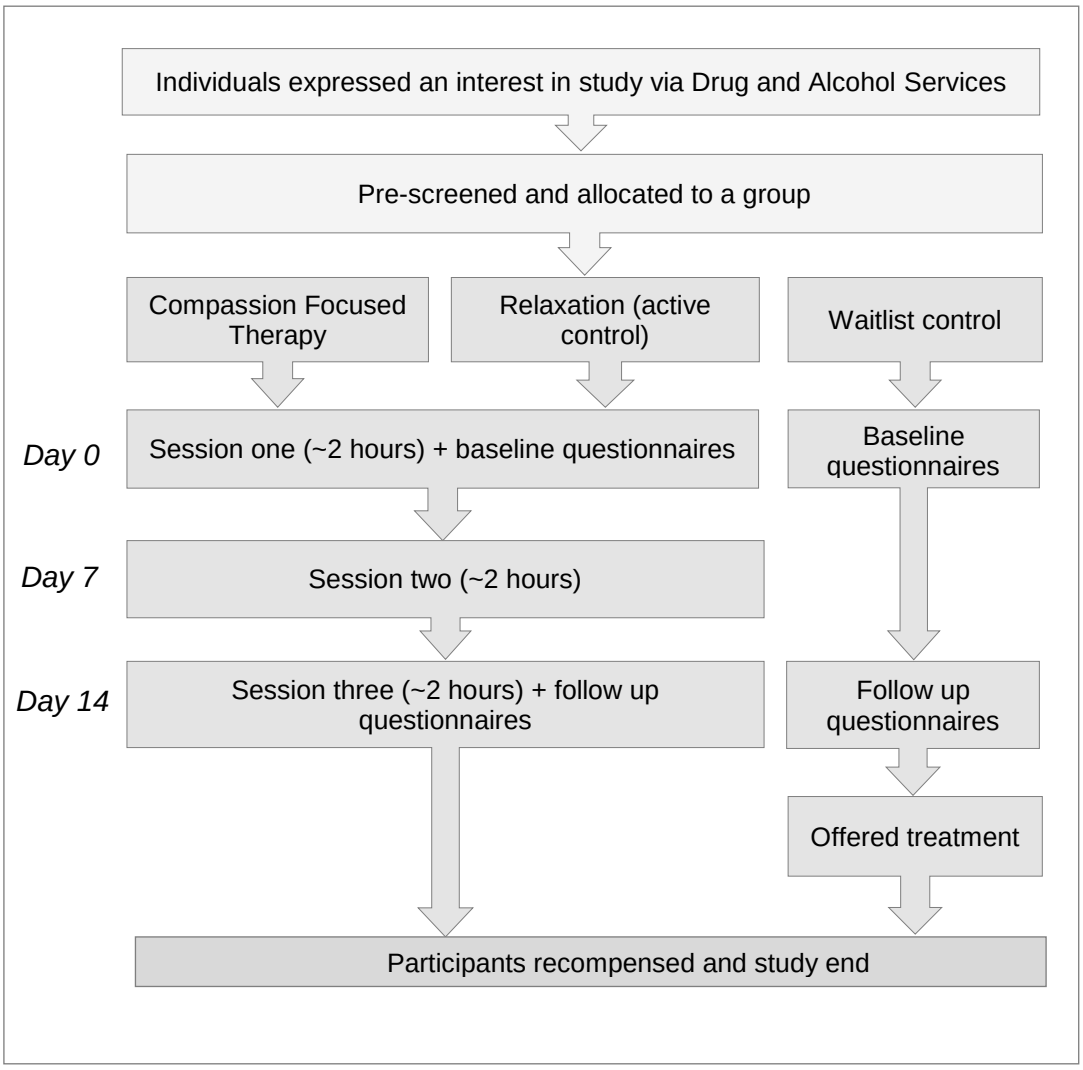


Figure 4.1. The study procedure.

Prior to participating in the study, participants were contacted for screening. This involved a brief assessment of participant's history with opioid drugs and their opioid prescription. Once screened, participants were allocated to either the CFT, relaxation, or waitlist control group.

On arrival for session one, participants provided informed consent and were then asked to complete the self-report baseline measures (OCDUS; VAS; DASS; FSCRS), which were completed again at the end of session three. Between sessions, participants in the active groups were asked to engage in practical activities related to the session content. This included listening to guided recordings

on an MP3 device, and read a short booklet. Upon completion of the study, participants were reimbursed for their time with a voucher.

4.2.5 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS), version 23. Data were checked for normality and homogeneity, and in cases where data were non-parametric a Kruskall-Wallis H test was used.

The effect of the intervention on indices of craving and well-being were each assessed using a 3×2 mixed repeated measures analyses of variance (ANOVA), with treatment group (CFT; relaxation training; waitlist control) as the between-subjects factor, and measurement time (baseline; follow up) as the within-subjects factor. A Chi-square test was used to assess dropout between the three groups. The treatment effect on the change during the treatment phase and on the change from baseline through follow-up were also expressed as eta-squared (small effect size: 0.01; medium: 0.06; large: 0.14) (Cohen, 1977). In line with recent recommendations for reporting pilot studies (Cumming, 2013; Lee, Whitehead, Jacques, & Julious, 2014), results were interpreted not only if they meet statistical significance at 0.05 level, but also if there was a medium or greater effect size for the interaction without corresponding statistical significance: If the latter was true for the interaction terms, we also reported the mean differences and 80% confidence intervals between compassion with relaxation and waitlist groups. Since this was a preliminary pilot study, an intention-to-treat analysis was not conducted, as this would be more appropriate for a randomised-controlled trial.

4.3 Results

4.3.1 Demographics

The treatment groups were matched in age, gender, years in education, and indices of past illicit opioid use (Table 4.2).

Table 4.2. *Participant Demographics between Treatment Conditions (Means and Standard Deviations).*

		Compassion-focused therapy (n=15)	**Relaxation (n=12)**	**Waitlist control (n=11)**	**test statistic**	***p*-value**
Age		41.07 (12.70)	43.33 (8.27)	34.82 (7.94)	F= 2.17	.129
Gender (male; female)		11; 4	7; 5	6; 5	χ^2= 1.14	.566
Years in education (mean rank)		11.77 (2.24)	12.42 (2.23)	11.73 (0.79)	F= 0.49	.620
History of mental health problems (n=yes)		12	6	9	χ^2= 4.80	.091
Opioid prescription type (methadone; buprenorphine; morphine)		8, 6, 0	11, 1, 0	8, 2, 1	χ^2= 6.83	.145
Opioid prescription dose in mg, per day	Methadone	55.63 (60.62)	42.36 (22.54)	51.25 (6.41)	F= 0.34	.717
	Bupren-orphine	10.00 (4.56)	16.00 (0.00)	14.00 (2.83)	F= 1.24	.355
	Morphine		-	560.00 (0.00)	-	-
Length taken opioid prescription, years		9.79 (7.70)	6.80 (4.66)	7.39 (5.84)	F= 0.76	.475
Last use of illicit opioids (excluding prescription), days		21.46	16.33	16.95	$\chi^2(2)$= 61.50	.398
Time since first started using opioids, years		17.41 (12.13)	20.25 (6.47)	14.50 (8.57)	F= 1.04	.365
Peak use of opioids following onset, months		46.46 (29.98)	60.38 (34.56)	24.72 (34.17)	F= 2.88	.073
Money spent on opioids at peak use (pound sterling), per day		175.80 (144.52)	105.50 (101.80)	88.80 (77.61)	F= 1.63	.215
Use of other illicit substances (n=yes)		7	8	8	χ^2= 1.51	.471

Note. Means and standard deviations are provided where parametric tests are used; otherwise the mean rank is given in cases that are non-parametric. Total counts are given for categorical variables.

4.3.2 Treatment uptake and Adherence

One hundred and three individuals were interested and contacted by the research team. After given more information, 69 (66.99%) of these individuals agreed to take part in the study. 47(68.12%) of these individuals attended the first session (baseline), and 38 (80.85%) of these individuals continued to complete the full study: n=15 in the CFT group (4 drop outs), n=12 in the relaxation training (1 drop out), and n=11 in the waitlist control group (4 drop outs). There were no significant differences in number of drop outs between the three groups (χ^2=2.62, n=38, *p*=.270).

4.3.3 Craving (OCDUS)

3×2 mixed ANOVA on the subscale “thoughts and intentions around opioid use” shown a main effect of group (F(2,34)=4.88, *p*=.014, η^2=0.22), associated with a large effect size, where pairwise comparisons revealed the waitlist control group had lower scores overall than both the compassion (*p*=.005) and relaxation (*p*=.021) groups (figure 4.2). There were no significant differences in scores from baseline to follow up (F(1,34)=1.26, *p*=.269, η^2=0.04), and no interaction between group and time (F(2,34)=0.06, *p*=.939, η^2<0.01).

For the subscale “desire and control over opioid use”, there were no main effects of group (F(2,24)=1.50, *p*=.242, η^2=0.11), time (F(1,24)=0.09, *p*=.769, η^2<0.01) and no interaction (F(2,34)=1.37, *p*=.273, η^2=0.10), although the latter was a medium effect size (figure 4.2). Mean difference scores between the compassion and relaxation group were 0.22 (80% CI [-0.40,0.83]), and compassion group and the waitlist group were 0.71 (80% CI [0.15,1.25]). Confidence intervals indicate the compassion group is scoring higher at follow up than baseline, with little change in scores in the waitlist group.

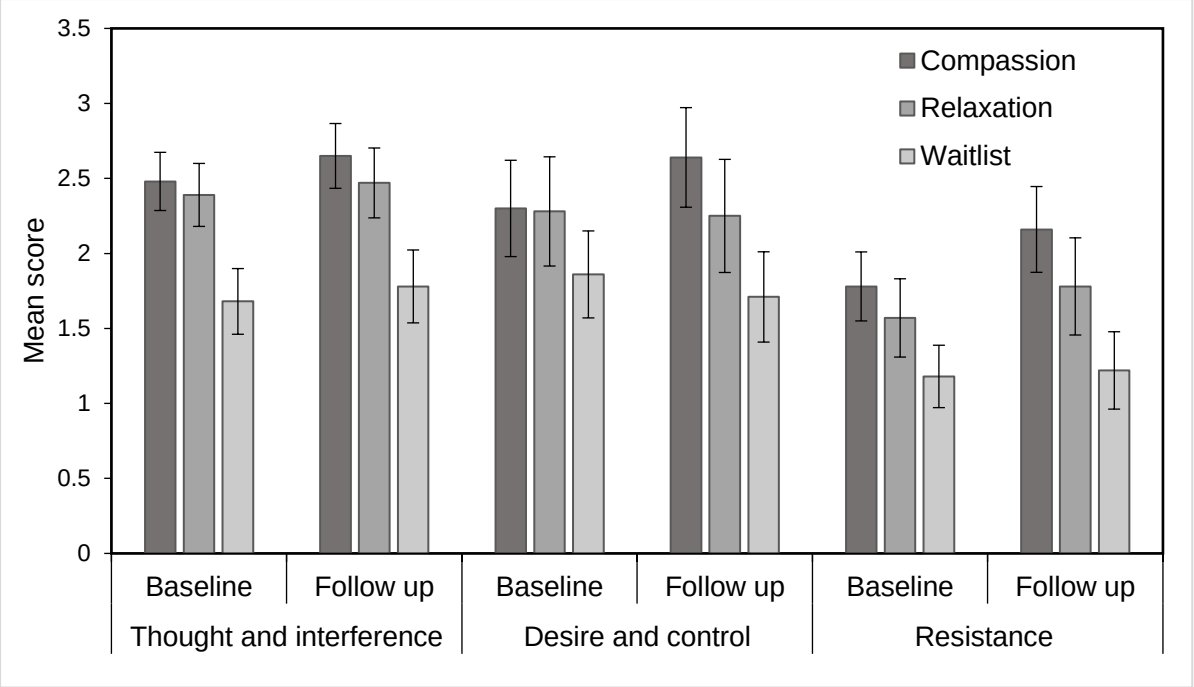


Figure 4.2. Scores on craving subscales between each group. There were medium effect sizes for 'desire and control', and 'resistance' subscales which were followed up by mean differences and confidence intervals. These indicated that the compassion group were experiencing a larger change in scores from baseline to follow up than the waitlist control group, where scores were higher at follow up. Error bars represent ± 1 SEM.

For the subscale "resistance to thoughts and intentions surrounding opioid use", there was a difference in scores between baseline and follow up measures that approached significance ($F(1,24)=3.43$, $p=.077$, $\eta^2=0.12$) (figure 4.2). There was also a trend for a difference in scores between groups ($F(2,24)=2.91$, $p=.074$, $\eta^2=0.20$). The interaction between group and time ($F(2,24)=0.82$, $p=.452$, $\eta^2=0.06$) were associated with a medium effect size (figure 4.2). Mean difference scores between the compassion and relaxation groups were 0.29 (80% CI [-0.18,0.77]), and between the compassion and waitlist group were 0.77 (80% CI [0.34,1.19]). Confidence intervals indicate the compassion group are scoring higher at follow up than baseline, with little change in scores in the waitlist group.

4.3.4 Feelings surrounding prescription (VAS).

One item examined self-rated coping if participants reduced their (opioid) prescription, on which there was an overall increase in scores from baseline to follow up ($F(1,22)=4.54$, $p=.045$, $\eta^2=0.16$) (figure 4.3). The group difference ($F(2,22)=1.12$,

p=.344, η²=0.09) and the interaction (F(2,22)=1.18, *p*=.327, η²=0.08) were associated with medium effect sizes. Mean difference scores between the compassion and relaxation groups were 6.63 (80% CI [-13.97, 27.22]), and between the compassion and waitlist control group were 20.48 (80% CI [1.12, 39.83]). Confidence intervals indicate the compassion group are scoring higher at follow up than baseline, with little change in scores in the waitlist group.

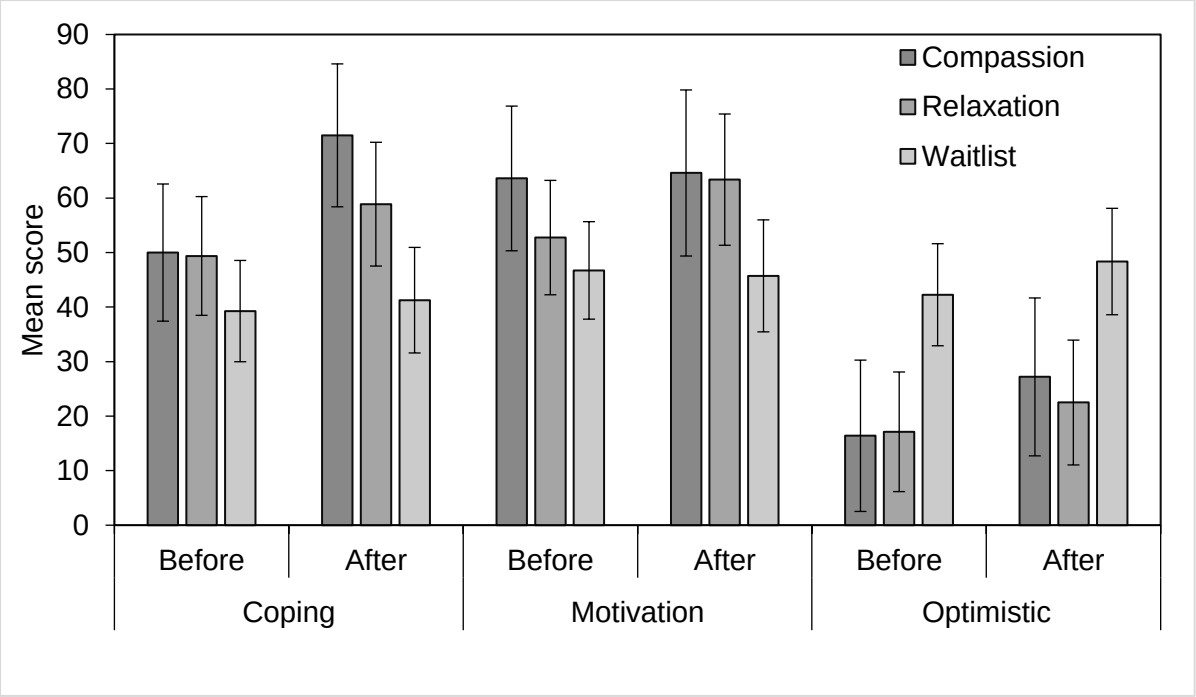


Figure 4.3. Feelings of coping, motivation, and optimism regarding participant's opioid prescriptions. There were medium effect sizes for 'coping' and 'motivation' were followed up with mean differences and confidence intervals, and indicated a larger change in scores from baseline to follow up (i.e. scores were higher at follow up) in the compassion group compared to the waitlist control group for perceived coping if to reduce their prescriptions. Error bars represent ± 1 SEM.

When asked about motivation to reduce their prescription, the difference between groups was associated with a medium effect size (F(2,21)=0.71, *p*=.504, η²=0.06), there were no differences between baseline and follow up (F(1,21)=0.71, *p*=.412, η²=0.03). There was an interaction associated with a medium effect size (F(2,21)=0.85, *p*=.441, η²=0.07). Mean difference scores between the compassion group with relaxation and waitlist control groups were 6.04, 80% CI [-16.88,28.96] and 17.87, 80% CI [-3.81,39.56], respectively.

When asked whether participants felt they would need a prescription forever (optimism), there was a large effect size associated with the group ($F(2,21)=2.22$, $p=.134$, $\eta^2=0.17$), a medium effect of time ($F(1,21)=1.65$, $p=.213$, $\eta^2=0.07$) but no interaction ($F(2,21)=0.07$, $p=.932$, $\eta^2=0.01$).

4.3.5 Depression, anxiety, and stress (DASS: Table 4.3)

A 3×2 mixed ANOVA on depression scores found a main effect of time ($F(1,35)=6.83$, $p=.013$, $\eta^2=0.16$), where there was an overall decrease in scores from baseline to follow up, associated with a large effect size. There were no differences between groups ($F(2,35)=0.97$, $p=.389$, $\eta^2=0.05$), and no interaction ($F(2,35)=0.01$, $p=.995$, $\eta^2<0.01$).

For anxiety scores, there was an interaction between treatment type and time that approached statistical significance ($F(2,33)=3.08$, $p=.059$, $\eta^2=0.15$) and was associated with a large effect size. The mean difference scores between the compassion group with relaxation and waitlist control groups were -0.38 (80% CI [-3.01, 2.25]), and 1.40 (80% CI [-1.46, 4.27]), respectively. There were no main effects of group ($F(2,33)=0.33$, $p=.723$, $\eta^2=0.02$), or time ($F(1,33)=0.79$, $p=.381$, $\eta^2=0.02$).

There was a main effect of time on stress scores ($F(1,35)=9.21$, $p=.005$, $\eta^2=0.19$) associated with a large effect size, where scores reduced from baseline to follow up in all groups. There were no differences between groups ($F(2,35)=0.31$, $p=.734$, $\eta^2=0.01$), or statistically significant interaction ($F(2,35)=1.91$, $p=.163$, $\eta^2=0.08$), however the interaction was associated with a medium effect size. The mean difference scores between the compassion group with relaxation and waitlist control groups were 1.49 (80% CI [-1.31, 4.30]) and -0.08 (80% CI [-2.96, 2.80]), respectively.

Table 4.3. *Means and Standard Deviations for Scores for the DASS and FSCRS.*

		Compassion	Relaxation	Waitlist
DASS				
Depression	Baseline	12.13 (5.32)	12.08 (6.96)	14.55 (4.80)
	Follow up	9.93 (5.32)	10.00 (6.35)	12.55 (4.41)
Anxiety	Baseline	9.53 (3.91)	11.17 (6.90)	7.11 (5.69)
	Follow up	9.05 (5.59)	8.18 (5.38)	8.67 (6.34)
Stress	Baseline	12.62 (5.25)	12.29 (7.49)	12.55 (4.16)
	Follow up	11.49 (6.01)	8.83 (6.13)	11.73 (5.37)
FSCRS				
Self-inadequacy	Baseline	20.47 (2.33)	22.60 (2.37)	24.29 (3.37)
	Follow up	21.21 (2.10)	20.68 (2.18)	20.43 (3.77)
Self-hate	Baseline	7.59 (1.42)	7.53 (1.38)	10.00 (2.07)
	Follow up	8.33 (1.29)	7.65 (1.69)	9.29 (2.17)
Self-reassurance	Baseline	12.35 (1.40)	16.46 (2.14)	11.14 (2.21)
	Follow up	13.00 (1.44)	16.12 (2.23)	12.71 (2.01)

Note. Values reflect the mean total score.

4.3.6 Self-criticism (FSCRS) (Table 4.3).

3×2 mixed ANOVA's were conducted on subscales of self-criticism. The analysis of scores for the self-inadequacy subscale found an interaction associated with a medium effect size ($F(2,35)=0.77$, $p=.185$, $\eta^2=0.09$), however mean difference scores and 80% CIs revealed no further differences between the compassion and relaxation or waitlist control group 0.09 (80% CI [-0.58,0.40]) and <0.01 (80% CI [-0.49,0.51]), respectively. There were no main effects of group ($F(2,35)=0.04$, $p=.963$, $\eta^2=0.01$) or time ($F(1,35)=2.62$, $p=.115$, $\eta^2<0.01$).

For self-hate, there was no interaction between time and group ($F(2,35)=0.62$, $p=.544$, $\eta^2<0.01$), no main effects of time ($F(1,35)<0.01$, $p=.959$, $\eta^2<0.01$) or group ($F(2,35)=0.22$, $p=.808$, $\eta^2=0.01$), and all effect sizes were small. For self-reassurance, there was no interaction between time and group ($F(2,32)=0.07$, $p=.928$, $\eta^2<0.01$), and no main effects of time ($F(1,32)<0.01$, $p=.961$, $\eta^2<0.01$), and

effect sizes were small. There was no significant main effect of group ($F(2,35)=2.40$, $p=.107$, $\eta^2=0.10$).

4.4 Discussion

The current study piloted a novel intervention aimed at fostering compassion in opioid users on an opioid substitution medication (OSM). In relation to the primary aim of the study, a short-course of compassion-focused therapy (CFT) in opioid drug users appears to be feasible in this population. Whilst we were not statistically powered to detect clinically significant differences, our analyses found medium to large reductions in depression and stress from baseline to follow up, as well as overall increases in feelings of coping if participants were to reduce their opioid prescription. Furthermore, effect sizes and mean differences indicated that the compassion intervention may produce larger changes in craving and coping, compared to the waitlist control group.

The results of the study suggest that the intervention is feasible, and may warrant further investigation in a larger randomised control trial. Retention rates across the study were high: of all the 47 individuals that attended the first session, 81% of these individuals continued to complete the full study. The number of dropouts did not differ between groups. Drop outs during CFT are common, particularly among individuals high in self-criticism and those that have not had previous experience of compassion with significant others (Gilbert et al., 2011). Treating oneself with compassion can feel alien, and has the potential to cause distressing emotional reactions in those with histories of abuse and neglect, thus causing individuals to discontinue treatment (Gilbert et al., 2011). Despite this, our study had particularly high retention for this population, with similar mindfulness-based interventions in opioid users reporting retention rates between 45% to 75% (Zgierska et al., 2009). Since CFT had equally good retention as relaxation indicates that, although this population has particular high levels of self-criticism and might therefore find the concept more challenging, it may be a promising approach for opioid users with trauma history.

Although inferential testing did not highlight any benefit of this compassion-orientated treatment above an active control or no treatment, this novel treatment should not be deemed as lacking clinical utility on the basis of this. Pilot studies have

been criticised for relying on inferential statistics and hypothesis testing when they are underpowered to detect clinically meaningful effects (Leon, Davis, & Kraemer, 2011). It has therefore been suggested that examining effect sizes and reporting the mean differences and confidence intervals can be more informative to identify whether the intervention is worth taking forward to a larger, randomised controlled trial. In the current project, the compassion group showed increased scores following treatment on craving (resistance to thoughts and behaviours; desire and control), as well as feelings of coping if they were to reduce their opioid prescriptions, compared to the wait-list control group. Individuals in the compassion intervention group were rating higher than the waitlist group in trying to resist the use of opioids and coping if they reduced their prescription, but were also experiencing more desire to use opioids.

There were also suggestions of increased levels of coping if participants were to reduce their opioid prescription in the groups which had undertaken the CFT. Studies suggest higher self-compassion is related to more adaptive, emotion-focused coping strategies (Neff, Hsieh, & Dejitterat, 2005; Sirois, Molnar, & Hirsch, 2015), such as seeking emotional support and acknowledging negative emotions. This is opposed to avoidance-focused coping strategies, where individuals seek to avoid stress and negative mood (Neff et al., 2005), and is consequently associated with negative, self-orientated feelings of shame (Elison, Pulos, & Lennon, 2006). In the current study, potential increases in feelings of coping, alongside increases in desire and efforts to resist the use of opioids, may indicate that participants are adopting more emotion-focused coping strategies: As they are acknowledging (rather than avoiding) their cravings, but also rating higher in ability to cope. Further, by reducing avoidance-coping mechanisms using compassion, this could also have positive repercussions on ‘de-shaming’ participants, in line with past suggestions (Gilbert & Irons, 2005). Feelings of shame are a central characteristic in both those with substance use disorders (Luoma et al., 2019) and trauma patients (McLean, Steindl, & Bambling, 2017), and are a key aspect that CFT wishes to alleviate (Irons & Lad, 2017). An increased emphasis on the de-shaming power of compassion may be particularly useful for a short intervention such as this. Thus, although these suggestions are speculative, they could provide potential reasons for larger

increases in coping in the CFT group over the waitlist control group, and indicate the therapeutic value of CFT.

The overall declines in depression and stress observed in all three groups may be a result of being in a research study, where all participants are shown to benefit, or regression to the mean, where participants' ratings on these scales are more extreme at baseline and closer to the average at follow up. One method of correcting for regression to the mean may be to covary for baseline responses; however, this form of analysis should be considered in a randomised control trial with a larger sample size and higher statistical power.

One limitation of the study is its scope: other researchers have suggested that feasibility studies should predominantly assess qualitative data (Eldridge et al., 2016). Furthermore, we also found lower baseline scores of craving related to thoughts and inference surrounding opioid use in the waitlist control group versus the two active groups, which could be related to why this group did not show much change in the other craving subscales (desire to use and resistance). It is possible that pre-existing differences between the groups could have contributed to this, such as their histories of opioid use.

One strength of the current study is the use of two control groups; including an active comparator group to investigate the feasibility of such a trial design. The active groups were carefully matched in time and duration of sessions, and containing an equal balance of psychoeducation and exercises. This design, if followed through to a fully powered trial, would enable us to understand the relative benefits of CFT in comparison to a similarly structured intervention, as well as the absolute benefits when compared to no treatment (Karlsson & Bergmark, 2015).

In summary, the use of compassion-focused therapy as an intervention for those with opioid addiction is feasible. There were differences in change scores between the compassion and waitlist control group – particularly in craving – where differences from baseline to follow up were considerably larger for the CFT group but reflected both a positive and negative clinical change. Overall, these results indicate this new treatment to be feasible, and hence this should be systematically investigated in a higher powered, randomised control trial. Past research has largely ignored the importance of social functioning in individuals suffering with addictions,

and only now the clinical importance of these processes are being emphasised (Heilig et al., 2016). This novel treatment in opioid users is the first attempt at explicitly improving social functioning in opioid users via fostering feelings of compassion, with the overall aim to enhance quality of life for those living with opioid addiction.

Chapter 5: Greater Empathy in MDMA users

5.1 Introduction

This thesis thus far has investigated the role of social risk factors and social cognition in opioid use disorder (OUD), as well as trialled the feasibility of a psychological therapy. Currently the treatments for opioid use disorder are limited in their long-term efficacy, highlighting a need for novel approaches. One potential approach is looking at drug-assisted psychotherapies, where 3,4-Methylenedioxymethamphetamine (MDMA) conjunct with psychological therapy may be a suitable candidate in the treatment of opioid addiction.

MDMA has recently been approved for Phase III clinical trials of post-traumatic stress disorder (PTSD), based on evidence from several studies that it improves clinical outcomes in PTSD when given as an adjunct to psychotherapy (Mithoefer et al., 2018; Oehen, Traber, Widmer, & Schnyder, 2013). More recently, the use of MDMA is also being considered for addictions, and has been deemed well-tolerated in a proof of concept study in patients with alcohol use disorder (Sessa, Sakal, O'Brien, & Nutt, 2019), however this was only with four patients and further research is required to assess the effectiveness of this novel treatment for drug use disorders. When used alongside psychotherapy, MDMA has been suggested to enable patients to address painful emotions and memories without experiencing an overwhelming emotional response, which can help facilitate recovery (Feduccia & Mithoefer, 2018). Amongst recreational drug users, MDMA is used for its capacity to enhance social functioning (Heifets & Malenka, 2016). Investigative studies looking at the acute effects of MDMA on social cognition have reported heightened levels of compassion (Kamboj et al., 2015), trust (Dolder, Müller, Schmid, Borgwardt, & Liechti, 2018; Stewart et al., 2014), generosity (Kirkpatrick, Delton, Robertson, & de Wit, 2015), and empathy (Hysek, Schmid, et al., 2014; Kuypers et al., 2014; Kuypers, Dolder, Ramaekers, & Liechti, 2017), mirroring the effects reported by recreational users (Peroutka, Newman, & Harris, 1988; Siegel, 1986). In addition to augmenting prosocial processes, MDMA can also reduce the perception of negative emotions (Dolder, Müller, et al., 2018; Hysek, Domes, & Liechti, 2012; Hysek, Schmid, et al., 2014; Hysek, Simmler, et al., 2014), lessen responses to negative social events by acutely reducing responses to social threat (Bedi, Phan, Angstadt, & de Wit, 2009; Wardle & de Wit, 2014), and alleviate the impact of social exclusion i.e. 'social pain' (Frye, Wardle, Norman, & de Wit,

2014). These positive effects of MDMA on social functioning has led researchers to investigate the potential for using MDMA-assisted psychotherapy to treat social anxiety in autism spectrum disorders (ASDs), with promising results (Danforth et al., 2018; Danforth, Struble, Yazar-Klosinski, & Grob, 2016). These effects of MDMA in boosting prosocial processes whilst reducing the experience of social distress may also highlight the therapeutic potential of this psychoactive substance for treating OUD.

Both empathy and the experience of social pain are key social processes that have been investigated under the acute influence of MDMA. As discussed in preceding chapters, the two are suggested to be connected; as empathy for others is affected by socially painful events (DeWall & Baumeister, 2006), and impairments in the ability to empathise can lead to social difficulties (Krull, Wilbert, & Hennemann, 2018). Several acute drug studies have found that MDMA can increase empathy (Hysek, Schmid, et al., 2014; Kuypers et al., 2014; Kuypers et al., 2017; Schmid et al., 2014), with particular enhancements to the emotional component (experiencing the emotional state of others) more so than the cognitive component (understanding the perspective of others). Cognitive empathy has been likened to 'Theory of Mind', and encompasses the ability to transpose oneself into the perspective of others and to accurately identify their emotional state (Baron-Cohen & Wheelwright, 2004; Blair, 2005). Meanwhile emotional empathy has been likened to sympathy and emotional contagion, signifying to the ability to spontaneously experience the emotions of others (Blair, 2005; Nummenmaa et al., 2008). MDMA has also been found to reduce the drop in mood and self-esteem experienced after being socially excluded during the Cyberball Game (Frye et al., 2014). Social exclusion is considered one facet of the experience of 'social pain'.

Acutely MDMA elicits serotonin, dopamine and noradrenaline release, but its actions at the 5-HT transporter, along with its induction of the release of hormones like oxytocin, are thought to be responsible for the drug's prosocial effects (Francis, Kirkpatrick, de Wit, & Jacob, 2016; Hysek, Schmid, et al., 2014; Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007; van Wel et al., 2012; Vizeli & Liechti, 2018). The exact role of oxytocin on the prosocial effects of MDMA is less clear, however, as some studies have found it to be unrelated to empathy (Kuypers et al., 2017). It is well-known that in the short term MDMA impacts upon the 5-HT

transporter and serotonergic system, and a meta-analysis of preclinical and neuroimaging studies suggests that a 40-70% reduction in the density of the 5-HT transporter may occur with chronic MDMA use (Roberts, Jones, & Montgomery, 2016). Though recent work has indicated that these effects may be more modest: Imaging studies have generally recruited exceptionally heavy MDMA users in order to maximise the likelihood of detecting an effect (individuals that consume 720% more MDMA than the average user) (Szigeti, Winstock, Erritzoe, & Maier, 2018). These exceptionally large levels do not necessarily reflect what is used by recreational users on a whole, where serotonergic depletion may not be so extreme (Szigeti et al., 2018). Supporting this, preclinical research comparing self-administered, lower doses of MDMA (0.3-2.3mg/kg) reported no differences in 5-HT transporter availability (Banks et al., 2008), whereas previous research where much greater doses are administered on a regular schedule (5mg/kg twice a day for four days) reports reduced 5-HT transporter availability in non-human primates (Reneman et al., 2002; Scheffel et al., 1998). A recent systematic review investigating dose and neurotoxicity has claimed that there is limited evidence of neurotoxicity in preclinical research where a dose of 3mg/kg or smaller is used, and even when larger doses are used the evidence is mixed (Pantoni & Anagnostaras, 2019). Moreover, it is unknown whether pre-existing group differences or a reversible neuroadaptation account for the reduction in density of 5-HT transporter markers seen in chronic MDMA users. Increasing serotonergic activity via agonists and selective serotonin reuptake inhibitors (SSRI's) have shown positive effects on social functioning and empathy (Crockett, Clark, Hauser, & Robbins, 2010; Dolder, Schmid, Müller, Borgwardt, & Liechti, 2016; Preller et al., 2016), and concurrently blocking 5-HT activity using a serotonin antagonist has shown to obstruct the prosocial effects of MDMA in animals (Morley, Arnold, & McGregor, 2005). Since serotonin may be involved in the empathogenic effects of MDMA, serotonergic depletion over long-term use may plausibly have a downstream effect on empathy and other social processes; however, this may only be the case in extreme users.

To our knowledge, only one human study has investigated this potential link. This study investigated processes of empathy among chronic MDMA users and reported heightened cognitive empathy in this group, thus indicating an increased ability to discriminate the emotional states of others (otherwise known as 'theory of

mind') (Wunderli et al., 2018). However, this increased cognitive ability was only present in lower-level users, and in fact cognitive empathy appeared to deteriorate with heavier use. Alongside empathy, empirical research into whether chronic use of MDMA affects the experience of social pain has not been conducted – despite concerns that prolonged use of this drug could heighten levels of social distress (Parrott, 2007). However, the acute effects of MDMA on empathy and openness are thought to help the extinction of traumatic memories as well as overall engagement during psychotherapy, and it is hoped that this will promote long-term changes in reducing distress (Bedi, 2018). Only recently is MDMA-assisted psychotherapy being explored in addictions, where the treatment has been deemed well-tolerated in those with alcohol use disorder (Sessa, Sakal, et al., 2019), which may also extend to those with OUD. Thus, given the recent developments in the therapeutic use of the drug, it is important for researchers to fully characterise the acute and chronic effects of the MDMA in order to facilitate informed clinical use and establish a safety profile for this novel treatment.

The current study thus aimed to investigate whether repeated use of MDMA was associated with any changes to social functioning. The study specifically looked at empathy and responses to socially painful events, due to their clinical relevance, and a low level of repeated MDMA use was targeted to map more closely on likely therapeutic use. We aimed to recruit a poly-drug using group who did not use MDMA to control for differences between illicit drug users and non-drug users. In this study we use the term 'MDMA' to refer to street MDMA (otherwise known as ecstasy), which is generally taken in powder or crystal form and referred to by users as "MDMA". However, we understand that street MDMA can vary in purity and quantity compared with pharmaceutical MDMA given in acute studies. In line with evidence of serotonergic dysfunction from earlier studies of MDMA, it was hypothesised that chronic MDMA use would reduce empathic processes and heighten sensitivity to social pain, compared to non-MDMA poly drug users and alcohol only users. However, given recent findings (Wunderli et al., 2018) and suggestions from recent reviews (Bedi, 2018), it may also be possible that empathy increases and there is a reduction in social pain with repeated MDMA use.

5.2 Method

5.2.1 Design and participants

The current study used an independent groups design, where we examined differences between three groups (MDMA poly-drug users; non-MDMA poly-drug users; alcohol users only). All three groups completed all study procedures.

Seventy-five participants (25 male; 50 female) between the ages of 18 and 43 (*M* =21.41, *SD* = 3.27) were recruited from a community sample via advertisements on posters and word of mouth, along with snowball sampling. The study was advertised as looking at the long-term effects of drug and alcohol use on social perception, and thus participants were not aware the study was specifically investigating MDMA use, empathy, or social pain. To be included in the MDMA group individuals were required to have used MDMA at least once a month for the past 10 months, and/or more than 10 times in their lifetime. To be in the poly-drug using condition participants were required to have used any illicit substance excluding MDMA at least once a month for the past 10 months, and/or more than 10 times in their lifetime. All participants were asked to abstain from drugs and alcohol for 24 hours prior to study participation. Exclusion criteria were having: Autism spectrum disorder (ASD); a neurological disorder; a severe mental health problem (schizophrenia, bipolar disorder, etc.). Individuals with mild depression and anxiety (assessed by asking whether participants had previously sought treatment) were not excluded from the study. One participant was removed from this and all subsequent analyses on empathy indices due to the subsequent discovery that they had a diagnosis ASD. The study was approved by the institutional ethics committee and written valid informed consent was received from all participants.

5.2.2 Measures

The Multifaceted Empathy Test (MET) (Dziobek et al., 2008). This is a computerised task that measures and discriminates between both cognitive and emotional empathy (also see Chapter 2 Section 2.3 for figure, and Chapter 3 Section 2.2). The task involved showing participants 40 photographs of people with emotionally charged expressions, which were given in eight blocks each consisting of 10 pictures. In four of these blocks, participants were required to identify the correct mental state of the subject in each scene by picking one from a choice of four

emotion labels (cognitive empathy). In the other four blocks, participants were asked to rate how much they empathise with the individual in each scene on a 9-point Likert scale (1 = not at all; 9 = very much) (emotional empathy) before being presented with the next trial, i.e. the task is self-paced. The task lasted approximately 15 minutes.

The Cyberball Game (Williams, Yeager, Cheung, & Choi, 2012). This is a computerised game that uses ball tosses between the participant and fictitious virtual players, and has been reliably shown to simulate the experience of social rejection (also see Chapter 2 Section 2.3 for figure, and Chapter 3 Section 2.2). Participants were told that they were playing with two other participants on a virtual network in a mental visualisation experiment. Unbeknown to them, the two other players were not real and were programmed to socially exclude them. There were two conditions (inclusion status') that simulated either social inclusion or social exclusion. Conditions were counterbalanced between participants, and each condition included a block of two games that lasted approximately three minutes each. There were 30 ball throws for each game, and participants received exactly one-third (10 ±1 of 30) of all ball throws during the inclusion condition, and only one-sixth (5 ±1 of 30) of all ball throws in the exclusion condition. The task took approximately 15 minutes to complete, and responses were recorded via affective measures taken between each game (described below).

Post-Ostracism Cyberball Questionnaire (POCQ) (Williams et al., 2002). This 25-item scale was used to assess: positive and negative affect, belongingness, self-esteem, control, meaningful existence, anger, and hurt feelings. Responses were recorded on a 5-point Likert scale (1 = not at all; 5 = very much). It also incorporated three manipulation checks to ensure participants identified whether they had been included or excluded.

5.2.3 Questionnaires

Interpersonal Reactivity Index (IRI) (Davis, 1980). This 28-item scale assesses trait empathy, and differentiates between subjective emotional and cognitive empathy. Emotional empathy is characterised by subscales 'empathic concern' and 'personal distress', which respectively refer to the ability to feel sympathy and concern towards another individual's emotional state (other-oriented),

and the preoccupation by one's own feelings of distress and anxiety upon seeing other's distress (self-oriented). Cognitive empathy is characterised by the subscales 'perspective taking' and 'fantasy', which respectively refer to the ability to understand the point of view of others, and the ability to imagine the mental states of fictional characters (such as in books or movies). Responses were recorded on a 5-point Likert scale (A = does not describe me well; E = describes me very well).

Drug and alcohol use history. In an interview, participants were asked about their drug use history by going through each substance and asking whether it had been used in the past and, if yes, when they last used it, whether it was used regularly, and amount used in a typical session. Participants also gave information about their drug-use over the past two weeks by answering for each day, 1) if any substances were used and what these were, and 2) the amount of these substances used per session. Participants who met the criteria for chronic MDMA user group were asked further questions about their MDMA use.

Testing took place during the day in a testing laboratory at the University of Exeter, and the test took approximately 1 hour. Figure 5.1 gives a timeline of the testing in the current study.

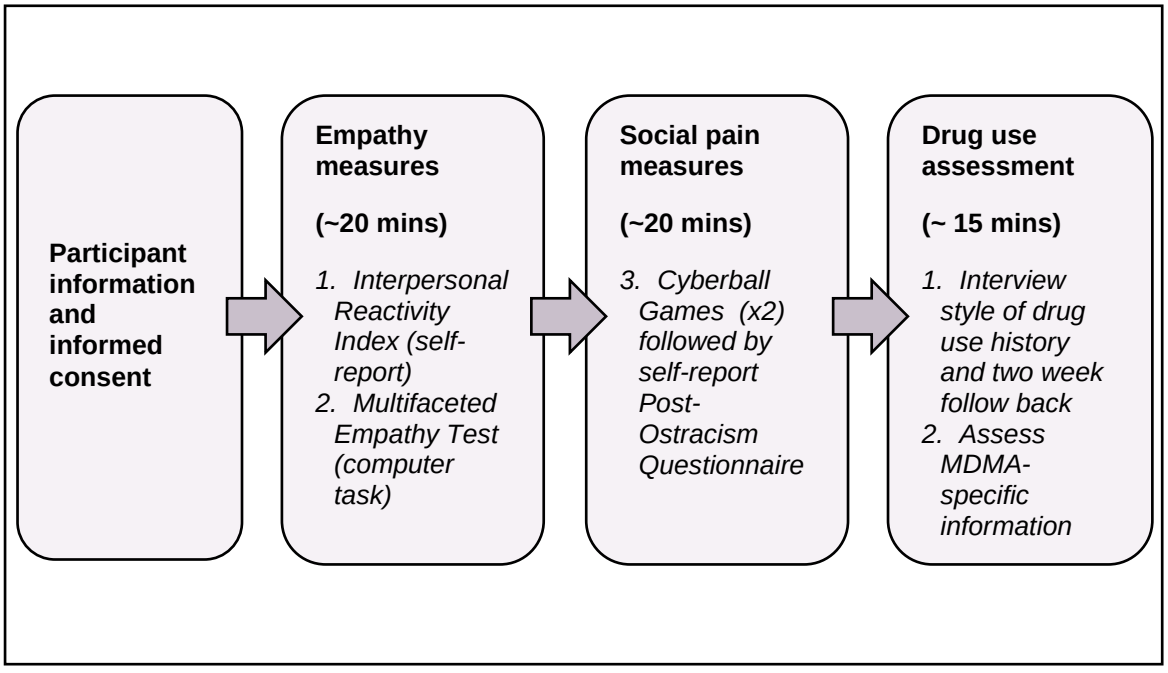


Figure 5.1. Study timeline.

On arrival, participants read the participant information sheet and provided written informed consent. They then completed both the subjective questionnaire (IRI) and computerised task (MET) that measured empathy. Upon completion of these measures, participants played the Cyberball Game, where affective measures (POCQ) were taken following each individual game. Once all computer tasks and associated measures were completed, participants provided an extensive history of their licit and illicit drug use.

5.2.4 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS), version 23. Data were checked for outliers, homogeneity of variance, skewness and kurtosis. Assumptions of normality were tested using the Shapiro Wilk test and histogram plots.

Group differences in both cognitive and emotional empathy using the subjective questionnaire (IRI) and a computerised task (MET) were assessed using a one-way ANOVA, with group (MDMA user; non-MDMA drug users; alcohol only) as the between-subjects variable. For the IRI, all four subscales (empathic concern; personal distress; perspective taking; fantasy scale) were assessed independently. For the MET, cognitive empathy was calculated by summing the total of correct responses participants made when identifying emotions, whilst emotional empathy was calculated as the mean overall score of empathy ratings over the emotional images. For the Cyberball Paradigm, group differences in the dependent variables were assessed using mixed measures ANOVA, with group as the between-subjects variable, and inclusion status (inclusion game; exclusion game) as the within-subjects variable. Chi Square tests were used to assess dichotomous, categorical dependent variables. Where data was found to be non-normally distributed, transformations were applied or non-parametric tests were used, namely the Kruskal Wallis test. Pearson's Correlations were used to assess exploratory relationships between key psychological variables and drug use, and all post-hoc tests were amended for multiple comparisons using Holm-Bonferroni corrections.

5.3 Results

5.3.1 Demographics and Drug Use (Table 5.1)

The three groups were matched in age, gender, years in education, and history of substance use problems. There was a trend to suggest there may be a group difference in history of mental health problems, with the MDMA poly-drug user group appearing to have a higher prevalence of historical treatment for mental health problems, but this did not reach the threshold for significance. Drug use history and recent use (in the two weeks prior to testing) were also assessed between the two groups (Table 5.1), where information regarding: the number of years that each substance has been used for; the number of days each substance (licit and illicit) is used per month; the amount of the substance that is used per session; the number of individuals that have used each substance in the last two weeks; the total amount of units used in the last two weeks is reported. There were minor reports of MDMA use in the non-MDMA poly-drug user group; however there were no recent reports of MDMA use except for one isolated occasion 14 days prior to testing. Number of individuals who have used the substance is reported alongside regular use for each substance, which was calculated as the number of individuals who had used that substance for over a year and used it within the year. A Chi-squared test was used to assess group differences in regular use between the two drug using groups, as there were no reports of regular drug use in the alcohol only group. There were significant group differences in tobacco and cannabis use. Significance values were adjusted for multiple comparisons using Holm-Bonferroni corrections.

Table 5.1. *Demographic Information, Drug Use History and Recent Drug Use between the Groups (M and SDs)*

	MDMA poly-drug users (n=25)	**Non-MDMA poly-drug users (n=19)**	**Alcohol users only (n=23)**	**F or χ^2**	***p*-value**
Age	21.3 (1.6)	21.1 (2.9)	20.8 (1.3)	0.38	.684
Gender (male, female)	12,13	5,14	5,18	4.26	.119
Years in education	16.0 (1.8)	16.5 (1.0)	16.6 (1.1)	1.06	.351
History of mental health problems (n=yes)	8	1	3	5.38	.068
History of substance use problems (n=yes)	1	0	0	2.90	.574
Alcohol (n=used, n=regular)	**25, 23**	**19, 17**	**23, 21**	0.00	1.00
Years used	6.7 (0.46)	6.1 (0.67)	5.7 (0.50)		

Days per month	10.6 (0.96)	9.0 (1.2)	7.3 (0.85)		
Units per session	12.1 (0.98)	10.7 (0.84)	10.1 (1.0)		
Used in past two weeks (n=yes, units)	25, 52.2 (27.4)	18, 23.0 (32.5)[a]	22, 33.0 (40.9)[a]		
MDMA (n=used, n=regular)	**25, 23[b]**	**13, 0**	**5, 0**	42.00	<.001***
Years used	3.1 (0.35)	1.0 (n/a)[a]	0.0		
Days per month	2.0 (0.31)	1.0 (1.8)	0.0		
Units per session	0.5 (0.25)[a]	0.5 (0.67)[a]	0.0		
Used in past two weeks (n=yes, units)	10, 0.2 (0.40)[a]	1, 0.5 (0.00)	0.0		
Tobacco (n=used, n=regular)	**24, 20**	**18, 6**	**10, 0**	10.47	.008**
Years used	5.5 (3.0)[a]	5.5 (4.0)[a]	3.5 (0.50)		
Days per month	21.5 (27.0)[a]	9.0 (11.0)[a]	3.0 (22.8)[a]		
Units per session	2.0 (3.0)[a]	2.0 (1.8)[a]	1.0 (2.5)[a]		
Used in past two weeks (n=yes, units)	8, 34.5 (73.5)[a]	5, 30.0 (81.5)[a]	0.0		
Cannabis (n=used, n=regular)	**23, 15**	**18, 3**	**8, 0**	8.73	.021*
Years used	4.8 (0.44)	2.8 (0.86)	0.0		
Days per month	3.5 (10.3)[a]	1.0 (2.0)[a]	0.0		
Units per session	0.5 (0.75)[a]	0.37 (0.08)[a]	0.0		
Used in past two weeks (n=yes, units)	12, 0.5 (2.0)[a]	1, 0.2 (0.0)	0.0		
Cocaine (n=used, n=regular)	**22, 4**	**11, 3**	**2, 0**	<0.01	>.999
Years used	1.8 (0.37)	1.0 (0.00)	0.0		
Days per month	2.0 (5.0)[a]	1.0 (3.0)[a]	0.0		
Units per session	0.58 (0.10)	0.51 (0.11)	0.0		
Used in past two weeks (n=yes, units)	3, 0.25 (n/a)[a]	2, 0.63, (n/a)[a]	0.0		
Ketamine (n=used, n=regular)	**15, 5**	**5, 0**	**0, 0**	4.29	.228
Years used	1.0 (3.0)[a]	n/a	0.0		
Days per month	2.0 (3.0)[a]	1.0 (2.5)[a]	0.0		
Units per session	0.25 (0.29)[a]	0.25 (n/a)[a]	0.0		
Used in past two weeks (n=yes, units)	4, 0.45 (45.0)[a]	3, 0.25 (n/a)[a]	0.0		
Amphetamines (n=used, n=regular)	**8, 1**	**1, 0**	**0, 0**	0.79	>.999
Years used	2.5 (2.5)[a]	0.0	0.0		
Days per month	4.0 (n/a)[a]	0.0	0.0		
Units per session	0.33 (3.6)[a]	0.0	0.0		
Used in past two weeks (n=yes, units)	1, 4.5 (0.0)	0.0	0.0		
Benzodiazepines (n=used, n=regular)	**6, 1**	**0, 0**	**0, 0**	0.78	>.999
Years used	1.5 (n/a)[a]	0.0	0.0		
Days per month	n/a	0.0	0.0		

Units per session	0.2 (n/a)[a]	0.0	0.0		
Used in past two weeks (n=yes, units)	1, 1.5 (0.0)	0.0	0.0		
Hallucinogens (n=used, n=regular)	**17, 5**	**4, 1**	**2, 0**	1.99	.790
Years used	2.1 (0.42)	2.5 (1.5)	0.0		
Days per month	0.50 (n/a)	1.0 (n/a)	0.0		
Used in past two weeks (n=yes, units)	0.0	0.0	0.0		

Note. Units used are as follows: grams for MDMA, cannabis, cocaine & ketamine; units for alcohol; number of cigarettes for tobacco. Units for hallucinogens were not excluded due to inconsistency in units for the different hallucinogenic drugs (i.e. grams of mushrooms, tabs of LSD).

[a] Non-normally distributed data where the median and interquartile range are reported.

n/a Missing data or not enough data for calculating the interquartile range (n>3), or the standard deviation (n>1).

[b] For regular use of MDMA, there was one missing value for two individuals which is why n=23 for regular users. * p<.05, ** p<.01, *** p<.001

Within the MDMA poly-drug user group, on average the greatest amount of MDMA used in a single session was 0.50 grams (IQR = 0.76). When asked how often individuals mix MDMA with other drugs, 59.1% of responses indicated always, 27.3% indicated often, and 13.6% indicated sometimes. Alcohol was the primary drug used alongside MDMA (81.8%), followed by cannabis (13.6%), and then hallucinogens (4.5%). When asked which drug individuals would use to 'chill out' after MDMA use, the majority of individuals indicated cannabis (61.9%), with others reported nothing (19%), ketamine (14.3%), or benzodiazepines (4.8%). When asked about low mood the week following MDMA use, 90.9% of respondents indicated yes, and 100% of these believed it was due to the MDMA. When asked if they had ever experienced difficulties concentrating as a consequence of their MDMA use, 81% reported no, whilst 19% reported yes. When participants were asked what form they used street MDMA, 24 individuals (96%) reported using it as crystals/powder, whilst one (4%) reported using pills. Participants were also asked whether they felt their interactions with other people changed as a consequence of their MDMA use, where 54.5% reported yes and were asked to briefly elaborate. Fourteen individuals provided qualitative responses and these are summarised in Table 5.2.

Table 5.2 *Qualitative Reports on how MDMA Influences Social Interactions*

	Qualitative response
1	more confident and easier to strike up conversations with unknown people
2	After the first time, I remember feeling friendly and happy afterwards and I think its made me more open-minded
3	More intune with what other people are feeling, maybe more self-conscious in what I say/ how I act.
4	More energetic on the night and more chatty. More confident
5	I feel more connected to people, especially when we touch. I feel more in tune with people.
6	It makes you more open to all the people on a night out. More likely to talk to a randomer/ talk to a stranger (when on it)
7	I think I empathise more, I connect with people more. I feel more able to express love and appreciation for people.
8	I am generally more outgoing now and feel more able to talk to people now. It made me more social and less scared of socialising.
9	Positive effect - given life experience - more sociable, no mental health effect, can see why people do drugs.
10	Increase in empathy. Anxiety period with repercussions
11	If angry/arguing, what it's like on MDMA - helps yes when during
12	More social
13	fundamental in some of life-long friendships
14	makes more sympathetic

5.3.2 Empathy

Subjective empathy (Interpersonal Reactivity Index; IRI).

For emotional empathy, there was a significant group difference in empathic concern ($F(2,64) = 6.42$, $p = .003$, $\eta^2 = .17$), where Holm-Bonferroni corrected t-tests revealed MDMA users scored significantly higher than the non-MDMA drug users ($t(42) = 3.54$, $p = .004$, $\eta^2 = 0.23$) (figure 5.2), but not significantly different from the alcohol only users ($t(46) = 2.19$, $p = .066$, $\eta^2 = 0.09$). There were no significant differences between non-MDMA drug- and alcohol users only ($t(40) = 1.46$, $p = .152$, $\eta^2 = 0.05$). On the personal distress subscale, there were no significant group differences ($F(2,64) = 1.74$, $p = .185$, $\eta^2 = .05$).

For cognitive empathy, there was a trend to suggest a significant group differences on the sub-scales of fantasy ($F(2,64) = 3.06$, $p = .054$, $\eta^2 = .09$). There were no significant group differences in perspective taking ($F(2,64) = 1.06$, $p = .352$, $\eta^2 = .03$) (figure 5.2).

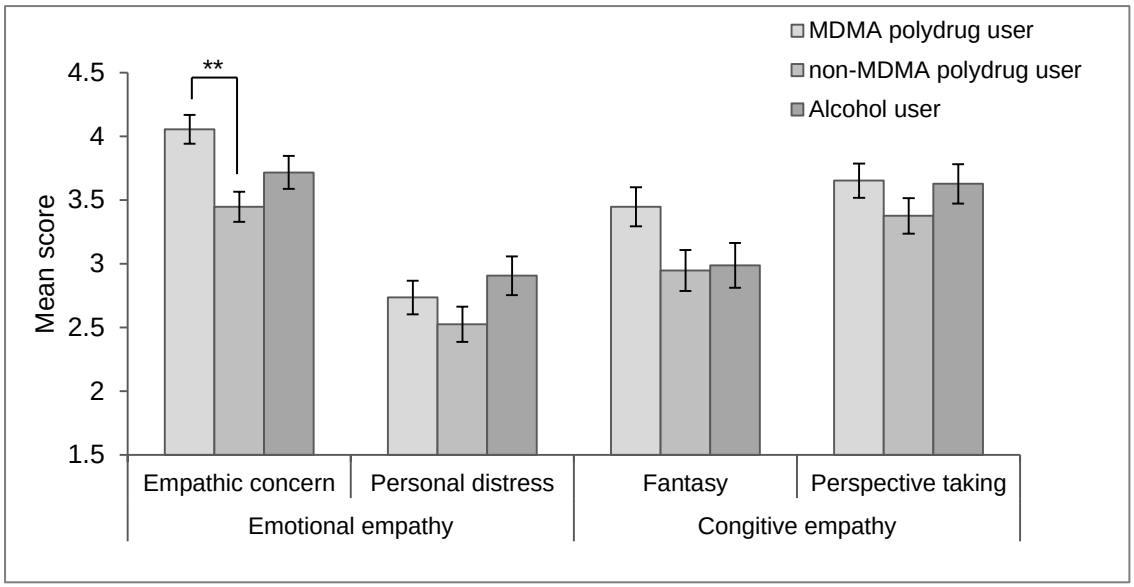


Figure 5.2. Cognitive and emotional empathy measured by the Interpersonal Reactivity Index (IRI). The MDMA poly-drug users rated significantly higher than non-MDMA poly-drug users for empathic concern (emotional empathy subscale), and there was a trend to suggest a difference with the alcohol users, too. Additionally there was a trend to suggest a significant group difference in fantasy (cognitive empathy subscale). ** p<.01. Error bars represent ± 1 SEM.

Computerised task (Multifaceted Empathy Test; MET). When looking at cognitive empathy, there was a significant difference in group ($F(2,64) = 3.69$, $p = .031$, $\eta^2 = .10$). Holm-Bonferroni corrected t-tests revealed that the MDMA user group scored significantly higher than the non-MDMA drug user group ($t(42) = 2.85$, $p = .028$, $\eta^2 = .16$) but no differently to the alcohol only group ($t(46) = 1.39$, $p = .342$, $\eta^2 = .04$), and no significant differences between the non-MDMA drug users or alcohol users ($t(40) = 1.30$, $p = .342$, $\eta^2 = .04$) (figure 5.3a). There were no significant group differences in emotional empathy ($F(2,64) = 0.71$, $p = .496$, $\eta^2 = .02$) (figure 5.3b).

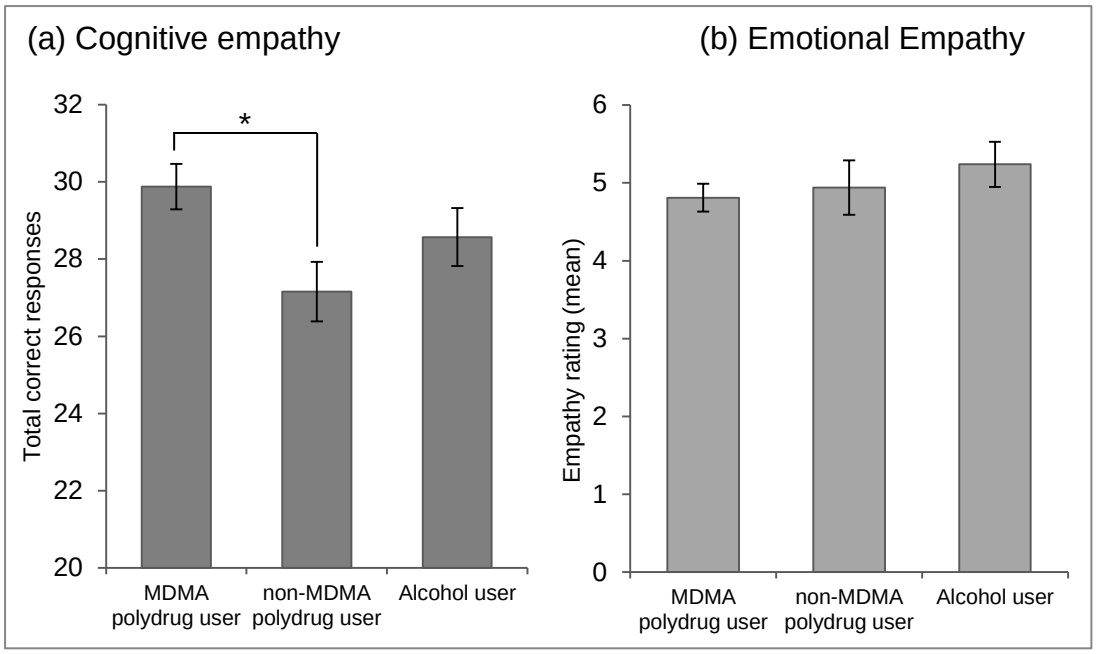


Figure 5.3. Results from the Multifaceted Empathy Test. (a) cognitive empathy was significantly greater for MDMA poly-drug users when compared with non-MDMA poly-drug users, and (b) there were no significant differences in ratings of emotional empathy between the groups. * p<.05. Error bars represent ± 1 SEM.

5.3.2 Social Pain

A mixed repeated measures ANOVA compared the effect of group (MDMA users, non-MDMA drug users, and alcohol users only) and inclusion status (inclusion, exclusion) on the following dependent variables: 1) positive affect, 2) negative affect, 3) self-esteem, 4) control, and 5) as well as perceived percentage of ball throws received (manipulation check). The other subscales (sense of belongingness, meaningful existence, anger, and hurt feelings) were highly skewed and did not improve following transformation, thus these were converted to change scores and where there were no statistical group differences (see Appendix 5.1).

There were significant overall decreases in positive affect, self-esteem, control, and perceived percentage of ball throws from inclusion to exclusion (Table 5.3). There were also significant increases in negative effect from inclusion to exclusion. There were no significant main effects of group, and no significant interactions between group or inclusion status on any of these indices. All analyses co-varied for order of Cyberball games due to significant order by condition by inclusion status interactions.

Table 5.3. *Statistical Assessments on Outcome Measures for the Cyberball, Alongside Means and Standard Deviations.*

	Inclusion status	MDMA polydrug user	Non-MDMA polydrug user	Alcohol only user	F-Statistic		p value	η²
Positive affect	Inclusion	3.41 (0.88)	3.51 (0.85)	3.68 (0.62)	Group	0.98	.383	0.04
	Exclusion	2.17 (0.75)	2.65 (0.93)	2.41 (0.83)	Inclusion status	7.84	.007**	0.10
					Group* inclusion status	0.97	.385	0.03
Negative affect	Inclusion	1.59 (0.74)	1.63 (0.67)	1.37 (0.41)	Group	1.48	.236	0.02
	Exclusion	2.49 (1.03)	2.77 (0.83)	2.38 (0.87)	Inclusion status	13.68	<.001***	0.08
					Group* inclusion status	0.13	.877	<0.01
Self-esteem	Inclusion	3.19 (0.99)	3.31 (0.95)	3.46 (0.76)	Group	1.66	.847	<0.01
	Exclusion	2.08 (0.78)	2.46 (0.92)	2.12 (0.76)	Inclusion status	24.38	<.001***	0.09
					Group* inclusion status	1.95	.151	0.01
Control	Inclusion	2.38 (0.81)	2.86 (1.04)	2.59 (0.69)	Group	3.28	.044*	0.07
	Exclusion	1.34 (0.44)	1.87 (0.72)	1.43 (0.53)	Inclusion status	15.19	<.001***	0.16
					Group* inclusion status	0.25	.783	0.01
Perceived number of ball throws	Inclusion	34.62 (11.00)	34.57 (8.17)	33.33 (4.52)	Group	0.65	.528	0.02
	Exclusion	13.52 (6.21)	14.83 (7.81)	12.21 (6.84)	Inclusion status	38.14	<.001***	0.34
					Group* inclusion status	0.16	.823	<0.01

Note. df for main effects = 1, 62, for interaction = 2, 62,*p<.05, **p<.01, ***p<.001

5.3.4 Exploratory analyses

Thirteen cases were identified where MDMA was used in the two weeks prior to testing. Due to the acute effects of MDMA on emotional empathy on the MET, a Pearson's correlation was conducted between recent MDMA use (grams used in the last two weeks) with emotional empathy, which was not statistically significant (r = 0.44, n = 11, p = .177).

Ecstasy use (number of days used per month) in the MDMA poly-drug user group was not correlated with empathic concern on the IRI (r= -0.20, n=24, p = .343),

nor was it significantly correlated with cognitive empathy on the MET (r= -0.19, n=24, *p* = .371). Empathic concern on the IRI and emotional empathy on the MET were also significantly correlated (r=0.42, n=67, *p*<.001), however perspective taking on the IRI and cognitive empathy on the MET were not (r=-0.11, n=67, *p* = .398).

Due to minor reports of MDMA use in the non-MDMA poly-drug and alcohol only groups, we conducted a sensitivity analysis looking at whether there was a significant difference between those who have used MDMA in the past and those who have never used MDMA on empathic concern on the IRI, finding that there was no significant difference between those who reported yes (*M* = 3.82, *SD* = 0.60) or no (*M* = 3.67, *SD* = 0.62) (F(1,65)=0.88, p =.351, η^2 = 0.01). A further analysis looked at the effect of Group on empathic concern excluding any individuals who ever reported ever using MDMA in the non-MDMA poly-drug users (n=13 reported having used MDMA) and alcohol only users (n=5 used MDMA), finding that there was a near-significant effect on emotional empathy between the MDMA poly-drug (*M*=4.07, *SD*=0.51), non-MDMA poly-drug (*M*=3.47, *SD*=0.80), and alcohol only group (*M*=3.74, *SD*=0.56) that became not significant upon correcting for multiple comparisons (F(2,46)=3.29, *p* = .092, η^2 = 0.13).

5.0 Discussion

The current study investigated the long term effects of repeated MDMA use on empathy and the social distress experienced as a consequence of social exclusion. Higher levels of subjectively rated emotional empathy in people who regularly used MDMA were observed when compared with non-MDMA poly-drug users. On the Multifaceted Empathy Test (MET), cognitive empathy was found to be greater in MDMA users when compared with non-MDMA poly drug users, mirroring the findings of previous research (Wunderli et al., 2018). However, no significant group differences were observed in emotional empathy during the MET or in subjective cognitive empathy. For social distress caused by exclusion, although there was a significant decline in both mood and self-esteem after being socially excluded, no differences were observed between the three groups in responses to social exclusion.

The main novel finding of the study is of enhanced self-reported emotional empathy in people with repeated reported use of MDMA. This was confined to the

empathic concern scale – which suggests a greater concern for others in these individuals compared to poly-drug users who do not take MDMA. Increased levels of cognitive empathy in long-term MDMA users were also observed, replicating the findings of the previous study by Wunderli and colleagues (2018). The current project recruited long-term but mild users (a minimum of ten times), in order to reflect doses that may be used in a therapeutic setting. Wunderli and colleagues (2018) studied heavier users and observed that cognitive empathy was inversely related to hair concentrations of MDMA, i.e. heavier use was associated with poorer cognitive empathy, suggesting that lighter MDMA users had greater cognitive empathy. The current study only assessed light MDMA users and thus the finding of improved cognitive empathy in light users are consistent with the Wunderli study. However, we did not find a correlation with self-reported MDMA use and cognitive empathy in our users, which may be due using subjective estimates in our study, compared to hair analysis. Furthermore, the current study differs from the latter study in that differences in empathy were only observed between the long-term MDMA users when compared to non-MDMA drug users, and not when compared with alcohol only users. Furthermore the similarity in scores between the alcohol only and the non-MDMA poly-drug group also suggest that this does not reflect a simple linear relationship between substance use and degree of subjective emotional empathy.

Acutely, studies have found that MDMA enhances emotional, but not cognitive empathy (Hysek, Schmid, et al., 2014; Kuypers et al., 2014; Kuypers et al., 2017; Schmid et al., 2014), and our study extends these findings to suggest that enhancement of emotional empathy may be a longer lasting consequence of MDMA use. Differences observed in emotional empathy may be down to pre-existing group differences which draw some users to take the substance; an explanation that is difficult to rule out without prospective studies. Although it did not meet the threshold for significance, there was a trend to suggest a greater incidence of mental health problems in the MDMA group, which is consistent with previous work in MDMA users (Verheyden, Henry, & Curran, 2003). Historical mental health problems may also play a role in empathy differences between groups, though previous literature has suggested empathy deficits in those with depression (Hoffmann et al., 2016) which conflicts with this explanation.

Greater self-reported emotional empathy following repeated doses of MDMA may be down to users having had heightened emotional experiences under the acute effects of the drug. For example, in the popular press there is an often reported reduction in football violence that corresponded with an increase in MDMA use among fans, which has been attributed to the prosocial effect of the drug in reducing aggression (Gilman, 1994). As such, it may be that autobiographical memories of such experiences facilitate a longer-term increase in prosocial emotion among individuals in the MDMA user group.

Heightened emotional empathy in MDMA users versus non-MDMA users in the current study was only observed using the subjective measure, and was not observed in the computerised task despite the two measures being correlated. The discrepancy in findings between the IRI and MET may have been influenced by multiple factors. One potential explanation is that the questionnaire measures 'trait' empathy which is more stable over time, whilst the computerised task (the MET) measures 'state' empathy which is more fluid. Many previous studies have used the MET to assess 'state' empathy (Dolder et al., 2017; Dolder et al., 2016; Dolder, Strajhar, Vizeli, Odermatt, & Liechti, 2018; Hysek, Schmid, et al., 2014; Kuypers et al., 2017; Pokorny, Preller, Kometer, Dziobek, & Vollenweider, 2017; Vizeli & Liechti, 2018). It is thus possible that differences in how both the IRI and the MET operationalise empathy could explain why significant differences in emotional and cognitive empathy were observed in one measure and not the other. For example, for emotional empathy, the MET is looking at the spontaneous ability to adopt the emotional state of someone on the screen (i.e. emotional contagion), whilst the IRI requires introspection and memory to more broadly assess sympathy and distress for others. As the study was relatively small and the effects between the groups expected to be subtle, it is possible that the IRI was slightly more sensitive to these subtle group differences as it assessed emotional empathy more broadly, compared to the MET.

Repeated MDMA use was not found to impact on the experience of social exclusion: users did not differ from the two control groups. Together with findings from the empathy measures, this could suggest that repeated MDMA use at this level may not have a negative impact on social functioning. Indeed our findings tentatively suggest that repeated MDMA use, at a low level, is associated with

increased concern and sympathy for others as well as improved cognitive empathy. However, the ability to draw conclusions from the Cyberball in our study is limited, as there are no differences between the three groups on responses to social exclusion (i.e. the MDMA group are not less or more sensitive). It is also possible that the absence of any effect of group on the Cyberball 'needs' measures (self-esteem, meaningful existence, sense of belonging, and control) are due to the questions fitting a two-factor structure, rather than the current four factor structure, as recently suggested (Gerber, Chang, & Reimel, 2017). Nonetheless, if chronic MDMA use causes serotonergic dysfunction and/or changes in psychological wellbeing, then it may only occur at high, repeated doses.

There have been suggestions previously that long-term MDMA use may cause heightened social distress (Parrott, 2007). The current findings do not support this claim; however, as the current study reports a null finding this must be interpreted with caution. Nonetheless, assessing social functioning is useful for understanding the utility of MDMA therapeutically, as many psychological disorders are associated with impaired empathy e.g. schizophrenia (Lysaker, Hasson-Ohayon, Kravetz, Kent, & Roe, 2013), alcohol use disorder (Dethier & Blairy, 2012), and chronic pain (Song et al., 2018). Although they did not show social distress, a large proportion of the MDMA users did report experiencing a lowered mood in the days following MDMA, all of which believed this was due to using MDMA. This is possibly misleading: when used therapeutically, observed low mood following MDMA is not different to placebo, suggesting that it is perhaps the drug set and setting associated with recreational use that is causing a consequent lowering of mood (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011). For example, recreational use is related to sleep deprivation and adulterants that are added to street MDMA, which would not be present when using MDMA therapeutically. Understanding the longer-term effects of MDMA can further enable clinicians to decipher whether such a treatment could have therapeutic uses beyond PTSD, indeed recent work is underway testing MDMA in patients with autism spectrum disorder (Danforth et al., 2018; Danforth et al., 2016) and in alcohol use disorder (Sessa, 2017).

The present study inevitably had several limitations. We relied solely on self-report measures of drug use, and the use of objective measures e.g. hair analysis or urine drug screen would be advisable in future. Another limitation is that the cross-

sectional design of the study does not rule out alternative explanations for the differences in empathy; for example, pre-existing differences in empathy prior to MDMA use. A strength of the current study was that it recruited low level MDMA users, who were fairly mild users but used the substance regularly. Mild users have largely been overlooked in the literature (Szigeti et al., 2018), however these levels are more likely to mirror the levels which can be used in therapeutic settings. Another strength is the inclusion of a non-MDMA poly-drug user group; this is unlike other studies and was incorporated to elucidate any specific effects of MDMA (as MDMA users are likely to have used other substances), in addition with comparing them with drug-naïve controls. All three groups were matched on all demographic variables, but the two drug using groups were not well matched on regular drug use (excluding MDMA), particularly regarding tobacco use. As the study was fairly small it is also possible that this three-group design may have been underpowered to detect other important group differences; for example, the number of mental health problems between groups.

In summary, the current study suggests that mild, repeated use of MDMA is not associated with any impairment to interpersonal functioning. Rather, it was associated in the present sample with enhanced levels of subjective emotional empathy, which has not been reported before, as well as greater cognitive empathy on a computer task, which replicates previous findings. Based on this research it is not possible to identify whether differences in empathic processes precede or are a consequence of MDMA use, nonetheless these data strengthen the argument that MDMA may be used safely in a therapeutic setting without negative repercussions on empathy and sensitivity to social pain. Future work could investigate whether there are any protective effects of mild MDMA use in clinical populations; for example in those with affective disorders, or autism spectrum disorders. Research could also extend the clinical investigations of MDMA when given in conjunction with psychotherapy to OUD, where social functioning is impaired (Chapter 3) and there are high rates of trauma history (Chapter 3; Naqavi et al., 2011).

Chapter 6: General Discussion

6.1 Summary of findings

In my Ph.D, I set out to investigate how social risk factors, including childhood trauma and social stress, are involved in the onset and maintenance of opioid use disorder. I also began to investigate the potential of two novel treatments that may hold promise for opioid use disorder through their effects on social functioning.

I looked at social cognition, which is how individuals relate and interact with others emotionally and behaviourally, via processes such as empathy, compassion, and responses to social events (Patin & Hurlemann, 2015). Deviations in social cognition are clearly observed in addiction (Heilig et al., 2016), however little was known about how these impairments are involved in the onset of opioid use disorder, or how they are affected as a consequence of opioid use. Understanding the aetiology of these impairments and how they are a risk factor for opioid use may be important in developing preventative measures against opioid addiction. In addition, understanding how they are affected as a consequence of drug use may help inform novel treatments to restore these difficulties, with positive repercussions on interpersonal relationships and well-being. I shall briefly summarise my findings and then consider my work in light of the model I proposed in Chapter 1, alongside the wider social and clinical implications of the findings of this thesis.

6.1.1 Childhood trauma as a risk factor for opioid use disorder

Experiences of childhood abuse and neglect are disproportionately higher in opioid use disorder compared to the general population (Heffernan et al., 2000; Naqavi et al., 2011). Preclinical work has linked early trauma with heightened sensitivity to opioid reward, where researchers have suggested that these early adverse experiences cause hypofunction of the endogenous opioid system (Kalinichev et al., 2001; Vazquez et al., 2005). Little was known about whether this was also the case in human subjects. The study reported in Chapter 2 investigated the link between childhood trauma, the endogenous opioid system, and responses to opioid drugs by assessing responses to an acute dose of morphine in the laboratory. Healthy volunteers with histories of childhood abuse and neglect were recruited and compared with individuals with no childhood trauma. Endogenous opioid activity was assessed by using pain threshold, a cost-effective and easy to implement method previously shown to be sensitive to opioid activity (Johnson & Dunbar, 2016). In this

study, we reported heightened positive responses to morphine in those with childhood trauma – where they rated higher in liking of the drug effects, feeling euphoric, and wanting more morphine at multiple time points post-drug administration. Conversely, disliking the effects was higher in the non-trauma control group, alongside increased ratings of nausea and dizziness. We did not report any differences between groups in pain threshold or tolerance, however we did report greater pain catastrophising, depression, anxiety, stress, and reduced self-compassion in the trauma group.

Chapter 2 therefore highlighted childhood trauma as a vulnerability factor for opioid use disorder via a greater sensitivity to the rewarding effects of opioids and a blunted response to the negative effects. The role of psychological mechanisms (e.g. emotional regulation or numbing) was highlighted, especially in light of no differences in physical pain threshold. Heightened opioid reward may also have been due to interactions with other neurobiological pathways (e.g. dopamine, glucocorticoids).

6.1.2 Impaired social cognition pre- and post-opioid use disorder

Social risk factors (such as social deprivation, isolation, and stigma) may cause permanent alterations to the development of the endogenous system (section 1.3); although we did not observe that childhood trauma affected this system in our study (section 6.1.1). In addition, chronic use of opioid drugs also alters this neurobiological pathway via a downregulation of endogenous opioid receptors. Thus, social risk factors and chronic opioid use may result in a dampened opioid system, which could consequently cause heightened social distress following negative social events, and impaired social cognition that may predate an opioid use disorder as well as maintain it.

We investigated this in three populations: healthy volunteers with childhood trauma and without histories of any drug/alcohol use disorder (Chapter 2) in order to assess whether impairments exist prior to drug use; in individuals with opioid use disorder (Chapter 3) to assess whether these are impaired post-drug use; and in mild MDMA users (Chapter 5) to assess whether social processes are negatively impacted by low level, repeated MDMA use in order to investigate the safety of using MDMA as a potential treatment for opioid use disorder. In all three studies, we assessed social distress in response to a period of social exclusion using the

Cyberball, as well as deviations in emotional and cognitive empathy (the ability to identify and feel the emotional states of others, respectively) using the MET.

In the chronic opioid users (Chapter 3), we observed partial support for heightened social distress in opioid users in the form of anger, where opioid users who were not recently treated with their OSM at the time of testing shown greater increases in anger after being socially excluded, whilst anger did not change in those who had recently taken their OSM. We also reported reduced emotional empathy on the MET in those who had not recently used their OSM, whilst emotional empathy in the recently treated user group was higher and equivalent to opioid-naïve controls. These findings suggest the role of opioid intoxication in raising the threshold for tolerating social exclusion and difficult affective states, as well as for potentially remediating difficulties in relating with others' emotional experiences (particularly when faced with positive emotions).

This study also reported a trend towards greater rates of interpersonal childhood trauma in the opioid user groups, as well as greater loneliness, potentially indicating the role of prior social risk factors preceding drug use that could be responsible for these findings. However, this was to a lesser extent than expected as prior research has reported considerably higher rates of childhood trauma in opioid users compared with the general population (Heffernan et al., 2000; Naqavi et al., 2011). Moreover, there was a medium effect size for the negative correlation between opioid substitution medication (OSM) dose and emotional empathy within the non-treated group, tentatively suggesting a more severe addiction (indicated by higher OSM dose) was associated with poorer emotional empathy.

In healthy volunteers with childhood trauma (Chapter 2), we did not report any differences in emotional or cognitive empathy compared to those without childhood trauma, nor did we observe any group differences in social distress following a period of social exclusion. Those with childhood trauma did report other social risk factors, such as greater loneliness and lower perceived social support. On face value, when interpreting these findings alongside Chapter 3, this would suggest that heightened social distress (via anger) and impaired emotional empathy may occur as a consequence of chronic opioid use – either by increased exposure to social stressors as a consequence of drug use, or by a downregulation of opioid receptors

(or both). Nonetheless, we did report reduced concern for others' pain on the empathy for pain task in the trauma group, suggesting that childhood trauma could be linked with disrupted empathy for pain specifically, which could linked to a preoccupation with one's own pain and negative thought patterns. Unfortunately empathy for pain was not assessed in opioid users.

In the MDMA users, we reported greater cognitive empathy using the MET compared to drug users who did not use MDMA, in line with prior research (Wunderli et al., 2018) and greater subjective empathic concern using a questionnaire (Chapter 5). There were also no significant group differences in social distress as a consequence of social exclusion. Together these findings may indicate that MDMA may be a suitable treatment when given in conjunction with psychotherapy for opioid use disorder, and does not negatively impact social cognition.

6.1.3 Improving social functioning in opioid use disorder

The first-line treatment for opioid use disorder is using an OSM to stabilise the individual enough for them to abstain from using illicit opioids, with the purpose to reduce the harms associated with illicit opioid use and help them remain healthy (National Institute for Health and Care Excellence, 2017). Patients are also offered the option to detoxify from opioids by gradually reducing the OSM dose when they feel ready. However, unfortunately there are drawbacks with using OSMs and they are limited in their long-term efficacy (see section 1.5). Psychological treatments may also be offered alongside pharmacotherapy, including CBT, counselling or family therapy, however the type of psychological treatments available vary by local care providers and are not necessarily aimed at improving social functioning. One of the aims of this thesis was to investigate novel psychological and pharmacological approaches that may address problems in social functioning in opioid use disorder.

Compassion-focused therapy. We assessed the feasibility of a brief intervention of compassion-focused therapy (CFT) in opioid use disorder (Chapter 4). Compassion can be defined as feeling warmth and affection towards oneself and others in times of hardship and distress, with a commitment to relieve it (Gilbert, 2005; Neff, 2003), and is inversely related to risk of substance use disorder (Phelps et al., 2018). In this study we reported high retention rates, alongside indications that CFT increased desire and efforts to resist the use of opioids, as well as feelings of

coping. These findings suggested greater awareness of cravings and also emotion-focused coping strategies as a consequence of CFT, as opposed to avoidance-focused strategies where individuals seek to avoid stress and negative affective states (Neff et al., 2005). Opioid use could be considered as an avoidance coping method, which is supported by prior research indicating high levels of avoidance coping in patients in treatment for drug and/or alcohol abuse, which was also correlated with childhood trauma (Simons, Ducette, Kirby, Stahler, & Shipley Jr, 2003).

Unfortunately prior trauma history was not assessed in the opioid users recruited into the brief CFT intervention as it was felt by the drug service (who co-created the intervention) that the childhood trauma questionnaire may bring up many issues in the group. We measured self-criticism, however we did not report any group differences or indicators of change in self-criticism as a consequence of the intervention. We measured self-criticism using the Forms of Self-Criticising/Attacking & Self-Reassuring Scale (FSCRS) because this scale assesses both feelings of self-inadequacy and self-hate, as well as the ability to self-reassure (an index of self-compassion), thereby allowing us to investigate both components in one scale. Upon reflection, I realised we should have also included a direct measure of compassion such as using the Self-Compassion Scale (SCS; Raes et al., 2011), as the FSCRS may measure more 'trait' qualities that are chronic and enduring, and unlikely to be changed over a brief intervention. Although there were no indication of changes in self-criticism over the intervention, the opioid users did score considerably higher in self-criticism when compared with normative data using the FSCRS (Baião, Gilbert, McEwan, & Carvalho, 2015). The opioid users in the current study rated considerably greater in self-inadequacy (M=22.45) and self-hate (M=8.37) than the normative data for the FSCRS (self-inadequacy: M=17.27, self-hate: M=3.88), as well as much lower in ability to self-reassure (M=13.32 in the opioid users in the current sample, vs M=20.27 in healthy population). The high self-criticism and low self-compassion observed in the current sample indicate that opioid users could greatly benefit from CFT in fostering compassion, with potentially positive repercussions on mental wellbeing and coping with emotional distress.

We did measure self-compassion using the SCS in Chapter 2, finding lower self-compassion in those with childhood trauma, which tentatively concurs with the

findings from the opioid user group in Chapter 4, despite using two different questionnaire measures. Childhood trauma is related to a difficulty in regulating emotions and an inability to self-soothe (Hien et al., 2005), where drugs can be used as an avoidance coping strategy and for emotional numbing (Simons et al., 2003; Vowles et al., 2018). It is possible that the greater rates of self-criticism observed in the opioid users in Chapter 4 could be linked to prior history of trauma. Furthermore, recent research has identified self-compassion and fears of self-compassion (finding self-compassion and compassion from others aversive) as independently mediating the relationship between trauma and problematic alcohol use (Forkus, Breines, & Weiss, 2019). To investigate this link within our own study (Chapter 2), we correlated self-compassion and liking the effects of morphine and wanting more at peak effects within the childhood trauma group, yet these were not significant. This could be down to the small sample size for a correlation (n=27), or it may be that the trauma group in this sample were particularly resilient, as they did not have histories of addiction or severe mental health problems. It may also be that self-compassion is more important for coping with cravings or withdrawal and is less involved in the acute experiential effects of opioids, which is why we did not observe a relationship between self-compassion and liking or wanting more morphine. Nonetheless, the current thesis supports the suggestion that childhood trauma is associated with reduced self-compassion, which could be related to poor emotion regulation and addiction later in life. Intervening with CFT in addicted individuals may foster more adaptive responses to stress and to difficult emotional states, which should be investigated in a fully powered randomised controlled trial.

MDMA-assisted psychotherapy. There is now some evidence supporting the therapeutic use of MDMA adjunct to psychotherapy for treating a vast variety of mental health problems (see Sessa, Higbed, & Nutt, 2019, for a review), including PTSD (Mithoefer et al., 2019), depression (Yazar-Klosinski & Mithoefer, 2017), alcoholism (Sessa, Sakal, et al., 2019), and autism (Danforth et al., 2018). It is thought that MDMA may work therapeutically through increasing fear extinction via re-exposure to painful memories, but also via increasing empathy and attenuating social distress (see Heifets & Malenka, 2016; Sessa, Higbed, et al., 2019, for a review). For these reasons, MDMA-assisted psychotherapy could be a good candidate in the treatment of opioid use disorder, where trauma levels are high and

social functioning is impaired (Chapter 3). Prior to this, it is important to fully characterise any longer-term impacts of MDMA on social functioning before administering it as a treatment. As it is likely that MDMA will be administered over multiple sessions in clinical settings (alongside non-MDMA therapeutic sessions) (Sessa, Higbed, et al., 2019), Chapter 5 assessed the impact of low-level, repeated MDMA use on empathy and social distress caused by social exclusion. The study used the MET and Cyberball task (which were similarly implemented in Chapter 2 and 3), as well as looking at subjective empathy via the IRI.

In Chapter 5, repeated MDMA users show greater cognitive empathy on the MET, as well as greater subjective emotional empathy on the IRI. Repeated MDMA use did not cause any differences in social distress following social exclusion. Whilst we cannot rule out pre-existing differences in a cross-sectional study such as this, these results may suggest that low-level repeated MDMA use is not associated with impaired social functioning, therefore highlighting its therapeutic potential for treating social dysfunctions in opioid use disorder.

6.2 The social risk factor model

The social risk factor model proposed in Chapter 1 (figure 1.3) tried to depict aspects of the relationship between social risk factors and opioid use disorder. Factors predating opioid use, such as childhood trauma and social stressors (e.g. deprivation and marginalisation), may cause neurobiological changes to the HPA axis, as well as the endogenous opioid and dopaminergic systems. These dysregulations may potentially lead to impaired social cognition, which negatively impacts the ability to relate to others, and heightens social distress to negative social events – as the stress pathways are hyperactive whilst the endogenous opioid pathways are hypoactive. Opioid use may therefore be initially used to alleviate these difficulties. However, exposure to social stressors (e.g. isolation and stigma) may also increase as a consequence of opioid use, which also chronically activates the stress system causing further neurobiological dysregulations. Individuals then enter a vicious cycle: Opioids are used to attenuate difficulties in social functioning, whilst abusing them also escalates other social stressors encountered as a consequence of opioid use. Independent of this cycle, neurobiological changes (such as greater stress sensitivity, or altered dopaminergic/opioidergic activity) may also be

a risk factor for opioid use, where repeated opioid use also causes neurobiological changes irrespective of the presence of social stressors.

The current thesis supports many aspects of this model, however some areas remain unclear and I have now proposed an updated model based on the findings presented in this thesis (figure 6.1). Chapter 2 did not necessarily support the link between childhood trauma and impaired endogenous opioid activity (as there were no differences in pain threshold), however further research using other methods to confirm this is required (see section 6.4.2 for discussion on how to better probe this system). It is also possible that childhood trauma may have caused neurobiological changes to other pathways (such as HPA axis, and dopaminergic system) which – as well as psychological mechanisms – could be partly responsible for the heightened sensitivity to the rewarding and pleasurable effects of morphine.

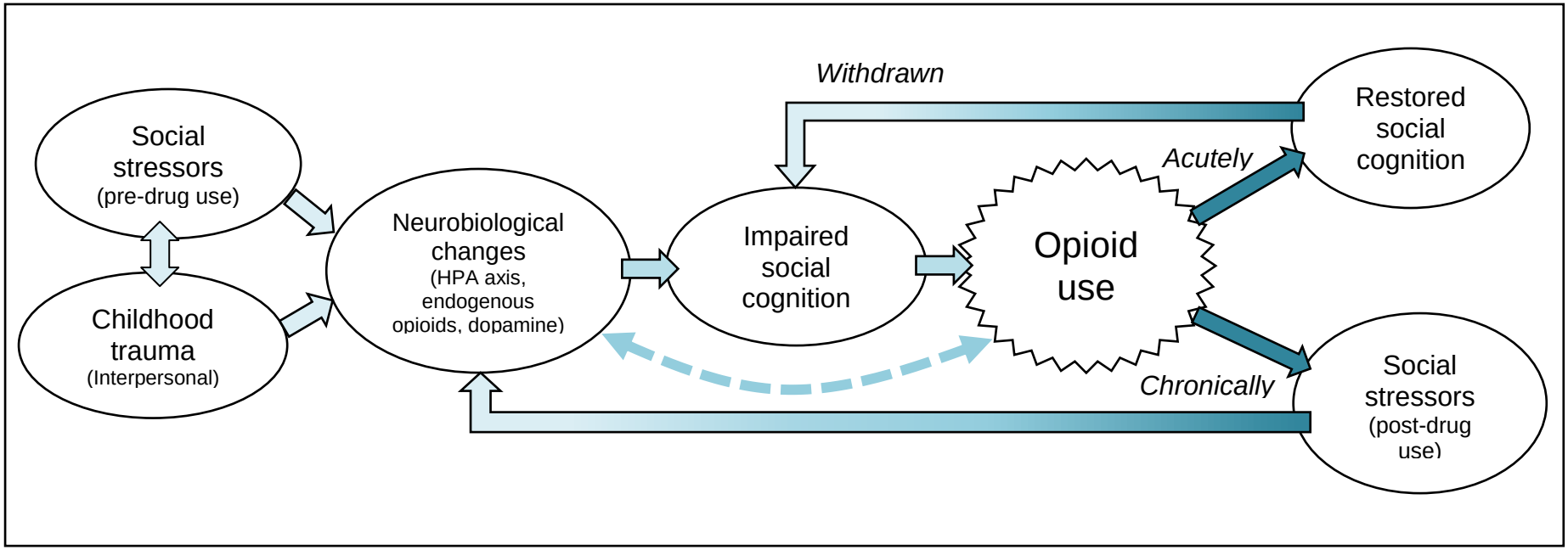


Figure 6.1. The social risk factor model for opioid use disorder updated on the basis of findings from this thesis.

There was also evidence of current social stress in those with histories of childhood trauma, including greater rates of loneliness and less social support. Although childhood trauma can also be considered a social stressor, there could potentially be a bidirectional link between childhood trauma and exposure to other social stressors predating drug use, which has now been incorporated into the model. Inadequate emotional support systems and poor attachments in childhood could lead to greater incidence of social stress factors (such as loneliness) via negative repercussions on adult relationships and interpersonal functioning (Feeney & Noller, 1990). Equally, social stressors such as deprivation and marginalisation may be linked to greater risk of childhood trauma: One study looking at the effect of poverty (one facet of social deprivation) reported that childhood maltreatment reduces as minimum wage increases (Raissian & Bullinger, 2017), where researchers have highlighted the role of parental stress caused by poverty as a primary driving factor (Steele et al., 2016). It is important to note that the vast majority of parents in poverty do not mistreat their children, and the connection between social deprivation and childhood trauma is thought to be the result of a complex interaction between poverty, stigma, poor neighbourhoods, and mental health problems (Gupta, 2017; Shanahan, Runyan, Martin, & Kotch, 2017). Childhood trauma is also more likely to occur if a parent has also experienced abuse or neglect, highlighting the importance of intergenerational effects of trauma which may be higher in deprived areas (Shanahan et al., 2017).

The updated model now also differentiates between acute and chronic opioid use due to the findings reported in Chapter 3. Greater anger post-exclusion in non-treated opioid users in Chapter 3 indicated a reduced threshold for coping with social stress when not acutely affected by opioids, whilst recent opioid use alleviated this anger state. This suggests that opioids could be used to reduce social distress from social stressors that are frequently encountered by opioid users (such as social stigma and ostracism). The finding of poorer emotional empathy for positive emotions in non-treated opioid users suggests that social cognition is impaired in this group, whilst emotional empathy in the treated group was equal to that of controls. Opioids may therefore increase the ability to experience others' positive emotions, potentially by increasing positive affect in the individual. With regards to the model, chronic exposure to social stressors as a consequence of opioid use may cause

neurobiological dysregulations to the HPA axis and endogenous opioid system. This negative emotional state in turn could precipitate opioid use, which acutely alleviates social distress and restores emotional empathy. I suggest that opioids are used to improve social functioning and cope with social stressors, but exposure to social stressors as a consequence perpetuates opioid use.

We found limited support for impaired social cognition as a consequence of childhood trauma alone (Chapter 2), and our results suggest that impaired social functioning in opioid users is likely secondary to opioid use. However I am cautious in concluding this because there may have been important protective factors in those with childhood trauma in Chapter 2, as these were individuals with no history of severe mental health problems or addiction, highlighting them already as a resilient group. Although there was heightened pleasure from acute opioids and blunted negative effects in these individuals, they may not have encountered other social stress preceding opioid use that could be linked with the trajectory to addiction, for example, social deprivation. However, we did report greater levels of loneliness and lower perceived social support, indicating this group still experienced social stress. One potential resilience factor could be self-efficacy, which was equivalent between the trauma group and the controls in this study. Research has linked reduced self-efficacy with drug relapse (Abdollahi, Taghizadeh, Hamzehgardeshi, & Bahramzad, 2014), however this finding is inconsistent (Lu, Wen, Deng, & Tang, 2017). Childhood trauma is also associated with reduced self-efficacy (Lu et al., 2017), yet this was not true for the current sample, which potentially suggests they had higher self-efficacy than what is typical for individuals with childhood trauma. Therefore it is possible that the individuals in Chapter 2 have resilience factors, which is why we did not observe impaired social functioning. It may be that childhood trauma is not always sufficient to impair social functioning, and other social stress may be necessary. Future research should investigate which factors can buffer the impacts of childhood trauma for some individuals.

There was also a trend to suggest greater rates of childhood trauma (pre-drug use) in the opioid groups in Chapter 3, as well as a trend for greater rates of loneliness – tentatively supporting that opioid use disorder is associated with social stressors that precede and co-occur with opioid use (in line with prior studies with larger numbers of participants). This study also assessed HPA functioning in

response to social exclusion by analysing salivary cortisol and heart rate to assess neurobiological changes in stress reactivity. Cortisol was overall lower in the opioid users currently treated with opioids, alongside larger reductions in heart rate, in line with the pharmacological effects of opioids and supporting the direct influence of opioids in causing neurobiological changes in the model. However, this was only acutely, as there were no differences in either physiological measure between the non-treated opioid users and opioid naïve controls, or as a consequence of being socially excluded. This was unexpected as prior research has reported greater cortisol in response to rejection in non-intoxicated opioid users (Kroll et al., 2019). This could either suggest that HPA functioning is not altered in the non-treated opioid users in our study, or it is possible that our social distress manipulation was not powerful enough to produce physiological changes in stress (problems using this task is discussed further in section 6.3.1).

6.3 Methodological Limitations

The current thesis included measures of social distress caused via social exclusion using the Cyberball Game, and emotional- and cognitive empathy using the MET (Chapter's 2, 3, and 5). Although these measures are widely implemented in research, the use of them has highlighted potential pitfalls that will be reviewed in the following section.

6.3.1 Social distress.

There have been many tasks developed to emulate the social distress one may experience following social exclusion (often termed 'social pain'). These tasks have been used and validated in a wide expanse of studies, where the most commonly used is the 'Cyberball Game' (Williams & Jarvis, 2006), having been published in more than 200 studies (Wolf et al., 2015) and it was used in the current thesis. The use of this task has highlighted some fundamental issues with the Cyberball game. An extensive review of social exclusion tasks was undertaken because, as part of the work of this thesis, we explored developing a novel social exclusion task to overcome these issues (Appendix 6.1). Because of this, we reviewed prior exclusion tasks in detail and these are summarised in Appendix 6.2.

Firstly, the demand characteristics of the Cyberball Game are generally apparent. Participants quickly work out the nature of the manipulation occurring

during the task: In Chapter 2, 82% participants did not believe the other players in the task were real (unfortunately this was not assessed in Chapter's 3 & 5). Although research has shown that it is not necessary for the participant to believe that they are playing against real people, as the experimental effects (reductions in mood and self-esteem) are equivalent if they know they are playing with the computer (Zadro, Williams, & Richardson, 2004). This therefore suggests that knowledge of the demand characteristics does not impact on the use of the task. However, it is difficult to disentangle whether the participant is really experiencing social distress if they are aware of the task manipulation, or whether their responses are a consequence of demand characteristics. In future, I would suggest that attempts are made to make the task more believable, such as having multiple participants attend the study session, and updating the interface of the task so it is more contemporary.

Secondly, participants are not required to make a profile or provide any personal information during the Cyberball, and the exclusion they experience is for abstract motives. This is not necessarily reflective of real world ostracism where individuals may be discriminated for some visual or personality characteristic, or because of their membership to a social group. However, from a clinical perspective, many clinical populations experience marginalisation and exclusion very regularly, where being excluded based on abstract reasons may not be enough to produce social distress. More recently, a new task 'Ostracism Online' has addressed this, where participants choose an Avatar that reflects themselves and are asked to complete a descriptive paragraph about their personality (Wolf et al., 2015). Making the social exclusion feel more personal may be more effective and realistically emulate real-life exclusion, particularly in clinical groups that face ostracism regularly, as participants feel they have been rejected on their personal qualities.

Lastly, the Cyberball involves computerised ball throwing and mental visualisation, yet participants may not feel invested and interested in playing the game. The Cyberball Game is very simple, and was first developed nineteen years ago (Williams, Cheung, & Choi, 2000), where in the meantime there have been vast technological advancements in computerised gaming. There has been a rise in 'gamification' of cognitive tasks within psychology, aiming to keep participants interested and engaged in the task (Lieberoth, 2015) whilst also maintaining the scientific validity when implemented correctly (Lumsden, Edwards, Lawrence, Coyle,

& Munafò, 2016). The Cyberball Game is outdated in light of these recent advancements, which may contribute to why so many subjects quickly work out the latent nature of the task. Newer tasks are more ecologically valid, such as 'Ostracism Online' (Wolf et al., 2015) which is a social media-based ostracism task. Thus, the Cyberball Game may not be so appropriate to use nowadays, where more updated exclusion paradigms would be preferred.

Based on our experience with this task, I therefore make the following suggestions when assessing social distress caused by social exclusion. Firstly, I would make efforts to increase the likelihood that the participant will believe they are playing against other people. This could be done by asking multiple participants to attend a testing session (so they see the other individuals), or by asking participants to attend together with friends. However, testing multiple participants simultaneously is not always possible if the study design is complex, therefore using confederate participants would be preferable if possible. Secondly, I would suggest containing a personal profile to enhance the magnitude of feelings of exclusion. This may also make the task more believable if participants are able to read the profiles of others (computerised confederates) playing the game. Thirdly, the task should be easily implemented in any setting, including in a controlled laboratory environment. Lastly, the task should be accessible to any population – therefore being easy to navigate and not relying on prior experience e.g. with social media. During this thesis, a novel task was developed in attempt to address these issues (named 'E-Splat'), however there were issues during validation of the task which is why it is not included as a chapter in this thesis. However, a description of this novel task can be accessed in Appendix 6.2.

Although these issues were highlighted through using the Cyberball, there are some positives to using this task. As it has been so widely used, this does make the results easily comparable across studies. In addition, the simplicity of the task makes it very easy to implement in laboratory settings, and it does seem to purely emulate social exclusion, which makes the results easy to interpret (opposed to other tasks such as 'Atimia' that measures exclusion via evoking feelings of being burdensome). These reasons are why I chose to use the Cyberball task in the studies reported within this thesis. With hindsight, a task such as Ostracism Online may have been

more appropriate, although marginalised groups such as opioid users are less familiar with social media and therefore the task may operate differently in this group.

6.3.2 Empathy.

Empathy has been notoriously difficult to define and has been suggested to contain many facets (Preston & Hofelich, 2012). The current thesis focused on cognitive and emotional empathy, which was measured using the Multifaceted Empathy Test (MET) (a computerised task) as well as the Interpersonal Reactivity Index (IRI) (a subjective questionnaire). Empathy for another's pain was also measured. The use of these measurements has highlighted issues with these tasks but also some overarching problems with the study of empathy more generally.

One issue I encountered is that there does not seem to be a clear consensus on the definition of empathy. There are many different constructs that fall under the empathy umbrella, which can include emotional (or affective) empathy, cognitive empathy, emotional contagion, theory of mind, mentalising (or 'mind reading'), sympathy, and empathy for pain. Many of these are overlapping in the processes that they describe; for example, cognitive empathy describes the ability to understand and infer other's mental states which can also be seen as similar to theory of mind or mentalising, whilst emotional empathy is defined as the spontaneous and automatic ability to experience the emotions of others, which can be similar to emotional contagion. Researchers have attempted to describe the similarities and differences to enhance clarity: emotional empathy is feeling the emotions of another individual, but is different to emotional contagion as it is having the awareness that the emotion arose from somebody else, and it is different to empathic concern which is equally called sympathy (Hein & Singer, 2008). Emotional contagion is suggested as a simpler precursor to emotional empathy, and empathic concern occurs later than emotional empathy as a prosocial response (Hein & Singer, 2008). Perspective taking overlaps with theory of mind and is suggested as highly similar to cognitive empathy, which requires conscious effort to understand other's emotions (Preston & Hofelich, 2012).

Despite these attempts to better define empathy, the overlapping nature of these constructs makes their measurement complex. The MET measures emotional empathy by asking individuals to rate how much they feel the emotions of the person

on the screen based on seeing them (e.g. how much seeing someone feel sad makes them feel sad as a consequence), which confusingly has been described by the task creators as empathic concern (Dziobek et al., 2008) despite other researchers claiming that empathic concern is separate to emotional empathy and occurs later (Hein & Singer, 2008). The measurement of emotional empathy in the MET also seems similar to emotional contagion by spontaneously feeling the emotions of others upon seeing them. Conversely, the IRI measures empathic concern as well as personal distress, which are both suggested to be forms of emotional empathy. Clearly, emotional empathy, empathic concern, and emotional contagion are overlapping, however using the term emotional empathy to describe them all is confusing; this is especially because 'emotional empathy' in the MET is different to what is considered emotional empathy in the IRI. There is therefore a need to operationalise the subtypes of empathy across studies in order to enhance the measurement of these distinct but overlapping processes.

If we are guided by the distinctions between the empathy subtypes provided by Preston and Hofelich (2012) and Hein and Singer (2008), there may be more consistency in the terminology and measurement of these over research studies, and it may allow for more fine-grained measurements of the different subtypes of empathy. For example, using facial electromyography (EMG) to measure facial mimicry during the MET could disentangle the difference between emotional empathy and emotional contagion, as the EMG responses to emotional images could measure emotional contagion, whilst subjective responses would reflect emotional empathy. Facial EMG responses were strongly related to emotional empathy on the MET (Drimalla, Landwehr, Hess, & Dziobek, 2019), supporting emotional contagion as the sub-type of empathy measured by this task. The addition of EMG has the added benefits of being more objective, as it is still possible for participants to answer higher on emotional empathy because of social desirability bias during the MET. Also, asking participants how much they feel the emotion of the person on the screen relies on trusting that they are engaging in the task, and it is hard to know whether they genuinely are *feeling* these emotions – where facial EMG would be a convincing measure that participants are also feeling others emotions.

Another issue that became apparent when using the MET during cognitive empathy was the vocabulary used to describe emotions. Some of the words were

complex and not commonly used, such as nostalgia or crestfallen, which therefore relies on the participant to understand the meaning of these words. Because the task included complex emotions such as these, which may not be familiar to everyone, the outcomes may be dependent on verbal intelligence rather than the ability to genuinely infer and understand other's emotions. In Chapter 3 we assessed the number of words where the meaning was known to participants, and covaried for these in the analyses of cognitive empathy. Future research should perhaps consider checking understanding of each word with participants within the computer task; for example, if the questions are asked at the beginning of the task, the level of verbal vocabulary could be adjusted to each individual's verbal abilities. Equally if this is assessed after completion of the task, where trials containing unknown words could be excluded from the overall mean.

Emotional empathy and empathy for pain have been suggested to depend on whether the individual can experience that in oneself – potentially via the activation of mirror neurons – such that empathy for pain relies on the ability to feel pain in oneself (Rutgen et al., 2015), and empathy for others emotions may also be linked with being able to identify and describe those in oneself i.e. is inversely linked with alexithymia (Swart, Kortekaas, & Aleman, 2009). Empathy must therefore depend on whether an individual has access to a mental representation of that emotion. It may be interesting to ask participants completing the MET about how often they encounter each emotion to investigate whether reduced emotional empathy is due to less exposure to that emotion or due to other reasons, such as the inability to describe it in oneself.

Other tasks have been developed to measure empathy, however not all of them compartmentalise cognitive and emotional empathy. One novel task that does is called EmpaToM, which was developed to differentiate between theory of mind, compassion, and emotional empathy (called 'affective empathy' in the task) (Böckler, Kanske, Trautwein, & Singer, 2014; Kanske, Böckler, Trautwein, & Singer, 2015). This task presents a naturalistic video scene that is either emotionally painful (someone describing a social loss or threat) or neutral (control). After the video, participants are asked to answer a theory of mind question ("Anna thinks that…") or a factual reasoning question ("It is correct that…") to assess theory of mind. Emotional empathy was assessed by a question asking how they felt after the video,

they were also asked how much compassion they felt for the individual in the video. This novel task does not necessarily rely on verbal acuity such as the MET, and it also seems to be a more stimulating measure of empathy because it involves watching an emotionally charged video clip of a person in distress (rather than responding to images on a screen). They also separately measure emotional empathy and compassion, which is a more fine-grained assessment of the different components of empathy. My only suggestion would be the addition of another question asking whether the participant is aware that their emotions came from somebody else, which was suggested to be the main difference between emotional empathy compared with emotional contagion.

Other tasks that measure empathy include the false-belief task that assesses theory of mind, which can be either by answering a series of true/false questions (Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011), or by presenting participants with a practical scenario where objects are hidden or moved by different characters, and the participant has to try and mentalise the states of mind of the characters in the scenario (Bernstein, Thornton, & Sommerville, 2011). There is also the Reading the Mind in the Eyes Test (RMET) which measures mentalising by presenting participants with a series of pictures of eye-regions, and are asked to identify what words best describe what that person is thinking or feeling using two words (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Both of these tasks require the participant to take the perspective of another individual, however by doing so are limited in that they only assesses cognitive aspects of empathy, rather than more emotional components.

The majority of this section has focused on empathy for other's emotions, as many Chapters of the current thesis included the MET as a measure of this. However, I did also use a measure of empathy for pain reported in Chapter 2. Similar to empathy for emotions, empathy for pain has been suggested to depend on the ability to feel pain in oneself (Rutgen et al., 2015), supporting the notion that a core aspect of empathy is the ability to activate mental representations or memories of an emotional experience from another individual based on prior experiences (Preston & Hofelich, 2012). The limitation of assessing empathy for emotions is that not everybody has had the same emotional experiences or responses as others, whereas pain is a universal experience that everybody has memories and

experiences of, which is why it has been suggested as a good starting place to test the shared-representations theory of empathy (Preston & Hofelich, 2012). Research using analgesics such as opioids is particularly useful to test this theory due to alleviating physical pain, which is why we included a measure of this in Chapter 2.

Thus, although studying empathy has highlighted some overarching issues in how its subparts are defined and measured, there are limited tasks available to assess both cognitive and emotional components of empathy, and the MET has been widely used and is easy to implement and navigate. The widespread use of the MET in psychopharmacology research has allowed for comparison between studies and to elucidate the long-term or acute impact of different psychoactive substances, which is why it was deemed suitable for the current research. However, the EmpaToM task also differentiates between different components of empathy, including compassion, and is potentially more emotionally evocative where participants may feel genuine empathy and concern. In future, I would try using the EmpaToM to probe differences in empathy, however if I were to use the MET again it would be alongside use a more objective index of empathy i.e. assessing facial EMG to try and disentangle emotional empathy from emotional contagion.

6.3 Novel treatments

Assessing novel treatments for opioid use disorder based on the proposed social risk model would aim to break the cycle between social impairments, opioid use, and social stressors. Our CFT intervention in Chapter 4 would provide a repertoire of self-compassionate exercises and strategies to thus increase one's ability to cope with social stressors, as well as improve social functioning. Although this was only a feasibility trial, there were promising indications of increased control over cravings and coping, however we did not observe changes in self-criticism (inversely linked to self-compassion and well-being), despite self-criticism being considerably higher in these opioid users than in a normative healthy population (Baião et al., 2015). If assessed in a randomised-controlled trial, assessments of social cognition should be included to investigate whether self-compassion enhances these, and whether this is related to reduced opioid use and greater coping with social stressors.

MDMA assisted psychotherapy may also be of therapeutic value in breaking the cycle perpetuating opioid use, as it could improve social functioning in the long-term and address past trauma. Studies investigating the acute effects have observed increases in emotional empathy (Hysek, Schmid, et al., 2014; Kuypers et al., 2014; Kuypers et al., 2017), compassion (Kamboj et al., 2017), and attenuated psychological distress following social exclusion (Frye et al., 2014). Chapter 5 reported that low-level repeated MDMA use was not related to impaired social functioning, but was actually associated with heightened empathic processes. This could suggest that MDMA increases empathy via heightening the emotional experience under the drug, and increased exposure facilitates the development of these; however this remains to be explored in more controlled settings where the purity of the drug can be guaranteed.

Chapter's 4 and 5 have also highlighted the possibility of MDMA-assisted CFT, where MDMA could potentiate the therapeutic efficacy of CFT in enhancing social functioning in opioid use disorder. One of the major drawbacks of CFT are the fears of compassion – where treating oneself or receiving compassion from others can be actively aversive in those who are high in self-criticism (Gilbert et al., 2011), where compassion can induce a fear response. Often those with histories of trauma or poor childhood attachments show fears of compassion (Baldwin, Bandarian-Balooch, & Adams, 2019), however these individuals would benefit the most from this therapy. Due to the effects of MDMA on reducing the fear response (which has been shown as clinically useful for trauma memories), it is possible that MDMA could have the same effects on compassion, therefore allowing the individual to experience emotions that are often avoided or feared. Repeated exposure to these positive emotions during CFT under the influence of MDMA may serve to extinguish this fear response.

A major limitation of using MDMA-assisted psychotherapy is the cost, as it typically requires two skilled therapeutic facilitators (Sessa, Sakal, O'Brien, & Nutt, 2019). However, a more cost-effective approach to overcome this may be to use MDMA in conjunction with group therapy sessions. Social context has been shown to potentiate some of the effects of MDMA (Kirkpatrick & de Wit, 2015), which could have a positive effect on enhancing social functioning. In addition, MDMA may also increase group cohesion due to its acute prosocial effects, where greater group

cohesion is linked with better therapeutic success (Burlingame, McClendon, & Alonso, 2011; Crowe & Grenyer, 2008). Prior to being banned, the early therapeutic uses of MDMA were in couples therapy (Sessa & Nutt, 2015), which has also been suggested to help with trauma therapy more recently (Almond & Allan, 2019) due to enhancing empathy and openness. A group setting for MDMA-assisted therapies could therefore be a potential avenue for research.

In the early stages of the PhD I had planned a mechanistic study to investigate whether MDMA has an effect on social functioning in opioid users. This was planned to help build a foundation of evidence to better inform the therapeutic uses of MDMA in opioid users, which has not yet been investigated. This was also why we conducted a study investigating the long-term effects of low-level, repeated MDMA use on social functioning in Chapter 5. Whilst this is still an area that I feel very passionate to research, this proved unfeasible to investigate within a PhD timeline. One major barrier included the time-consuming nature to set up such a study using a Schedule 1 Substance, as well as raising questions regarding the production, transportation, and storage the drug. Although this is a very important area to research, with potentially vast clinical implications for the treatment of opioid use disorder, this highlighted the difficulties of researching the therapeutic use of a Schedule 1 substance such as MDMA. Future studies should aim to address this however.

6.4 Is the endogenous opioid system central to social functioning?

One of the overarching themes of the current thesis was to investigate how the endogenous opioid system is involved in social functioning pre- and post-opioid use disorder. This neurobiological approach was tested in those with childhood trauma (non-addicts) to investigate whether childhood trauma caused disruptions to the development of this system, as well as in those with opioid addiction who have disrupted this system through chronic opioid use. To support this neurobiological approach, I expected we would observe a greater sensitivity to physical pain in those with childhood trauma, which would negatively impact social functioning (indicated by greater social distress following exclusion and reduced empathy). I also expected that opioid addicts who were non-intoxicated with opioids would show greater social

distress following exclusion accompanied by a greater cortisol response. This would therefore indicate a dampened endogenous opioid response, as endogenous opioids are released in response to social distress – termed 'emotional analgesia' – which lowers cortisol. I additionally expected this distress would be shielded by the intoxication of opioids. Whilst the results of these studies provided partial support for this, the results indicated that this is not the only mechanism involved in social functioning, and that psychological perspectives and other neurobiological pathways may be of equal or more importance.

6.4.1 The importance of psychological mechanisms

Within Chapter 2 we reported no group difference in pain threshold, however we did observe greater pain catastrophising in those with childhood trauma. Pain catastrophising is thought to entail magnification of pain sensations, ruminating about pain, and feelings of helplessness (Sullivan et al., 1995), and has been consistently shown as predictive of physical pain sensitivity (see Sullivan et al., 2001, for a review). However, the relationship between pain catastrophising and pain sensitivity was not supported in Chapter 2, and research has suggested that frequency of painful experiences may moderate this relationship (Kjøgx et al., 2014). The role of psychological pain catastrophising may have roots in social functioning, where it may be instrumental for eliciting social support or empathic responses from others as a form of coping with stress, and is reinforced by social support which may in turn exaggerate pain expression in the future (Sullivan et al., 2001). Additional to seeking social support, research has also indicated pain catastrophising to be linked to ambivalence over emotional expression – which refers to the desire to express emotions to others but either feeling unable to or regretting doing so – which similarly implies the role of pain catastrophising in social communication (Van Denburg, Shelby, Caldwell, O'Sullivan, & Keefe, 2018).

This may also have implications for chronic pain, a condition that has been linked to greater rates of childhood trauma history (You et al., 2018) and opioid addiction (Garland et al., 2019). The findings of the current study suggest that psychological mechanisms around pain interpretation (such as catastrophising) may have an important impact in this subgroup of chronic pain patients with childhood trauma. If pain catastrophising is a psychological mechanism for seeking social support, this could highlight the potential importance of addressing both pain

catastrophising and increasing social support in the treatment of chronic pain. Additional to this, there were greater rates of anxiety, stress, and depression in those with childhood trauma in Chapter 2, which could also play a role in pain perception. More recently a biopsychosocial approach to pain sensitivity has been proposed, which integrates social factors such as trauma, as well as psychological states such as depression and anxiety in the traditional neurobiological understanding of pain (Meints & Edwards, 2018). This approach integrates the role of these contextual factors as being dynamically related to pain, highlighting the importance of social context and affective states in pain sensitivity, which should be considered alongside biological pain mechanisms.

6.4.2 Alternative ways to probe the endogenous opioid system

Prior research has consistently suggested that a simple and cost-effective means of measuring endogenous opioid activity is via looking at pain tolerance (Dunbar et al., 2011; Dunbar et al., 2012; Johnson & Dunbar, 2016). We therefore used this technique in attempt to probe opioid activity in those with childhood trauma in Chapter 2, however we did not report any differences in pain sensitivity compared to controls with no trauma history. This would suggest that there may not be differences in endogenous opioid activity; however, because pain is just a proxy measure of the endogenous opioid response, we cannot infer from this that childhood trauma does not cause any alterations to this neurobiological system.

Pain threshold and tolerance may not have been the most appropriate form of assessing endogenous opioid activity. Ideally, using a more sophisticated method such as positron emission tomography (PET) would offer the best case for assessing alterations to endogenous opioids by using the radiotracer [^{11}C] Carfentanil, which has a high affinity for MOR. One issue with using PET is that even when using a highly selective MOR agonist like [^{11}C] Carfentanil, there is still cross-binding and cross activation between MOR and DOR, making it difficult to disentangle the exact effects of either MOR or DOR stimulation (Murphy, 2015), as well as being a very expensive imaging technique.

The most effective and superior method to assess endogenous opioid activity would be using an in-vivo method such as microdialysis, however this is highly invasive and requires a lesion to the area of interest (see Murphy, 2015, for a

review), and is therefore not appropriate in healthy human subjects. Less invasive methods, such as assessing endorphins peripherally in cerebrospinal fluid or plasma, are not generally advised because opioid peptides are also synthesised in the gut and pituitary gland, therefore opioids measured in these fluids may not accurately reflect levels in the brain (Murphy, 2015).

There are clearly difficulties in assessing endogenous opioid activity in humans. Microdialysis is the superior method to directly measure endogenous opioids, however is highly invasive in nature and therefore only used in preclinical studies. PET imaging is the most appropriate method we have thus far, however this technique still only indirectly measures opioid activity and is also associated with drawbacks (e.g. the lack of specificity in detecting between opioid receptor subtypes, as well as cost).

6.5 The common denominator: Stress

The major component connecting childhood trauma, social deprivation, isolation, exclusion, and stigma is that they all chronically activate the HPA axis (stress system). The allostatic load (the chronic activation of a normally fluctuating neuroendocrine responses to stress) caused by these stressors is believed to amplify drug reward and addiction via increasing incentive salience and negative affect, whilst impairing executive control (see Ruisoto & Contador, 2019, for a review). This is because stress downregulates reward pathways (such as the mesolimbic dopamine pathway) whilst correspondingly upregulates stress pathways (such as the HPA axis and amygdala), causing a heightened sensitivity to drug reward and stress. Stress also causes an impairment to hippocampal and PFC regulation of emotions and executive control, which is required to inhibit amygdala and HPA responses to drug-related cues. Either reducing social stressors, or increasing resilience to stress would be important for attenuating the link between stress and addiction. Therefore, attempts to reduce chronic stress, or to increase resilience to stress in vulnerable groups i.e. in socially deprived areas may reduce the impact of allostatic load on addiction vulnerability.

One of the most difficult issues to address with the allostatic load caused by social stressors is that they can be a consequence of socioeconomic divide (Nurius, Green, Logan-Greene, Longhi, & Song, 2016). Wider political changes that consider

the social context of addiction would have the greatest impact in reducing problematic drug use, such as introducing stress-reduction-based policies aimed at attenuating social stress in socially deprived areas where resources are limited (Ruisoto & Contador, 2019). Policies could also be aimed at increasing resilience to stress, as activating neural reward pathways have been shown to combat stress (Dutcher & Creswell, 2018) (where drugs are used) and therefore introducing other rewarding activities may reduce stress responsivity and reduce the need to use substances.

6.6 The converse of social stress: Social support

One of the key themes to emerge from the research reported in this thesis is the potential protective involvement of social support. Social support was significantly lower in individuals with childhood trauma, alongside greater rates of loneliness and pain catastrophising (Chapter 2). The research discussed in section 6.4.1 suggests that pain catastrophising may actually be a socially-driven coping mechanism, where pain is magnified in order to seek social support and empathy from others. These individuals may not have appropriate support networks, which could consequently perpetuate pain magnification and rumination, and put these individuals at risk of an opioid use disorder. There were also trends to suggest greater loneliness within the opioid user groups in Chapter 3.

Social support has been shown to help alleviate the negative impact of stigma in those with opioid use disorder, and is inversely related to illicit opioid use and poor mental health (Cooper, Campbell, Larance, Murnion, & Nielsen, 2018). Improving social functioning (for example via CFT or MDMA-assisted psychotherapy) in those with opioid addiction is therefore likely to assist in building positive relationships that would provide social support for those individuals. In terms of the wider public sphere, there is also a need to change attitudes towards addicted groups in order to increase general support for policies aimed at helping this group and to reduce stigma. Currently, policies that criminalise addicts for drug use perpetuate the image of these individuals as criminals. The work in this thesis suggests vulnerable individuals who have histories of trauma are more susceptible to the rewarding and reinforcing effects of opioid drugs as a consequence. This therefore highlights that

the current policies may disproportionately affect vulnerable people, where help should be offered in place of punishment.

6.6.1 The legal stance

The current situation in the UK is to criminalise the use of opioids as well as many other drugs listed by the UK Misuse of Drugs Act (Home Office, 2017) . Opioids are considered a Class A drug, where unlawful possession is subject to punishment. This approach to drug use and addiction is more recently being challenged. This is partly due to the lack of progress in helping alleviate the problem of addiction; in fact, drug-related deaths in the UK were at a record high in 2016 with opioids accounting for over half of these, and deaths have almost doubled between 2012 to 2015 (Hurley, 2017). These numbers suggest the current policies surrounding the treatment of drug misuse and addiction require drastic change, where decriminalisation of drugs may offer an alternative avenue: this change could redirect the current costs of policing drug use from the criminal justice sector into the health sector, in order to provide more effective treatments and rehabilitation (Hurley, 2017). The current harsh political approach also reduces social support and increases stigma towards opioid addicts, which are linked to reduced treatment seeking, and greater likelihood of engaging in unsafe practices associated with drug use i.e. sharing needles (Hurley, 2017). The work in this thesis also suggests that the current policies particularly affect vulnerable groups with childhood histories of abuse and neglect, where such experiences are related to a predisposition to the rewarding effects of opioid drugs (Chapter 2). In addition, current practices perpetuate the social stressors associated with drug use (such as stigma and marginalisation), which may impair social functioning further and perpetuate opioid use (Chapter 3).

Decriminalisation of personal drug use and greater investment in drug treatment practices may therefore be the way forward in breaking down the stigma associated with opioid addiction, as well as reducing opioid-related mortalities. This approach has proved to be effective in Portugal, where personal drug use was decriminalised in 2001. Since then, there has been a paradigm shift from seeing addicts as criminals to seeing them as people who need help and treatment; this has been accompanied by vast reductions in drug-related deaths and infections, reduced illicit drug use (excluding cannabis) and problematic drug use, reduced overcrowding

in prisons, and greater treatment uptake (see Stevens & Hughes, 2016, for a review). Decriminalisation is therefore instrumental in tackling the social stigmas associated with drug addiction, and is important for changing perceptions and enhancing wider social support.

6.7 Clinical implications

The findings reported in the current thesis have a number of clinical implications spanning across potential treatments, societal perspectives, and policies surrounding opioid use disorder. Many of these implications have already been discussed within this Chapter and corresponding study discussions, and the following section will touch on these in addition to emphasising other implications of the current work.

One implication of the current work that has not yet been discussed is the potential impact on the prescribing of opioids. The findings reported in Chapter 2 highlight the role of childhood trauma as a pre-existing vulnerability factor in opioid addiction, where these experiences may alter sensitivity to the pleasurable effects of opioid drugs. In light of the recent opioid crisis, where opioid misuse has soared alongside overdose rates and also greater diseases related to injecting drugs (such as HIV and hepatitis C) (deShazo et al., 2018; Spencer et al., 2019), the need for more careful prescribing of opioids medically is clearly important in reducing the risk of addiction. The current findings imply that developmental history of trauma is an important factor that should be considered during this process, where a screening tool could be developed to identify the level of risk a patient poses, and how much the patient will need to be monitored. For example, buprenorphine has less abuse potential than pure opioid agonists and has been indicated as an effective, safe, and well-tolerated treatment for chronic pain yet it is not frequently used as a treatment (Fishman & Kim, 2018). Buprenorphine could be one such medication given for pain when risk of addiction is high. A screening tool which assesses trauma history could advise medical professionals during the prescribing process, and suggest potential treatments (e.g. buprenorphine) that are most suitable for that individual.

Another implication is the suggestion to consider more novel or unusual treatments for opioid use disorder. The effectiveness of administering drug-paired psychotherapies for treating mental health problems is recently being emphasised,

with researchers investigating the clinical utility of a range of substances (including MDMA, ketamine, LSD, psilocybin, and ibogane) (Schenberg, 2018). This revived area of research has shown promise for treating a vast array of mental health issues, where the use of MDMA in the treatment of opioid use disorder – to potentiate CFT, address prior trauma, improve social functioning and increase group cohesion – could be therapeutically beneficial and has been suggested within the current Chapter (section 6.3).

Other potential psychological treatments have also been suggested, in line with the findings from the current thesis. This includes emotion-regulation training for those with opioid use disorder proposed in Chapter 3 section 4, with particular attention to helping direct emotional responses to socially difficult events (e.g. how to cope with anger or unpleasant emotional states induced by social exclusion), as well as fostering empathy and self-compassion. There could also be efforts made to increase resilience to stress in vulnerable groups more generally, such as in socially-deprived areas, in order to attenuate the allostatic load caused by stress and break the cycle between stress and addiction (section 6.5). This also highlights the importance of stress-reduction-based policies aimed at attenuating social stressors in socially deprived areas. The findings also suggest that preventative measures to enhance emotion regulation, self-compassion and self-efficacy aimed at children and adolescents with childhood trauma may be effective at mitigating the risk of developing drug addiction later in life (discussed in more detail in future directions, section 6.9).

More generally, I hope one of the major implications of the findings reported in the current thesis is to de-stigmatise and de-shame opioid use disorder, which is also briefly discussed in section 6.6. Current attitudes to opioid addiction (and addiction more generally) are highly stigmatising, such as the perception that addiction is a ‘choice’, and such attitudes obstruct advancements in helping those with addictions. The findings presented within this thesis collectively suggest that these individuals are faced with prior stressful experiences that affect how rewarding opioids are. The findings also highlight a heightened sensitivity to ostracism, potentially via greater exposure to this as a drug user and lacking the emotional capacity to tolerate it, indicating that damaging stigmas may actually serve to perpetuate opioid use. With this in mind, efforts to counteract these damaging and

negative stigmas in the public could therefore be made, and could draw on findings reported in the current thesis to show that this is a vulnerable group who require social support.

6.8 Strengths and limitations

The current research had several strengths and limitations, many of which are mentioned in the discussions of each chapter, and the limitations of the various measurement tasks are discussed above. The following section will summarise the overarching strengths and limitations across the studies.

One limitation of the current work was the difficulties in the recruitment process of opioid users, which meant that we expanded inclusion criteria which could have consequently added noise to the data. Chapter's 3 and 4 include opioid users on an OSM such as methadone or buprenorphine; both of these drugs have differing pharmacological effects (methadone is a long-acting MOR agonist, whilst buprenorphine is a partial agonist with agonist effects on MOR and antagonistic effects on KOR), and also generally reflect individuals at who are at different points in their recovery (as buprenorphine is associated with detoxification from opioids towards the end of recovery). This could suggest that there might be differences within opioid users, depending on what OSM they are using and how far they are in their recovery. The reason for including both methadone and buprenorphine users in the current research was because recruitment of this clinical group was very difficult, potentially due to high rates comorbidity with mental health problems, use of antidepressants or other medications, many being vulnerably-housed, and high rates of additional opioid use and polysubstance use. This also meant that the research was very time-costly as often participants did not arrive for testing sessions. Access to inpatient opioid treatment services may offer an easier alternative for recruiting this difficult population. However, although this is a limitation it could also be considered as a strength of the research, as this may more reflective of real-life opioid users where there are high levels of comorbidity with mental health problems and who often lead chaotic lives.

Another limitation is that Chapter 3 did not include an assessment of pain threshold, which would have been useful for identifying whether there is a difference in pain threshold as a proxy of endogenous opioid activity in chronic opioid users.

This would have also been useful to compare with the childhood trauma group in Chapter 2. Including a measure of physical pain would have also been interesting to link with salivary cortisol as an index of HPA activity. Additionally, assessing deviations in plasma cortisol in Chapter 2 would have confirmed whether childhood trauma causes deviations in stress reactivity to social exclusion, however we were limited in financial resources to analyse these and therefore did not assess this.

A strength throughout is the matching with control groups across the studies. Chapter 2's childhood trauma and control group were well matched except for history of mental health problems (mild depression and anxiety), suggesting meaningful differences between the groups that were not down to pre-existing confounding factors. Chapter 3's opioid user groups were also well-matched with opioid-naïve controls. This was difficult providing the complex issues encountered with opioid users (unemployment, vulnerable housed, mental health problems), and prior studies with opioid users have not always well-matched control groups (e.g. Tomei et al., 2017). However, special efforts were made to try and match the control group to the opioid using groups as closely as possible in order to elucidate the specific effects of opioid use – such as recruiting through friends of opioid users or through employment and training agencies. In Chapter 3 we only reported a trend to suggest greater rates of childhood trauma in the opioid user groups, which did not align with prior work finding disproportionately higher rates of trauma in opioid addicts (Heffernan et al., 2000; Naqavi et al., 2011). As the groups were well matched, this lack of group difference could potentially indicate that the control group may also have been exposed to certain stressors, such as childhood trauma and loneliness, which may suggest higher overall rates of these stressors in those with lower socioeconomic status; however, this was not assessed in the study and therefore can only be speculated

6.9 Future directions

The findings in the current thesis have stimulated many more questions that could be answered by future research. Some new avenues for research have already been addressed in this Chapter, such as the potential to combine MDMA-assisted psychotherapy with CFT to help overcome fears of compassion in opioid addicts (section 6.3), as well as attempts to enhance resilience to stress in

vulnerable groups (e.g. in socially deprived areas to reduce the impact of allostatic load) as either a prevention or intervention in order to attenuate the link between stress and addiction (section 6.5). The following section will also discuss some other potential avenues for research that has been stimulated from the current thesis.

One of the main findings was greater sensitivity to the positive and pleasurable effects of opioids following childhood trauma. Therefore, a potential avenue for research could be to investigate the effectiveness of preventative measures given to children or adolescents who are identified as at risk or with known histories of trauma. This could include aspects of CFT, in order to foster feelings of self-compassion and improve overall emotion regulation to build resilience against later drug addiction. Research could also aim to identify potential resilience factors in those with trauma histories who have not developed addiction (such as in the participants recruited in Chapter 2), with the aim to incorporate these into the preventative measures. Because the research in the current thesis indicates that impaired social functioning (social distress and empathy) may be more affected as a consequence of opioid use (compared to preceding factors, such as childhood trauma), these preventative measures may be key to preventing the cycle of opioid use and social impairment as proposed by the social risk factor model (figure 6.1). Preventative measures given prior to drug use in those with childhood trauma may therefore have the largest impact in reducing drug use and the stressors encountered as a consequence.

Another consideration for future research is the influence of intergenerational trauma, which is considerably higher in socially deprived groups (McEwen & McEwen, 2017). The purpose of this would be to try and foster skills to cope with stressors in parents with histories of trauma, in attempt to reduce the influence of chronic stress and the cycle of trauma. Even if preventative measures are provided for at-risk children, the parent and family environment is still very influential in their social and emotional development, and maternal childhood trauma is a major risk factor (Folger et al., 2017). Protective factors reducing the transmission of childhood trauma include maternal social support and good mental health (Folger et al., 2017), and preventions that incorporate both resolving parental trauma as well as supporting the child-parent attachment are thought to be most effective in breaking the cyclical nature of intergenerational trauma (Isobel, Goodyear, Furness, & Foster,

2019). This could be done by assessing rates of childhood trauma in parents, and offering at risk individuals trauma-focused treatments (Steele et al., 2016); however it would be very important not to stigmatise or to come across as criticising parenting, as many parents with trauma histories do not transmit this to their children. For these reasons, such a prevention/intervention technique may be tricky to implement, however it may have a large impact on reducing the long-term negative effects of childhood trauma, for example in opioid addiction.

Another potential for future research could be to investigate avenues for increasing social support for individuals with opioid addiction, and to challenge pre-existing prejudices in society. This could be done via greater efforts to educate about the vulnerability factors involved in opioid addiction at school, in order to reduce the perpetuation of pre-existing stigmas around addiction.

6.10 Conclusions

The research presented within the current thesis was guided by many approaches, particularly the Brain Opioid Theory of Social Attachment (BOTSA; Machin & Dunbar, 2011) which highlights the role of the endogenous opioid system in social affiliation and bonding, as well as the impact of social risk factors in the onset and maintenance of opioid addiction. Addiction research has been criticised for a lack of empirical investigations into the role of social functioning and its neurobiological underpinnings, particularly regarding the endogenous opioid system (Heilig et al., 2016). The research I have conducted and presented in the current thesis has therefore made a significant theoretical contribution to this field by addressing this gap. Through my research, I have also proposed a social risk factor model that was initially formed from the existing literature (figure 1.3) and adjusted based on the current findings (figure 6.1), which I hope provides explanatory power describing the complex relationship between social stressors and opioid use that could inform future research. Through the current findings, I have also suggested preventative measures as well as interventions for treating social impairments in opioid use disorder. In summary, the study of social functioning in opioid use disorder is a promising approach in the search for more effective treatments and highlights the role of social connection in addiction.

6.11 What the PhD taught me about addiction research

The PhD has been a truly rewarding and fulfilling journey. Drug use is so prevalent in society and affects nearly everybody in some form or another, yet despite this there is still so far to go in our understanding of addiction and how to treat it effectively. To investigate addiction is to consider genetics, personality, biology, development, and environment, and it is this multifaceted nature of addiction which I find absolutely fascinating. To complete my PhD within three years has been a huge yet highly rewarding challenge, and I have felt extremely fortunate to have had the opportunity to conduct my own research into a field that I find captivating, and one that I hope to continue with for the rest of my academic career.

6.11.1 How social connection guided my research

Through my PhD I have been extremely fortunate to be faced with many opportunities that have helped guide both my research and my understanding of addiction. The people who have been most influential in guiding my perception of addition are the opioid drug users themselves. Upon beginning the PhD I had a naivety in believing that treating opioid addiction would be simple, however I did not fully appreciate the complexities and chaos that the lives of individuals with opioid use disorder frequently encounter.

Mental and physical health problems, societal stigmas, deprivation, poly-drug use and homelessness name but a few of the issues. Through my research, I have met a lot of colourful and kind people who have really opened my eyes to the everyday difficulties that individuals with opioid addiction encounter. I was struck by how many of these individuals wanted to help with my research in order to help others who have been in their position (although this did not always translate into people attending their study sessions, but at least the good intentions were there…). They were always very keen to discuss their experiences as an addict and I feel extremely lucky to have been in a position to be there to listen. Through my research, I also became increasingly aware of the prevalence of stigmas against opioid users from the general public, particularly regarding the perception that addiction is a ‘choice’, which was brought to my attention through conversations around my research. I always felt it was important to challenge these views by presenting my experiences and evidence, yet it made me recognise that part of the

challenge in treating opioid use disorder is to change the wider perceptions and stigmas associated with it, in order to accrue wider support to help treat this clinical group. Working alongside this marginalised group has also stimulated more questions about addiction, and intensified my desire to continue working with this population.

Alongside working with drug users and addiction services, I have also had the opportunity to run a study at the Clinical Research Facility, alongside NHS staff at the Royal Devon and Exeter Hospital. Working collaboratively with two consultant anaesthetists, Dr Rupert Broomby and Dr Graham Simpson, was extremely interesting and stimulated my interest in the overlap between childhood trauma, pain processing, and opioid addiction. Running this study as a team, we faced many challenges, but it was also extremely fun and rewarding. Working together with the nursing staff there was also very enjoyable, and the attention to detail required to run such a complex study organising a multidisciplinary team has forever changed how I will approach a research project for the better.

Alongside working with people, I was also very lucky to be taught procedures to analyse biological samples, such as learning to prepare and analyse plasma and saliva samples using immunoassay kits in the laboratory, as well as undergo phlebotomy training to take blood samples. I have felt very fortunate to learn this as it has meant that I have been involved in all stages of the analyses and has also equipped me with a broad range of skills. It is also thoroughly satisfying to be involved in all aspects of the research and analytical procedures, and means that my PhD experience has been extremely varied.

I was also fortunate to visit other laboratories outside of Exeter. I received a travelling scholarship which enabled me to visit Professor Harriet de Wit's Human Behavioural Psychopharmacology Laboratory at the University of Chicago, which specialises in understanding the cognitive, emotional, and physiological responses to substances by administering different drugs acutely. This experience was excellent preparation for one of my studies that gave an acute dose of morphine. I was also very lucky to be invited to talk to Professor Boris Quednow's research group at the University of Zurich, where engaging in scientific exchange has resulted in enduring academic relationships, and led to discussions on new study designs and research.

To summarise, I am extremely grateful to have met all the wonderful and influential people who have guided me through my PhD. Alongside those mentioned, I have also had unwavering support and kindness from my supervisors, colleagues, friends and family. I have felt so lucky to have embarked on this PhD journey, and I am excited for a future of research into addiction.

Appendices

Appendix 2.1: Morphine SmPC

Physical health problems and medications that could be deemed as negatively impacted by the administration of morphine, as listed in the summary of product characteristics (SmPC) including:

- Hypersensitivity to the active substance or to any of the excipients
- Respiratory depression or insufficiency
- Obstructive airways disease
- Cerebral trauma
- Increased intracranial pressure
- Coma
- Convulsive disorders
- Acute alcoholism
- Renal failure
- Ureteral stenosis
- Pancreatitis
- Liver failure
- Gall-bladder dysfunction
- Ileus
- Inflammatory bowel disease
- Hypotension with hypovolaemia
- Prostatic hypertrophy
- Myxoedema
- Pheochromocytoma
- Concurrent administration of MAO inhibitors or within two weeks of discontinuation of their use
- Alcohol
- Anti-arrhythmics
- Antibacterials
- Antidepressants, anxiolytics, hypnotics
- Antipsychotics
- Antidiarrhoeal and antiperistaltic agents (such as loperamide and kaolin)
- Antimuscarinics
- Metoclopramide and domperidone
- Sedative medicines such as benzodiazepines or related drugs

The full summary for intravenous morphine can be accessed in the electronic Medicines Compendium (eMC):
https://www.medicines.org.uk/emc/medicine/13143/SPC/Morphine+Sulphate+10mg+ml+Injection+BP/

Appendix 2.2: Blood plasma preparation and analysis

Blood samples were collected via a cannula inserted in the vein in the arm, and then centrifuged at 1500g x 15 minutes. Following this, the plasma was extracted and immediately stored at -80° until analysis. The plasma was later analysed using morphine-specific enzyme-linked immunoassay kits (Immunalysis) to detect levels of morphine (ng/ml), with a cut off of 10ng/mL. All samples were analysed in duplicate.

Appendix 2.3: Between group and session differences for mixed effect models

Log Likelihood Ratio Test for Each Outcome

Outcomes	Log likelihood ratio-test	
	χ^2 statistic	p- value
Feel	122.11	0.000
High	192.97	0.000
Dislike	235.19	0.000
Like	346.86	0.000
Want more	345.64	0.000
Nausea	70.22	0.000
Euphoric	267.11	0.000
Dizzy	116.68	0.000
Sedated	185.18	0.000

Mean Differences between Sessions and Groups (Primary and Secondary Outcomes).

Outcome	Time	Placebo session		Morphine session		Control group		Trauma group	
		Between-group difference (95% CI)	p-value	Between-group difference (95% CI)	p-value	Between-session difference (95% CI)	p-value	Between-session difference (95% CI)	p-value
Feel	15m	0.38 (-11.42 to 12.18)	.950	6.52 (-5.28 to 18.32)	.279	16.37 (6.44 to 26.30)	.001**	22.51 (13.17 to 31.85)	<.001***
	30m	-1.30 (-13.10 to 10.50)	.829	6.42 (-5.39 to 18.22)	.287	15.24 (5.32 to 25.17)	.003**	22.96 (13.62 to 32.30)	<.001***
	45m	2.05 (-9.75 to 13.85)	.733	3.78 (-8.02 to 15.58)	.530	22.74 (12.82 to 32.67)	<.001***	24.47 (15.14 to 33.81)	<.001***
	60m	2.57 (-9.23 to 14.38)	.669	0.35 (-11.55 to 12.25)	.954	30.08 (20.04 to 40.13)	<.001***	27.86 (18.52 to 37.20)	<.001***
	90m	-1.36 (-13.16 to 10.44)	.821	-0.77 (-12.58 to 11.03)	.898	32.33 (22.40 to 42.26)	<.001***	32.92 (23.58 to 42.25)	<.001***
	120m	-2.10 (-13.90 to 9.70)	.727	-2.54 (-14.34 to 9.27)	.673	23.12 (13.19 to 33.05)	<.001***	22.68 (13.34 to 32.02)	<.001***

	150m	2.02 (-9.78 to 13.82)	.737	-6.49 (-18.37 to 5.39)	.284	24.33 (14.40 to 34.26)	<.001***	15.82 (6.38 to 25.25)	0.001**
High	15m	3.59 (-6.68 to 13.86)	.493	10.07 (-0.20 to 20.33)	.055	9.54 (1.16 to 17.92)	.026*	16.02 (8.14 to 23.90)	<.001***
	30m	1.95 (-8.32 to 12.21)	.710	10.42 (0.16 to 20.69)	.047*	10.00 (1.62 to 18.38)	.019*	18.48 (10.59 to 26.36)	<.001***
	45m	-0.24 (-10.51 to 10.02)	.963	9.82 (-0.45 to 20.08)	.061	13.00 (4.62 to 21.38)	.002**	23.06 (15.18 to 30.94)	<.001***
	60m	3.82 (-6.45 to 14.08)	.466	6.44 (-3.91 to 16.78)	.223	15.61 (7.14 to 24.09)	<.001***	18.23 (10.35 to 26.11)	<.001***
	90m	-0.74 (-11.00 to 9.53)	.888	-0.13 (-10.40 to 10.13)	.980	17.04 (8.66 to 25.42)	<.001***	17.65 (9.77 to 25.53)	<.001***
	120m	2.84 (-7.43 to 13.10)	.588	1.39 (-8.87 to 11.66)	.790	8.04 (-0.34 to 16.42)	.060	6.60 (-1.28 to 14.48)	.101
	150m	1.65 (-8.62 to 11.91)	.753	2.06 (-8.26 to 12.39)	.695	3.00 (-5.38 to 11.38)	.483	3.42 (-4.54 to 11.38)	.400
Dislike	15m	-3.14 (-14.39 to 8.12)	.585	6.68 (-4.58 to 17.93)	.245	0.61 (-8.34 to 9.56)	.894	10.42 (2.00 to 18.84)	.015*
	30m	-3.22 (-14.48 to 8.03)	.575	-6.66 (-17.92 to 4.59)	.246	4.44 (-4.51 to 13.39)	.331	1.00 (-7.42 to 9.42)	.816
	45m	-5.79 (-17.04 to 5.47)	.314	0.68 (-10.57 to 11.94)	.905	-0.77 (-9.72 to 8.19)	.867	5.70 (-2.72 to 14.12)	.184
	60m	-4.82 (-16.08 to 6.43)	.401	-10.65 (-21.99 to 0.69)	.066	8.83 (-0.23 to 17.88)	.056	3.00 (-5.42 to 11.42)	.485
	90m	-2.46 (-13.72 to 8.79)	.668	-16.65 (-27.91 to -5.40)	.004**	24.19 (15.24 to 33.14)	<.001***	10.00 (1.58 to 18.42)	.020*
	120m	-4.28 (-15.53 to 6.98)	.456	-11.05 (-22.31 to 0.20)	.054	16.78 (7.82 to 25.73)	<.001***	10.00 (1.58 to 18.42)	.020*
	150m	0.14 (-11.12 to 11.39)	.981	-18.86 (-30.18 to -7.55)	.001**	24.11 (15.16 to 33.06)	<.001***	5.11 (-3.40 to 13.61)	.239
Like	15m	4.95 (-9.24 to 19.15)	.494	10.59 (-3.60 to 24.79)	.144	7.44 (-3.15 to 18.02)	.169	13.07 (3.12 to 23.03)	.010*
	30m	2.56 (-11.64 to 16.75)	.724	14.67 (0.48 to 28.87)	.043*	3.98 (-6.61 to 14.57)	.462	16.10 (6.14 to 26.05)	.002**
	45m	7.21 (-6.98 to 21.41)	.319	20.02 (5.82 to 34.21)	.006**	5.94 (-4.65 to 16.52)	.272	18.74 (8.78 to 28.70)	<.001***
	60m	7.40 (-6.79 to 21.60)	.307	13.15 (-1.13 to 27.44)	.071	8.39 (-2.32 to 19.10)	.125	14.14 (4.18 to 24.10)	.005**
	90m	3.63 (-10.57 to 17.83)	.616	18.20 (4.00 to 32.39)	.012*	0.06 (-10.53 to 10.65)	.991	14.63 (4.67 to 24.59)	.004**

	120m	2.76 (-11.44 to 16.96)	.703	20.14 (5.94 to 34.33)	.005**	-3.19 (-13.78 to 7.40)	.555	14.19 (4.23 to 24.15)	.005**
	150m	-1.30 (-15.49 to 12.90)	.858	20.97 (6.71 to 35.24)	.004**	-7.19 (-17.78 to 3.40)	.183	15.08 (5.02 to 25.14)	.003**
Want more	15m	9.00 (-3.87 to 21.87)	.170	23.42 (10.55 to 36.29)	<.001***	-0.64 (-10.70 to 9.42)	.901	13.78 (4.32 to 23.24)	.004**
	30m	12.87 (0.00 to 25.74)	.050	24.53 (11.66 to 37.40)	<.001***	4.53 (-5.53 to 14.58)	.378	16.19 (6.72 to 25.65)	.001**
	45m	12.61 (-0.26 to 25.47)	.055	29.90 (17.03 to 42.77)	<.001***	3.19 (-6.87 to 13.25)	.534	20.49 (11.02 to 29.95)	<.001***
	60m	11.35 (-1.52 to 24.21)	.084	38.05 (25.10 to 51.01)	<.001***	-4.10 (-14.27 to 6.08)	.430	22.61 (13.15 to 32.07)	<.001***
	90m	12.06 (-0.81 to 24.92)	.066	35.51 (22.65 to 48.38)	<.001***	-0.52 (-10.57 to 9.54)	.920	22.94 (13.48 to 32.40)	<.001***
	120m	12.81 (-0.06 to 25.67)	.051	31.09 (18.23 to 43.96)	<.001***	-3.02 (-13.07 to 7.04)	.557	15.27 (5.81 to 24.73)	0.002**
	150m	11.82 (-1.05 to 24.69)	.072	25.25 (12.31 to 38.19)	<.001***	-1.81 (-11.87 to 8.25)	.725	11.62 (2.07 to 21.18)	0.017*
Nausea	15m	1.68 (-6.03 to 9.40)	.669	6.03 (-1.68 to 13.74)	.125	-1.47 (-8.65 to 5.71)	.688	2.87 (-3.89 to 9.63)	.405
	30m	0.67 (-7.04 to 8.38)	.865	0.04 (-7.67 to 7.75)	.992	3.44 (-3.74 to 10.62)	.347	2.81 (-3.94 to 9.57)	.414
	45m	7.23 (-0.48 to 14.94)	.066	2.99 (-4.73 to 10.70)	.448	1.65 (-5.53 to 8.83)	.652	-2.59 (-9.35 to 4.16)	.452
	60m	1.40 (-6.31 to 9.11)	.722	-3.27 (-11.05 to 4.52)	.411	10.34 (3.07 to 17.60)	.005**	5.67 (-1.09 to 12.42)	.100
	90m	-0.06 (-7.77 to 7.65)	.989	-5.81 (-13.52 to 1.90)	.140	16.94 (9.76 to 24.12)	<.001***	11.19 (4.43 to 17.94)	.001**
	120m	-0.87 (-8.58 to 6.84)	.826	-9.27 (-16.98 to -1.56)	.018*	15.44 (8.26 to 22.62)	<.001***	7.04 (0.28 to 13.79)	.041*
	150m	-1.02 (-8.74 to 6.69)	.795	-10.24 (-18.01 to -2.47)	.010*	18.44 (11.26 to 25.62)	<.001***	9.23 (2.40 to 16.05)	.008**
Euphoria	15m	-0.32 (-11.63 to 10.98)	.955	17.99 (6.69 to 29.30)	.002**	3.58 (-5.36 to 12.51)	.433	21.90 (13.49 to 30.30)	<.001***
	30m	1.06 (-10.25 to 12.36)	.855	13.69 (2.39 to 25.00)	.018*	5.16 (-3.77 to 14.09)	.258	17.80 (9.39 to 26.20)	<.001***
	45m	-2.71 (-14.01 to 8.60)	.639	14.20 (2.89 to 25.50)	.014*	5.62 (-3.31 to 14.55)	.218	22.52 (14.12 to 30.92)	<.001***

	60m	0.58 (-10.72 to 11.89)	.919	14.84 (3.45 to 26.22)	.011*	3.03 (-6.01 to 12.06)	.512	17.28 (8.87 to 25.68)	<.001***
	90m	3.53 (-7.78 to 14.83)	.541	7.78 (-3.53 to 19.08)	.177	5.91 (-3.02 to 14.84)	.195	10.16 (1.76 to 18.56)	.018*
	120m	-2.85 (-14.16 to 8.45)	.621	10.40 (-0.91 to 21.70)	.071	-5.55 (-14.48 to 3.39)	.224	7.70 (-0.70 to 16.10)	.072
	150m	-1.34 (-12.65 to 9.96)	.816	8.95 (-2.42 to 20.32)	.123	-4.88 (-13.81 to 4.05)	.284	5.41 (-3.08 to 13.90)	.212
Dizzy	15m	-1.71 (-9.83 to 6.40)	.679	-3.40 (-11.52 to 4.71)	.411	6.91 (-0.29 to 14.11)	.060	5.22 (-1.55 to 11.99)	.131
	30m	-0.84 (-8.96 to 7.27)	.838	-7.51 (-15.62 to 0.61)	.070	7.45 (0.26 to 14.65)	.042	0.79 (-5.98 to 7.56)	.819
	45m	-2.71 (-10.83 to 5.40)	.512	-3.33 (-11.44 to 4.79)	.422	8.12 (0.92 to 15.31)	.027*	7.50 (0.73 to 14.27)	.030*
	60m	-1.84 (-9.95 to 6.28)	.658	-7.09 (-15.28 to 1.10)	.090	13.55 (6.28 to 20.83)	<.001***	8.30 (1.53 to 15.07)	.016*
	90m	-0.59 (-8.71 to 7.53)	.887	-12.81 (-20.92 to -4.69)	.002**	24.62 (17.42 to 31.81)	<.001***	12.40 (5.63 to 19.17)	<.001***
	120m	-0.46 (-8.58 to 7.65)	.911	-10.64 (-18.75 to -2.52)	.01*	21.28 (14.09 to 28.48)	<.001***	11.11 (4.34 to 17.88)	.001**
	150m	-0.74 (-8.85 to 7.38)	.859	-7.60 (-15.77 to 0.58)	.068	17.45 (10.26 to 24.65)	<.001***	10.59 (3.75 to 17.43)	.002**
Sedated	15m	3.10 (-8.44 to 14.64)	.598	2.34 (-9.20 to 13.89)	.691	14.07 (4.57 to 23.56)	.004**	13.31 (4.38 to 22.24)	.003**
	30m	-0.66 (-12.20 to 10.89)	.911	-1.99 (-13.53 to 9.55)	.736	15.07 (5.57 to 24.56)	.002**	13.73 (4.80 to 22.66)	.003**
	45m	3.74 (-7.80 to 15.28)	.525	4.67 (-6.87 to 16.22)	.427	15.73 (6.24 to 25.23)	.001**	16.67 (7.73 to 25.60)	<.001***
	60m	3.54 (-8.00 to 15.08)	.548	6.60 (-5.03 to 18.23)	.266	14.85 (5.24 to 24.45)	.002**	17.91 (8.98 to 26.84)	<.001***
	90m	5.18 (-6.36 to 16.72)	.379	-5.76 (-17.30 to 5.79)	.328	22.36 (12.86 to 31.85)	<.001***	11.42 (2.49 to 20.36)	.012*
	120m	5.82 (-5.73 to 17.36)	.323	0.13 (-11.41 to 11.68)	.982	21.06 (11.56 to 30.55)	<.001***	15.37 (6.44 to 24.31)	.001**
	150m	1.63 (-9.91 to 13.18)	.781	-0.95 (-12.56 to 10.66)	.872	15.85 (6.36 to 25.35)	0.001**	13.27 (4.25 to 22.29)	.004**

Note. * $p<.05$, ** $p<.01$, *** $p<.001$

Appendix 2.4: Statistical outcomes for mixed effect models

Random Effect Mixed Models for the Interaction between Time, Session and Group on Feeling Effects, Feeling High, Disliking Effects, Liking Effects, and Wanting More

Variables	Model-Feel Coef (95% CI)	p-value	Model-High Coef (95% CI)	p-value	Model-Dislike Coef (95% CI)	p-value	Model-Like Coef (95% CI)	p-value	Model-More Coef (95% CI)	p-value
Trauma (Ref: Control)	-0.23 (-12.03 to 11.57)	0.97	-0.90 (-11.16 to 9.37)	0.86	-2.79 (-14.05 to 8.46)	0.63	-8.50 (-22.69 to 5.70)	0.24	-0.69 (-13.56 to 12.17)	0.92
Measures: 15m (Ref: 0m)	7.17 (-2.74 to 17.07)	0.16	3.29 (-5.07 to 11.65)	0.44	4.57 (-4.36 to 13.50)	0.32	-0.37 (-10.94 to 10.19)	0.94	4.08 (-5.95 to 14.12)	0.43
30m	12.62 (2.72 to 22.53)*	0.01	6.42 (-1.94 to 14.78)	0.13	5.98 (-2.95 to 14.92)	0.19	3.88 (-6.69 to 14.44)	0.47	1.25 (-8.79 to 11.29)	0.81
45m	11.79 (1.89 to 21.70)*	0.02	7.46 (-0.90 to 15.82)	0.08	9.73 (0.80 to 18.67)*	0.03	0.63 (-9.94 to 11.19)	0.91	0.63 (-9.41 to 10.66)	0.90
60m	9.08 (-0.82 to 18.99)	0.07	5.25 (-3.11 to 13.61)	0.22	10.73 (1.80 to 19.67)*	0.02	0.92 (-9.65 to 11.48)	0.86	0.96 (-9.08 to 10.99)	0.85
90m	8.17 (-1.74 to 18.07)	0.11	6.25 (-2.11 to 14.61)	0.14	6.48 (-2.45 to 15.42)	0.15	1.88 (-8.69 to 12.44)	0.73	-1.42 (-11.45 to 8.62)	0.78
120m	7.50 (-2.41 to 17.41)	0.14	4.42 (-3.94 to 12.78)	0.30	5.82 (-3.11 to 14.75)	0.20	0.71 (-9.85 to 11.27)	0.90	-1.83 (-11.87 to 8.20)	0.72
150m	2.42 (-7.49 to 12.32)	0.63	3.12 (-5.24 to 11.49)	0.46	3.40 (-5.53 to 12.33)	0.46	-1.12 (-11.69 to 9.44)	0.83	-3.62 (-13.66 to 6.41)	0.48
TraumaX15m	0.61 (-13.00 to 14.23)	0.93	4.49 (-7.00 to 15.98)	0.44	-0.35 (-12.62 to 11.93)	0.96	13.45 (-1.07 to 27.97)	0.07	9.69 (-4.10 to 23.49)	0.17
TraumaX30m	-1.07 (-14.68 to 12.54)	0.88	2.84 (-8.65 to 14.33)	0.63	-0.43 (-12.70 to 11.85)	0.95	11.05 (-3.47 to 25.57)	0.14	13.56 (-0.23 to 27.36)	0.05
TraumaX45m	2.28 (-11.33 to 15.90)	0.74	0.65 (-10.84 to 12.14)	0.91	-2.99 (-15.27 to 9.28)	0.63	15.71 (1.19 to 30.23)*	0.03	13.30 (-0.49 to 27.09)	0.06
TraumaX60m	2.81 (-10.81 to 16.42)	0.69	4.71 (-6.78 to 16.20)	0.42	-2.03 (-14.31 to 10.24)	0.75	15.90 (1.38 to 30.42)*	0.03	12.04 (-1.75 to 25.83)	0.09
TraumaX90m	-1.13 (-14.74 to 12.48)	0.87	0.16 (-11.33 to 11.65)	0.98	0.33 (-11.94 to 12.61)	0.96	12.12 (-2.39 to 26.64)	0.10	12.75 (-1.04 to 26.54)	0.07
TraumaX120m	-1.87 (-15.48 to 11.74)	0.79	3.73 (-7.76 to 15.22)	0.52	-1.48 (-13.76 to 10.79)	0.81	11.25 (-3.26 to 25.77)	0.13	13.50 (-0.29 to 27.29)	0.06
TraumaX150m	2.25 (-11.36 to 15.86)	0.75	2.54 (-8.95 to 14.03)	0.66	2.93 (-9.34 to 15.21)	0.64	7.20 (-7.32 to 21.72)	0.33	12.51 (-1.28 to 26.31)	0.08
Morphine (Ref: Placebo)	-0.05 (-9.97 to 9.88)	0.99	0.50 (-7.88 to 8.88)	0.91	-2.11 (-11.07 to 6.84)	0.64	-5.23 (-15.82 to 5.36)	0.33	-5.35 (-15.41 to 4.71)	0.30
TraumaXmorphine	1.07 (-12.62 to 14.77)	0.88	0.55 (-11.01 to 12.11)	0.93	9.68 (-2.67 to 22.03)	0.12	7.91 (-6.70 to 22.51)	0.29	4.33 (-9.55 to 18.20)	0.54
15mXmorphine	16.42 (2.41 to 30.43)*	0.02	9.04 (-2.78 to 20.86)	0.13	2.72 (-9.91 to 15.35)	0.67	12.67 (-2.27 to 27.61)	0.10	4.71 (-9.48 to 18.90)	0.52
30mXmorphine	15.29 (1.28 to 29.30)*	0.03	9.50 (-2.32 to 21.32)	0.12	6.56 (-6.07 to 19.19)	0.31	9.21 (-5.73 to 24.15)	0.23	9.88 (-4.32 to 24.07)	0.17

45mXmorphine	22.79 (8.78 to 36.80)**	0.00	12.50 (0.68 to 24.32)*	0.04	1.35 (-11.28 to 13.98)	0.83	11.17 (-3.77 to 26.11)	0.14	8.54 (-5.65 to 22.73)	0.24
60mXmorphine	30.13 (16.04 to 44.22)***	0.00	15.11 (3.22 to 27.00)*	0.01	10.94 (-1.76 to 23.64)	0.09	13.62 (-1.41 to 28.64)	0.08	1.25 (-13.02 to 15.53)	0.86
90mXmorphine	32.38 (18.37 to 46.38)***	0.00	16.54 (4.72 to 28.36)**	0.01	26.31 (13.68 to 38.94)***	0.00	5.29 (-9.65 to 20.23)	0.49	4.83 (-9.36 to 19.03)	0.50
120mXmorphine	23.17 (9.16 to 37.18)**	0.00	7.54 (-4.28 to 19.36)	0.21	18.89 (6.26 to 31.52)**	0.00	2.04 (-12.90 to 16.98)	0.79	2.33 (-11.86 to 16.53)	0.75
150mXmorphine	24.38 (10.37 to 38.38)***	0.00	2.50 (-9.32 to 14.32)	0.68	26.22 (13.59 to 38.85)***	0.00	-1.96 (-16.90 to 12.98)	0.80	3.54 (-10.65 to 17.73)	0.62
TraumaX15mXmorphine	5.07 (-14.23 to 24.37)	0.61	5.93 (-10.36 to 22.22)	0.48	0.13 (-17.27 to 17.53)	0.99	-2.27 (-22.85 to 18.31)	0.83	10.09 (-9.46 to 29.64)	0.31
TraumaX30mXmorphine	6.65 (-12.65 to 25.95)	0.50	7.93 (-8.36 to 24.22)	0.34	-13.12 (-30.52 to 4.28)	0.14	4.21 (-16.37 to 24.79)	0.69	7.33 (-12.22 to 26.89)	0.46
TraumaX45mXmorphine	0.66 (-18.64 to 19.96)	0.95	9.51 (-6.78 to 25.80)	0.25	-3.21 (-20.61 to 14.19)	0.72	4.90 (-15.68 to 25.48)	0.64	12.97 (-6.58 to 32.52)	0.19
TraumaX60mXmorphine	-3.30 (-22.65 to 16.06)	0.74	2.07 (-14.27 to 18.41)	0.80	-15.51 (-32.96 to 1.95)	0.08	-2.16 (-22.80 to 18.49)	0.84	22.38 (2.77 to 41.99)*	0.03
TraumaX90mXmorphine	-0.48 (-19.78 to 18.82)	0.96	0.06 (-16.23 to 16.35)	0.99	-23.87 (-41.27 to -6.47)**	0.01	6.66 (-13.92 to 27.24)	0.53	19.13 (-0.42 to 38.68)	0.06
TraumaX120mXmorphine	-1.51 (-20.81 to 17.79)	0.88	-1.99 (-18.28 to 14.30)	0.81	-16.46 (-33.86 to 0.94)	0.06	9.47 (-11.11 to 30.05)	0.37	13.96 (-5.59 to 33.51)	0.16
TraumaX150mXmorphine	-9.58 (-28.93 to 9.76)	0.33	-0.13 (-16.46 to 16.20)	0.99	-28.69 (-46.13 to -11.24)**	0.00	14.36 (-6.26 to 34.99)	0.17	9.11 (-10.49 to 28.71)	0.36

*denotes p<0.05,**p<0.01, ***p<0.001

Random Effect Mixed Models for the Interaction between Time, Session and Group on Rated Nausea, Euphoria, Dizziness, and Sedation.

Variables	Model-Nausea Coef (95% CI)	p-value	Model-Euphoric Coef (95% CI)	p-value	Model-Dizzy Coef (95% CI)	p-value	Model-Sedated Coef (95% CI)	p-value
Trauma (Ref: Control)	2.40 (-5.31 to 10.11)	0.54	3.04 (-8.26 to 14.35)	0.60	1.75 (-6.36 to 9.87)	0.67	0.43 (-11.11 to 11.97)	0.94
Measures: 15m (Ref: 0m)	-0.87 (-8.04 to 6.29)	0.81	3.96 (-4.95 to 12.87)	0.38	0.95 (-6.23 to 8.13)	0.80	3.58 (-5.89 to 13.06)	0.46
30m	-1.42 (-8.58 to 5.75)	0.70	5.54 (-3.37 to 14.45)	0.22	3.45 (-3.73 to 10.63)	0.35	9.75 (0.28 to 19.22)*	0.04
45m	-1.79 (-8.96 to 5.37)	0.62	7.75 (-1.16 to 16.66)	0.09	2.95 (-4.23 to 10.13)	0.42	10.83 (1.36 to 20.31)*	0.02
60m	-1.33 (-8.50 to 5.83)	0.72	3.79 (-5.12 to 12.70)	0.40	5.37 (-1.82 to 12.55)	0.14	9.33 (-0.14 to 18.81)	0.05
90m	-1.87 (-9.04 to 5.29)	0.61	3.62 (-5.29 to 12.54)	0.43	0.49 (-6.69 to 7.67)	0.89	9.58 (0.11 to 19.06)*	0.05
120m	-1.92 (-9.08 to 5.25)	0.60	6.71 (-2.20 to 15.62)	0.14	0.03 (-7.15 to 7.21)	0.99	6.09 (-3.38 to 15.56)	0.21
150m	-1.83 (-9.00 to 5.33)	0.62	4.79 (-4.12 to 13.70)	0.29	-0.18 (-7.36 to 7.01)	0.96	5.09 (-4.38 to 14.56)	0.29
TraumaX15m (TraumaXMeassure)	-0.72 (-10.57 to 9.13)	0.89	-3.37 (-15.62 to 8.88)	0.59	-3.47 (-13.34 to 6.40)	0.49	2.68 (-10.34 to 15.69)	0.69
TraumaX30m	-1.73 (-11.58 to 8.12)	0.73	-1.99 (-14.24 to 10.26)	0.75	-2.60 (-12.47 to 7.27)	0.61	-1.08 (-14.10 to 11.94)	0.87
TraumaX45m	4.83 (-5.02 to 14.68)	0.34	-5.75 (-18.00 to 6.50)	0.36	-4.47 (-14.34 to 5.40)	0.37	3.31 (-9.70 to 16.33)	0.62
TraumaX60m	-1.00 (-10.85 to 8.85)	0.84	-2.46 (-14.71 to 9.79)	0.69	-3.59 (-13.46 to 6.28)	0.48	3.11 (-9.91 to 16.13)	0.64
TraumaX90m	-2.46 (-12.31 to 7.39)	0.62	0.49 (-11.76 to 12.74)	0.94	-2.34 (-12.21 to 7.53)	0.64	4.75 (-8.27 to 17.77)	0.47
TraumaX120m	-3.27 (-13.12 to 6.58)	0.52	-5.89 (-18.14 to 6.36)	0.35	-2.22 (-12.09 to 7.65)	0.66	5.39 (-7.63 to 18.41)	0.42
TraumaX150m	-3.43 (-13.28 to 6.42)	0.50	-4.38 (-16.63 to 7.87)	0.48	-2.49 (-12.36 to 7.38)	0.62	1.21 (-11.81 to 14.23)	0.86
Morphine (Ref: Placebo)	-1.56 (-8.74 to 5.62)	0.67	2.49 (-6.44 to 11.43)	0.58	0.28 (-6.92 to 7.47)	0.94	3.02 (-6.47 to 12.52)	0.53
TraumaXmorphine	-3.43 (-13.34 to 6.47)	0.50	-4.12 (-16.44 to 8.21)	0.51	0.69 (-9.23 to 10.62)	0.89	-1.42 (-14.52 to 11.67)	0.83
15mXmorphine	0.08 (-10.05 to 10.22)	0.99	1.08 (-11.52 to 13.69)	0.87	6.63 (-3.52 to 16.79)	0.20	11.04 (-2.35 to 24.44)	0.11
30mXmorphine	5.00 (-5.13 to 15.13)	0.33	2.67 (-9.94 to 15.27)	0.68	7.18 (-2.98 to 17.33)	0.17	12.04 (-1.35 to 25.44)	0.08
45mXmorphine	3.21 (-6.93 to 13.34)	0.53	3.13 (-9.48 to 15.73)	0.63	7.84 (-2.31 to 18.00)	0.13	12.71 (-0.69 to 26.10)	0.06
60mXmorphine	11.89 (1.70 to 22.08)*	0.02	0.53 (-12.15 to 13.21)	0.93	13.28 (3.06 to 23.49)*	0.01	11.82 (-1.65 to 25.30)	0.09
90mXmorphine	18.50 (8.37 to 28.63)***	0.00	3.42 (-9.19 to 16.02)	0.60	24.34 (14.19 to 34.50)***	0.00	19.33 (5.94 to 32.73)**	0.00
120mXmorphine	17.00 (6.87 to 27.13)**	0.00	-8.04 (-20.65 to 4.56)	0.21	21.01 (10.85 to 31.16)***	0.00	18.03 (4.64 to 31.43)**	0.01
150mXmorphine	20.00 (9.87 to 30.13)***	0.00	-7.37 (-19.98 to 5.23)	0.25	17.18 (7.02 to 27.33)***	0.00	12.83 (-0.57 to 26.22)	0.06
TraumaX15mXmorphine	7.78 (-6.19 to 21.74)	0.27	22.43 (5.07 to 39.80)*	0.01	-2.38 (-16.37 to 11.61)	0.74	0.66 (-17.79 to 19.12)	0.94
TraumaX30mXmorphine	2.80 (-11.16 to 16.77)	0.69	16.75 (-0.61 to 34.12)	0.06	-7.36 (-21.35 to 6.64)	0.30	0.09 (-18.36 to 18.55)	0.99
TraumaX45mXmorphine	-0.81 (-14.77 to 13.15)	0.91	21.02 (3.65 to 38.38)*	0.02	-1.31 (-15.30 to 12.68)	0.85	2.36 (-16.10 to 20.81)	0.80
TraumaX60mXmorphine	-1.24 (-15.24 to 12.77)	0.86	18.37 (0.95 to 35.79)*	0.04	-5.95 (-19.99 to 8.08)	0.41	4.48 (-14.03 to 23.00)	0.63
TraumaX90mXmorphine	-2.32 (-16.29 to 11.64)	0.74	8.37 (-9.00 to 25.73)	0.34	-12.91 (-26.90 to 1.08)	0.07	-9.51 (-27.97 to 8.95)	0.31

TraumaX120mXmorphine	-4.97 (-18.94 to 8.99)	0.49	17.37 (0.00 to 34.73)*	0.05	-10.87 (-24.86 to 3.12)	0.13	-4.26 (-22.71 to 14.20)	0.65
TraumaX150mXmorphine	-5.78 (-19.78 to 8.21)	0.42	14.41 (-3.00 to 31.81)	0.10	-7.55 (-21.58 to 6.47)	0.29	-1.16 (-19.66 to 17.34)	0.90

Appendix 2.5: Effort reward task analyses

Statistical Analyses for Effort Reward Task between Medium and Low Effort Choices.

	Group	Reward			Variable	F	*p*	η^2
		Low	Medium	High				
Medium effort acceptances								
Morphine	Trauma	2.96 (2.37)	4.17 (1.66)	4.96 (0.20)	Group	1.11	.298	0.03
	Controls	2.19 (2.14)	3.81 (1.91)	4.57 (1.36)	Session	<0.01	.994	<0.01
Placebo	Trauma	2.67 (2.32)	4.04 (1.76)	5.00 (0.00)	Group*Session	0.97	.329	<0.01
	Controls	2.05 (2.06)	4.14 (1.65)	4.76 (1.09)	Reward	41.84	<.001***	0.40
					Reward*Group	0.60	.528	0.01
					Reward*Session	1.02	.358	<0.01
					Reward*Session*Group	0.23	.775	<0.01
Low effort acceptances								
Morphine	Trauma	3.46 (2.19)	4.54 (4.33)	5.00 (0.00)	Group	0.63	.433	0.01
	Controls	2.90 (2.12)	4.33 (1.35)	4.76 (0.54)	Session	0.10	.757	<0.01
Placebo	Trauma	3.25 (2.17)	4.62 (0.77)	4.96 (0.20)	Group*Session	0.63	.431	<0.01
	Controls	3.24 (2.10)	4.38 (1.60)	4.76 (1.09)	Reward	25.07	<.001***	0.32
					Reward*Group	0.01	.972	<0.01
					Reward*Session	0.20	.773	<0.01
					Reward*Session*Group	2.05	.146	<0.01

Note. * p<.01, ** p<.05, ***p<.001

Appendix 2.6: Plasma morphine analyses

There was a main effect of session ($F(1,100)=127.43$, $p<.001$, $\eta^2=0.32$) and a main effect of measurement time ($F(2,100)=131.09$, $p<.001$, $\eta^2=0.24$). There was no main effect of group ($F(1,50)=0.03$, $p=.862$) or interaction between group, session and measurement time ($F(2,66.05)=0.10$, $p=.827$, $\eta^2<0.01$). Means and standard deviations between session and measurement time and group can be observed below:

		Trauma (n=27)	**Control (n=25)**
Morphine	Baseline	0.14 (0.46)	0.34 (1.34)
	30 minutes	22.65 (11.34)	22.61 (16.17)
	60 minutes	20.88 (10.31)	22.17 (15.87)
Placebo	Baseline	0.05 (0.10)	0.24 (0.56)
	30 minutes	2.54 (2.09)	2.26 (2.47)
	60 minutes	2.46 (1.71)	2.47 (2.18)

Appendix 2.7 Order effects

There were order effects of session for pain threshold and tolerance. For pain threshold, there was a significant interaction between order and session ($F(1,45)=6.27$, $p=.016$). When followed up with t-tests with 'order' as the between-subjects variable, there were no significant differences in threshold in morphine ($t(49)=1.45$, $p=.152$) or placebo ($t(48)=0.13$, $p=.895$) sessions. For pain tolerance, there was a near-significant interaction between order and session ($F(1,45)=3.86$, $p=.056$). When followed up with t-tests with 'order' as the between-subjects variable, there were no significant differences in tolerance in morphine ($t(49)=1.68$, $p=.100$) or placebo ($t(48)=1.46$, $p=.151$) sessions.

Summary of order effects (mean and standard deviation).

Physical pain		**Order 1 (morphine followed by placebo)**	**Order 2 (placebo followed by morphine)**
Threshold (morphine session)[a]		19.71 (1.95)	15.35 (1.75)
Threshold (placebo session)[a]		16.11 (1.91)	15.72 (1.90)
Tolerance (morphine session)[a]		76.14 (2.40)	51.25 (2.24)
Tolerance (placebo session)[a]		61.66 (2.32)	43.83 (2.22)
Cyberball task		**Order 1 (inclusion followed by exclusion)**	**Order 2 (exclusion followed by inclusion)**
Mood	*Inclusion*	2.64 (0.92)	2.10 (1.19)
	Exclusion	0.43 (1.80)	1.21 (1.70)
Self-esteem		2.59 (0.74)**	3.15 (0.65)**
Meaningful existence	*Trauma*	1.68 (0.52)*	2.27 (0.64)*
	Controls	2.29 (0.76)	2.05 (0.49)
Control		1.76 (0.58)*	2.13 (0.60)*

[a] Presented means and standard deviations have been back-transformed (10 raised to the power of the value) to account for log transformation on the original analyses.
* p<.05, ** p<.01, *** p<.001

There were order effects of 'game order' (inclusion followed by exclusion; exclusion followed by inclusion) on mood, self-esteem, meaningful existence and control during the Cyberball task. For mood, there was an interaction between game

order and inclusion status (F(1,48)=10.47, *p*=.002). T-tests with ‘order’ as the between-subjects variable did not indicate any significant differences following inclusion (t(50)=1.80, *p*=.078) or exclusion games (t(50)=1.61, *p*=.114). For self-esteem, there was a significant main effect of order (F(1,48)=8.19, *p*=.151), where a follow up t-test between order and overall self-esteem revealed higher self-esteem in those who experienced the exclusion game first (t(50)=2.91, *p*=.005). For meaningful existence, there was a significant interaction between order and group (F(1,48)=5.78, *p*=.020) where there was significantly higher ratings in those who experienced exclusion first in the trauma group (t(25)=2.56, *p*=.017) but no difference of order in the control group (t(23)=0.92, *p*=.367). For control, there was a significant main effect of order (F(1,48)=4.84, *p*=.033), where overall control was significantly higher in those who experienced exclusion first (t(50)=2.21, *p*=.032).

Appendix 3.1: Physiological measures and analyses

Physiological Measures. Seven saliva samples were collected by passive drool method using Cryovial 3.5mL collection tubes. Participants were required to provide approximately 2ml of saliva, which was immediately stored at -80°C until analysis. Saliva samples were analysed using enzyme-linked immunosorbent assay (ELISA) kits to assess cortisol levels, (Salimetrics) with an assay sensitivity of <0.007 ug/dL, as well as levels of methadone, buprenorphine, and opiates (Immunalysis) with a sensitivity of 5ng/mL, 1ng/mL, and 10ng/mL, respectively. All samples were analysed in duplicate. Other measures of physiological arousal included heart rate, which was assessed each time a saliva sample was taken using an automatic blood pressure monitor (Omron M3 IT Intellisense), where a cuff was placed around the upper arm of the participant.

Appendix 3.2: LGCM procedure

Statistical Analysis: Latent Growth Curve Modelling. We fitted growth models in which repeated measures of either heart rate (controlled for baseline) or cortisol represent indicators of continuous latent variables, growth factors, the intercept (i.e., mean starting value) and the linear (i.e., rate of growth) and quadratic (i.e., levelling off, or coming down) slopes. In order to understand the role of opioid exposure, we added dummy-coded variables 'treated, 'non-treated' and 'controls' as covariates to our growth-curve model. Resulting coefficients signify the contribution of each respective opioid level in the context of all other opioid level groups. Interpersonal trauma was added as an additional covariate for heart rate due to improving overall model fit, despite not having an independent contribution. We centred the intercept at minute 0 (baseline) for cortisol and minute 46 for heart rate (baseline-corrected), but also ran alternative models with differing centre points from minute 46-119 for cortisol and minute 60-119 for heart rate to describe the influence of opioid exposure at different times during the exercises.

Time point four (minute 68) was excluded from the model for cortisol due to severe interferences with model fit, causing non-convergence (implications are discussed).

In addition, when analysed using ANOVA's, there were no significant Group differences in AUCg and AUCi ($F(2,61)=0.20$, $p=.823$, $\eta^2=.01$ and $F(2,61)=0.30$, $p=.740$, $\eta^2=.01$, respectively.

Appendix 3.3: Drug use history

Detailed drug use history between the three groups. The data for each substance reported in the following table is only for the individuals who expressed using that drug regularly (either in the past and/or currently). The reported data includes: the total number of years the substance was used for, number of days the substance was used per month, and the amount of substance used per session.

	Treated (n=20)	**Non-treated (n=20)**	**Controls (n=24)**
Illicit opioids (n=ever used regularly)	**18**	**17**	**0**
Years used	16.42 (11.29)	12.03 (2.32)	
Days used per month (before OSM)	28.00 (0.00)[a]	28.00 (0.00)[a]	
Days used per month (after OSM)	3.80 (7.73)	5.64 (9.03)	
Amount used per day (heroin, grams)	0.30 (0.70)[a]	0.30 (0.30)[a]	
Alcohol	**16**	**14**	**16**
Years used	23.31 (13.17)	15.17 (9.51)	22.42 (14.47)
Days used per month	15.00 (20.00)[a]	28.00 (14.50)[a]	6.00 (12.00)[a]
Amount used per session (units)	13.50 (31.75)[a]	15.00 (19.00)[a]	12.00 (14.25)[a]
Tobacco	**17**	**14**	**9**
Years used	29.32 (10.42)	20.08 (9.73)	23.28 (14.11)
Days used per month	28.00 (0.00)[a]	28.00 (0.00)[a]	28.00 (11.00)[a]
Amount used per day (cigarettes)	15.77 (7.96)	15.72 (8.67)	12.88 (9.57)
MDMA	**13**	**13**	**1**
Years used	5.69 (3.90)	4.79 (3.09)	12.00 (n/a)
Days used per month	7.79 (5.61)	9.85 (6.72)	4.00 (n/a)
Amount used per session (grams)	2.98 (2.56)	3.65 (2.77)	0.50 (n/a)
Cannabis	**15**	**12**	**8**
Years used	25.03 (13.53)	19.08 (11.33)	15.19 (11.56)
Days used per month	28.00 (15.00)[a]	28.00 (0.00)[a]	16.50 (21.50)[a]
Amount used per day (grams)	1.80 (0.95)	1.18 (0.59)	1.05 (0.58)
Amphetamines	**14**	**8**	**5**
Years used	5.50 (10.13)[a]	6.00 (11.00)[a]	7.00 (16.50)[a]
Days used per month	20.00 (21.00)[a]	28.00 (21.75)[a]	10.00 (15.50)[a]
Amount used per session (grams)	1.00 (1.00)[a]	3.50 (3.50)[a]	1.00 (0.56)[a]
Benzodiazepines	**7**	**6**	**1**
Years used	9.25 (20.00)[a]	2.00 (4.00)[a]	0.20 (n/a)[a]
Days used per month	5.00 (20.50)[a]	28.00 (12.13)[a]	28.00 (n/a)[a]
Amount used per session (milligrams)	15.00 (61.50)[a]	55.00 (295.25)[a]	80.00 (n/a)[a]
Cocaine	**12**	**12**	**2**
Years used	6.00 (21.25)[a]	3.75 (2.88)[a]	12.50 (n/a)[a]
Days used per month	16.00 (22.50)[a]	24.00 (23.00)[a]	15.00 (n/a)[a]
Amount used per session (grams)	0.83 (0.73)[a]	0.80 (1.75)[a]	1.38 (n/a)[a]

Note. [a] non-parametric data: median and IQR are reported

Appendix 3.4: Craving analyses

Results for repeated measures ANOVAS on the effect of social exclusion on craving indices between the two opioid users, including ratings of 1) liking of opioids, 2) wanting opioids, and 3) motivation to use opioids:

	Inclusion status	Treated	Non-treated	F-Statistic		*p*	η^2
Opioid liking	Inclusion	19.19 (26.48)	17.00 (25.91)	Group	0.05	.827	.03
	Exclusion	20.42 (33.02)	16.30 (26.24)	Inclusion status	0.80	.376	.02
				Group* inclusion status	0.22	.646	.01
Opioid wanting	Inclusion	28.81 (35.04)	20.15 (21.83)	Group	0.07	.797	.03
	Exclusion	29.94 (37.83)	21.68 (23.55)	Inclusion status	0.01	.940	<.01
				Group* inclusion status	0.31	.580	.01
Opioid motivation	Inclusion	3.87 (5.91)	7.90 (22.09)	Group	3.70	.062	.59
	Exclusion	10.45 (16.37)	12.18 (18.58)	Inclusion status	1.10	.302	.01
				Group* inclusion status	0.10	.758	<.01

Note. All analyses were log transformed due to deviations from normality. Means and standard deviations presented are the raw data.

Appendix 3.5: Adjusting the intercept with LGCM's

LGCM data for when the intercept is adjusted to multiple other time points in the model for both salivary cortisol and heart rate (table below). Model one includes dummy coded groups 'intoxicated' and 'non-treated' users, where the 'control' group are excluded as a reference category. Model two includes dummy coded groups 'intoxicated' users and 'controls', where the non-treated group is excluded as a reference category. For Model 2, only the beta, standard error and significance values for the 'Intoxicated' group are presented, as the values for controls are identical to the non-treated user group in Model 1 (except that the direction of beta values are reversed). A summary for the model outcomes when the intercept is adjusted to each time point can be found below (i = intercept and s = slope).

Cortisol			Min 0		Min. 46		Min. 60		Min. 85		Min. 101		Min.119	
			i	**s**	**i**	**s**	**i**	**s**	**i**	**s**	**i**	**s**	**i**	**s**
Model 1	**Treated**	***b***	-.065	.005	-0.57	-.002	-.057	.002	-.053	.006	-.045	.010	-.034	.014
		SE	.027	.005	.024	.011	.020	.006	.019	.004	.018	.009	.023	.014
		p	**.016***	.326	**.016***	.864	**.005****	.740	**.004****	.189	**.012***	.264	.138	.340
	Non-treated	***b***	-.011	.003	-.003	-.008	-.009	.002	-.007	.004	<.001	.011	.014	.017
		SE	.035	.007	.031	.014	.027	.008	.026	.006	.026	.011	.031	.017
		p	.759	.690	.913	.541	.756	.800	.779	.499	.998	.324	.653	.320
Model 2	**Treated**	***b***	-.054	.002	-.054	.006	-.049	.004	-.046	.002	-.045	.001	-.048	.003
		SE	.028	.006	.026	.011	.023	.006	.022	.006	.024	.010	.032	.015
		p	.054	.761	**.035***	.546	**.031***	.532	**.039***	.795	.061	.931	.132	.931

Heart rate			Min.'s 46 & 85			Min.'s 60 & 101			Min.'s 68 & 119		
			i	**s1**	**s2**	**i**	**s1**	**s2**	**i**	**s1**	**s2**
Model 1	**Treated**	***b***	4.77	1.04	-1.46	-5.18	1.04	-1.46	-5.60	1.04	-1.46
		SE	2.17	0.55	0.84	2.30	0.55	.836	2.64	0.55	0.84
		p	**.028***	.057	.081	**.024***	.057	.081	**.034***	.057	.081
	Non-treated	***b***	-0.48	1.26	-0.48	0.30	1.26	-0.48	1.08	1.26	-0.48
		SE	2.14	0.71	0.97	2.19	0.71	0.97	2.60	0.71	0.97
		p	.882	.075	.620	.892	.075	.620	.679	.075	.620
Model 2	**Treated**	***b***	-4.28	-0.22	-0.98	-5.48	-0.22	-0.98	-0.36	-0.08	-0.19

	SE	2.65	0.78	1.04	2.62	0.78	1.04	0.15	.282	0.19
	p	.106	.783	.344	**.037***	.783	.344	**.013***	.786	.299

Note. Model 1 includes the dummy-coded variables 'Treaded' and 'Non-treated' user groups, excluding 'Controls' as the reference category. Model 2 includes the dummy-coded variables 'Treated' and 'Controls', excluding 'Non-treated' users as the reference category.
Minute 0 = baseline, minute 46 = post-inclusion, minute 60 = post-exclusion, minute 68 = post-empathy (not analysed in this report), minute 85 = first recovery period, minute 101 = second recovery period, minute 119 = third recovery period.
*p<.05

Appendix 5.1: Non-normally distributed Cyberball outcomes

Non-normally distributed data for the Cyberball outcomes that did not improve following transformations were converted to change scores, where normality was assessed and a univariate ANOVA was used to assess differences between the groups. We thus calculated the change from inclusion to exclusion, and conducted a Univariate ANOVA on these scores. See table below:

Analyses of Change Scores from Inclusion to Exclusion between Groups

	MDMA user	**Non-MDMA user**	**Alcohol only user**	**F**	**p value**
Anger	-0.81 (1.24)	-1.14 (0.97)	-0.89 (0.98)	0.49	.613
Hurt feelings	-1.00 (1.16)	-0.53 (0.81)	-0.80 (1.01)	1.10	.339
Sense of belonging	-1.67 (1.17)	-1.69 (1.02)	-1.91 (1.01)	0.34	.710
Meaningful existence	-1.15 (1.18)	-1.40 (1.01)	-1.63 (1.15)	1.10	.314

Appendix 6.1: Review of social exclusion tasks

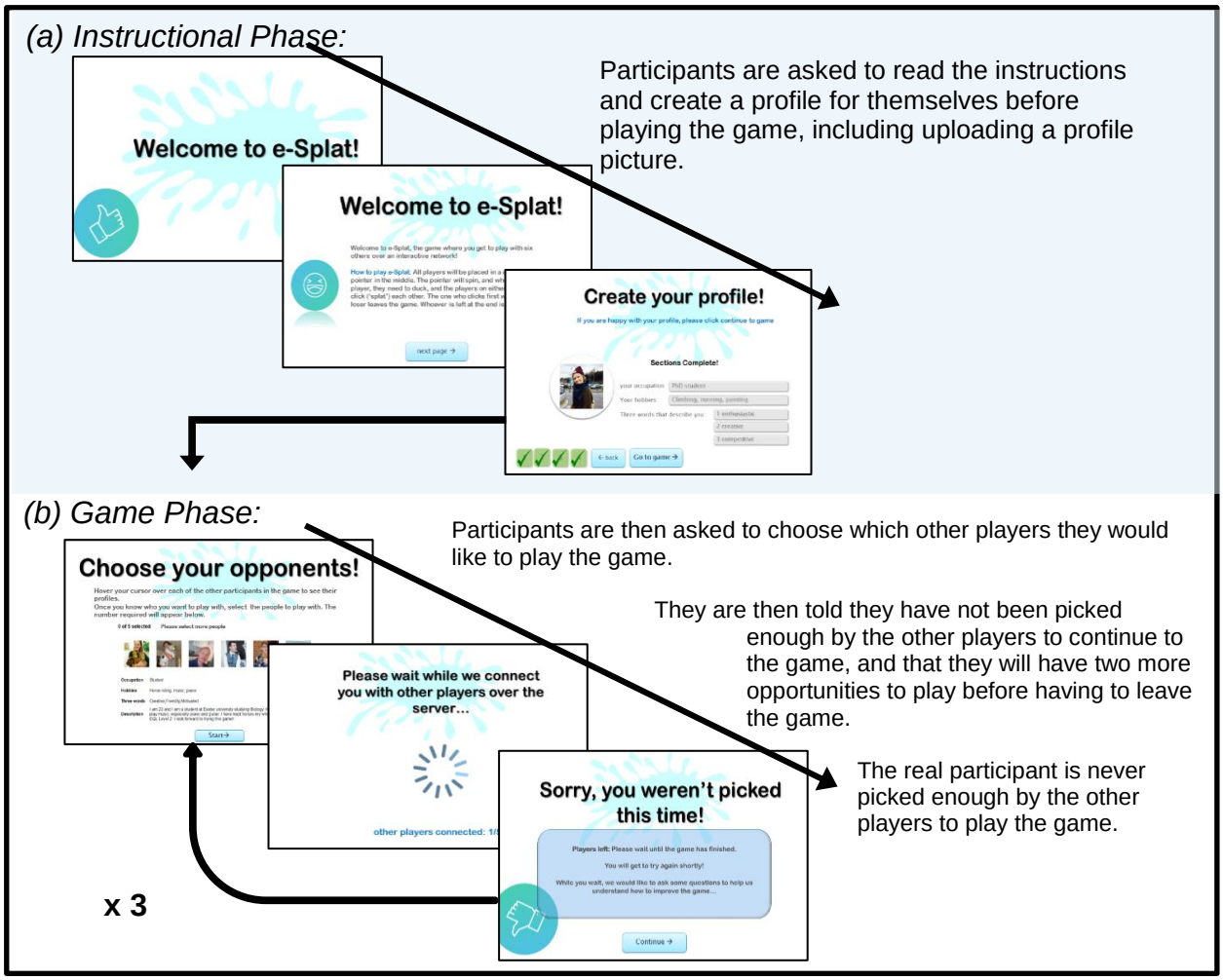
Tasks to Assess Social Pain, Alongside Strengths and Drawbacks.

Task	Authors	Task description	Strengths	Drawbacks
Cyberball Game	Williams and Jarvis (2006)	The classic social pain paradigm that has been most frequently used in past studies. Participants are told that they are playing a ball throwing game with two other participants over an online network. The game is described to participants as a 'mental visualisation' task, where they are asked to mentally visualise the experience and the other players. Unbeknown to the participants, the other participants are not real and are programmed to exclude them by not throwing the ball to them. There are many variations of the game, but generally there are two key games: inclusion by other players, and exclusion by the other players. Outcome measures are assessed using the post-Cyberball questionnaire (Williams et al., 2002) following inclusion and exclusion games, which investigates mood, the four basic needs, and manipulation checks.	• Highly replicated • Easy to implement • Simplistic form of exclusion, which makes it easy to interpret	• It is easy for participants to work out the latent nature of the game • The interface is outdated which makes the game less convincing • The game is not engaging
Atimia	Wirth, Turchan, Zimmerman, and Bernstein (2014)	This task attempts to emulate the experience of social pain by inducing feelings of being a burden to others, which causes the participant to be excluded from the group. Participants are told they are playing a strategy game with two other participants over the computer network, and all players are required to work together to achieve the highest number of points (i.e. achieve a group goal). During the game, there are a series of questions that each player can take turns to answer, and the other team players can see whether the others answered correctly. After answering, each player can choose which other player they would like to answer the next question. The game is manipulated so that participants incorrectly answer all questions and are not picked by the other players to answer any more questions. Following the game, mood and the four basic needs were assessed, but also feelings of pain and their consequent desire to interact with the group.	• Assessed feelings of pain specifically: asking participants to rate from 1 to 10 how much pain sensation they experienced. • Novel and different to simple social exclusion. • Convincing cover that hides the latent meaning of the game	• Feelings of burdensome may be different from exclusion

O'Cam	Goodacre and Zadro (2010)	Participants are told they will be trialling a new web-conference programme and asked to create a short presentation that they will give live over a computer to two other people. The listeners are pre-recorded by the experimenter and begin to talk amongst themselves over the real participant during their presentation. There are two conditions in this paradigm: inclusion where the listeners do not speak over the participant, and exclusion where they talk over the participant. Participants complete mood and physiological measures following the presentation. Mood and the four basic needs are assessed after the presentation, as well as revenge/retaliation against the listeners.	• Easier to implement than a real audience • Keeps the audience response identical and controlled between all participants	• Could be confounded with social anxiety
Social feedback task	(Hsu et al., 2013)	Participants are asked to upload a profile containing information about their personal qualities, as well as a picture of themselves. Individuals are then asked to rate the online profiles of the preferred-sex (all programmed by the experimenter) on how much they like that person, followed by how much they think that person would like them. Following this, the participant receives the rating from the individuals they rated, where they are rejected by those who they rated as most attractive. Outcome measures were ratings of feeling sad, rejected, happy, and accepted, as well as their consequent desire to socially interact.	• Simple • Novel in using attraction as a source of social pain	• Blocked design of inclusion and exclusion for use with PET imaging, which may not be convincing
Ostracism Online	Wolf et al. (2015)	Participants are told that they will be playing a group game, and are asked to create a profile about themselves and upload an avatar that reflects them. Prior to playing the game, participants can observe the other players[1] profiles, and can 'like' others profiles, similar to social media. During this introduction to the other players. To cause feelings of exclusion, the real participant does not receive many likes from the other players, but can witness the other players 'liking' others' profiles. The lack of likes from others is designed to emulate the exclusion one might experience on social media, such as on Facebook. There are two variations to this paradigm: inclusion where participants receive equal likes from others, and exclusion where they do not receive likes from others. Outcome measures assessed mood and the four basic needs, as well as subsequent conformity to the group.	• Ecological validity and relevant to modern day • Controlled and easy to implement	• Requires the user to be familiar with social media platforms

Appendix 6.2: ‘E-Splat’

The new task was disguised as a new online game called ‘E-Splat’, which is graphically illustrated below. During the task, participants are told they will be trialling this new online game which involves playing remotely with six other people over an online network. Prior to playing the game, participants are asked to upload a brief profile about themselves; describing what they do, their hobbies, and to briefly describe themselves. Alongside this they are also asked to upload a profile picture. In the instructions, participants are told that the game emulates the childhood game ‘Splat’, where each player will need to ‘splat’ (click on) their co-players before they are ‘splatted’ first. The time to splat will depend on an arrow in the middle of the players, which spins and falls between a pair of players who are then required to splat each other first. They are told that whoever is the last player in the game will win.



Also during this instructional phase, participants are told that they will be able to pick the other players that they wish to play with. They are asked to choose the other players based on their given profiles. However, participants are also told that they equally have to be picked by other players in order to play the game. They are told that there will be multiple opportunities to play the game, and each time the number of people required to play the game will vary (for example, “the next game will require 3 players” vs “the next game will require 5 players”). The amount of players for each game will always be less than the total amount of players available, and participants are told that they can only play the game if they have been picked enough by the other players.

Once they have created their profile, the participant is shown the profiles of the other players and is given the opportunity to read them. They are then asked to pick the individuals that they wish to play with based on their profiles (the amount of players they are required to pick will vary, based on how many people are required to play the game). One all players have picked who they wish to play with for the forthcoming game, the participant is presented with a loading symbol whilst they wait to see the result. What is not known to participants is that the other players are not real and have been set up by the experimenter to exclude them from the games. After each game, participants are told that they have not been picked enough by the others to play, and that they will have to wait for the next opportunity.

When participants are waiting whilst the other players are ‘playing the game’, they are asked to answer some questions regarding their feelings around the game. These questions are aimed to covertly assess their mood and self-esteem using a Visual Analogue Scale (VAS), and they are disguised as questions aimed to help improve the game. This process is then repeated, and after three attempts at playing the game, participants are told that they are no longer eligible to continue the game as they have not been picked enough throughout. The game finishes and they are debriefed on the true nature of the task.

7.0 References

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