

Intrusive Memories Following a Single Dose of Hydrocortisone: Examining the  
Effect of Hydrocortisone on Intrusive Memories in Healthy Volunteers

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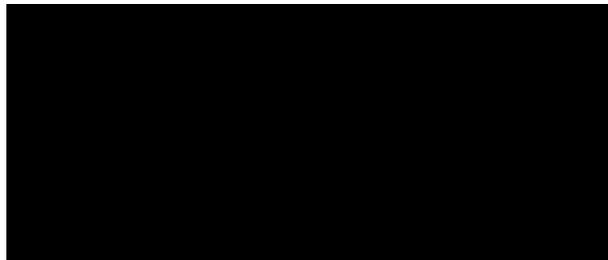
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**UCL Doctorate in Clinical Psychology**

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## Overview

This thesis focuses on the effects of pharmacological strategies on the development of post-traumatic stress disorders (PTSD) in the context of interpersonal violence. Part 1 reviews research literature examining the effects of pre-assault substance consumption on PTSD symptoms amongst victims of sexual assault. Specifically, it investigates the effects of acute substance intoxication and chronic pre-assault problematic substance use on the severity and course of PTSD symptoms. The review highlights characterological self-blame and negative social reactions as significant mediators of PTSD recovery in the context of pre-assault substance consumption.

Part 2 comprises an empirical study investigating the effects of a single dose of hydrocortisone on intrusive and declarative memories using the trauma film paradigm in a sample of female healthy participants. The findings highlight that hydrocortisone orally administered within the memory consolidation period can effectively reduce intrusive memories. Compared to the placebo group, although declarative memory was unaffected, the frequency and vividness of intrusive memories were significantly reduced in the hydrocortisone group. This research project was jointly conducted with another trainee from University College London (UCL) who investigated the effects of propranolol on intrusive and declarative memories and used the same placebo group.

Part 3, the critical appraisal, sets out a number of reflections on the process of conducting the research project. The appraisal discusses personal assumptions for this

project and how they were challenged and modified. The implications of the current project for future work are also considered.

## Impact Statement

This thesis demonstrates that a single dose of hydrocortisone orally administered shortly after a trauma film containing interpersonal violence can rapidly reduce the occurrence of involuntary intrusive memories, a canonical symptom of post-traumatic stress disorder (PTSD), while leaving voluntary declarative memory of the event intact. These findings suggest that hydrocortisone might have clinical applications as pharmacological vaccines against PTSD by interfering with emotional memory consolidation or retrieval if administered within the critical period of memory consolidation. Hydrocortisone administration can be used as a form of early preventative intervention that can reduce the risk of potentially developing PTSD over time and associated emotional distress that otherwise may lead to reduced quality of life post-trauma and the development of other comorbid mental health conditions such as depression, anxiety and substance use disorders. Such findings shed important light on public service delivery in terms of developing and implementing treatment approaches that may combine both pharmacological and psychological interventions complementarily. In addition, this thesis adds to the current literature on the effects of hydrocortisone, which, already known as an effective medication for a range of physical health conditions, may also have important clinical use in treating trauma-related disorders and promoting public mental health.

Furthermore, this thesis brings about more understanding of the memory processes and brain mechanisms under which hydrocortisone affects PTSD. It also identifies research areas that need more clarifications. For instance, whether the effects

of hydrocortisone generalise to men and other types of traumatic experiences, and to clinically realistic treatment timescales after a traumatic event, remains to be determined.

## Table of Content

<b>Overview</b> .....	3
<b>Impact Statement</b> .....	5
<b>List of Tables</b> .....	11
<b>List of Figures</b> .....	12
<b>Acknowledgements</b> .....	13
<b>Part 1: Literature Review</b> .....	15
<b>Abstract</b> .....	16
Aim .....	16
Method .....	16
Results .....	16
Conclusion.....	17
<b>1. Introduction</b> .....	18
1.1. Post-traumatic stress disorder (PTSD) .....	18
1.2. Substance consumption and substance use disorders (SUDs) .....	19
1.3. The relationship between PTSD and SUDs .....	20
1.3.1. <i>Self-medication model</i> .....	21
1.3.2. <i>Negative reinforcement model</i> .....	22
1.3.3. <i>Mutual maintenance model</i> .....	22
1.3.4. <i>High-risk and susceptibility hypotheses</i> .....	23
1.3.5. <i>Third variable model</i> .....	24
1.4. The relationship between PTSD and SUDs in interpersonal violence.....	24
1.4.1. <i>The effect of acute substance intoxication on PTSD</i> .....	26
1.4.2. <i>The effect of chronic pre-assault problematic substance use on PTSD</i> .....	26
1.4.3. <i>The relationship between PTSD and post-assault SUDs</i> .....	27
1.5. The purpose of current review.....	28
<b>2. Method</b> .....	29
2.1. Search strategy .....	30
2.2. Inclusion criteria .....	30
2.3. Critical appraisal of articles .....	31

<b>3. Result</b>	34
3.1. Relevant articles	34
3.2. Synthesis of articles	38
3.2.1. <i>The effects of acute substance intoxication on PTSD</i>	39
3.2.2. <i>The effects of chronic pre-assault problematic substance use on PTSD</i>	47
3.2.3. <i>Mediators of the relationship between acute alcohol intoxication and PTSD: Self-blame</i>	49
3.2.4. <i>Mediators of the relationship between acute alcohol intoxication and PTSD: Social reactions</i>	51
<b>4. Discussion</b>	51
4.1. Summary	51
4.2. Interpretation of findings	53
4.3. Limitations	58
4.4. Clinical implications	61
4.5. Future directions	62
<b>Reference</b>	64
<b>Part 2: Empirical Paper</b>	89
<b>Abstract</b>	90
Aim	90
Method	90
Results	90
Discussion	91
<b>1. Introduction</b>	92
1.1. Emotional memories	92
1.2. Intrusive memories in PTSD	93
1.3. Dual Representation Theory (DRT)	94
1.4. The stress response	96
1.5. The effect of glucocorticoids	97
1.5.1. <i>Memory consolidation</i>	97
1.5.2. <i>Memory retrieval</i>	100
1.5.3. <i>Intrusive memories</i>	103
1.6. The current study	106
<b>2. Method</b>	108

2.1. Design .....	108
2.2. Participants .....	109
2.3. Materials .....	113
2.4. Measures .....	114
2.4.1. <i>Trait measures</i> .....	114
2.4.2. <i>State measures</i> .....	115
2.4.3. <i>Physiological measures</i> .....	116
2.4.4. <i>Memory assessments</i> .....	117
2.4.5. <i>Sleep measures</i> .....	119
2.5. Procedure .....	120
2.6. Statistical analysis .....	123
2.7. Missing data and outliers .....	124
<b>3. Results</b> .....	124
3.1. Descriptive statistics .....	124
3.2. Manipulation checks: Response to the film .....	127
3.3. Response to drug .....	129
3.4. Intrusive memories Day 1 .....	132
3.5. Intrusive memories on Day 1-7 .....	135
3.6. Declarative memory on Day 8 .....	139
<b>4. Discussion</b> .....	143
4.1. Findings of the current study .....	143
4.2. Limitations .....	148
4.3. Clinical implications and future directions .....	151
<b>Reference</b> .....	154
<b>Part 3: Critical Appraisal</b> .....	177
<b>Introduction</b> .....	178
<b>1. Personal assumptions</b> .....	178
<b>2. Reflections on the research process</b> .....	180
<b>3. Implications for future work</b> .....	184
<b>Conclusion</b> .....	188
<b>Reference</b> .....	190
<b>Appendices</b> .....	200

Appendix 1: Quality and relevant assessment scales .....	201
Appendix 2: Trainee contribution to the project .....	206
Appendix 3: Ethical approval documents.....	208
Appendix 4: Project documentation.....	216
Appendix 5: Questionnaires and measures .....	232

## List of Tables

<b>Part 1: Literature Review</b> .....	15
Table 1a Details of Longitudinal/Cohort Studies Included in the Current Review .....	35
Table 1b Details of Cross-sectional Studies Included in the Current Review .....	36
Table 2 Quality and Relevance Ratings .....	37
<b>Part 2: Empirical Paper</b> .....	87
Table 1 Participant Demographics, Trait Characteristics, Physiological Variables and Baseline Ratings of Sleep Quality by Drug Treatment Group .....	121
Table 2 Physiological and Subjective State Responses at Time 1 and 2 .....	123
Table 3 Summary Statistics for Physiological and Subjective State Measures on Day 1 .....	126
Table 4 Diary Completion Time, Attentional Parameters, and Ratings of Sleep Quality on Day 1 by Drug Treatment Group .....	129
Table 5 Diary Compliance Rating, Subjective State Measures and IES-R Scores by Drug Treatment Group .....	136
Table 6 Free Recall and Cued Recall Scores by Drug Treatment Group .....	137

## List of Figures

<b>Part 1: Literature Review</b> .....	15
Figure 1 Flow chart for the selection of relevant articles. ....	33
<b>Part 2: Empirical Paper</b> .....	87
Figure 1. Participant flowchart.....	108
Figure 2. Salivary cortisol level on Day 1.....	127
Figure 3. The frequency of intrusive memories across Day 1-7.....	131
Figure 4. The vividness of intrusive memories across Day 1-7 .....	132
Figure 5. The distress of intrusive memories across Day 1-7 .....	133

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research have motivated me and will continuously motivate me in the pursuit of further research and study.

## Part 1: Literature Review

Post-Traumatic Stress Disorder in Victims of Sexual Assault with Pre-assault

Substance Consumption: A Systematic Review

## **Abstract**

### **Aim**

Post-traumatic stress disorder (PTSD) and substance consumption commonly co-occur in victims of sexual assault. Substance consumption can occur pre- and post-assault and may lead to pre-assault intoxication, resulting in different effects on the development of PTSD. This review aims to give an overview of current understanding of the effects of pre-assault substance consumption, namely acute substance intoxication and chronic pre-assault problematic substance use, on symptoms of PTSD amongst victims of sexual assault.

### **Method**

PsycINFO, EMBASE, and MEDLINE were searched using terms related to PTSD, sexual assault, and substance consumption. The search yielded 2004 articles, 262 of which were retrieved for more detailed evaluation. Thirteen articles were deemed to be relevant for inclusion and were appraised in detail.

### **Results**

Overall, the reviewed papers support the hypothesis that acute substance intoxication and chronic pre-assault problematic substance use are associated with fewer initial PTSD symptoms but less improvement over time, resulting in slower overall PTSD recovery. They also highlighted post-assault characterological self-blame and negative social reactions as mediators of recovery in the context of pre-assault substance consumption.

## **Conclusion**

Acute substance intoxication and chronic pre-assault problematic substance use appear to have an impact on the development of PTSD symptoms amongst victims of sexual assault. The importance of developing early intervention and routine screening and assessment for PTSD and pre-assault substance consumption is emphasised. Limitations and future research directions are discussed.

## **1. Introduction**

### *1.1. Post-traumatic stress disorder (PTSD)*

Many people report experiencing or witnessing a traumatic event over the course of their lifetime (Benjet et al., 2016). Traumatic events, defined in the most recent Diagnostic and Statistical Manual of Mental Disorders as “exposure to actual or threatened death, serious injury, or sexual violence” (DSM-5; American Psychiatric Association, 2013, p. 271), include interpersonal violence, road traffic accidents, and exposure to aversive details of trauma through electronic and online media. Research suggests that a clinically significant number of people who experience traumatic events may go on to develop post-traumatic stress disorder (PTSD; Green, 1994). The lifetime prevalence rate of PTSD in the population is approximately 5-12% (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; World Health Organisation, 2003).

Major PTSD symptoms include re-experiencing via intrusive memories, flashbacks and nightmares; (hyper)arousal in the form of exaggerated startle response and hypervigilance; and protective reactions, including emotional numbing, avoidance, amnesia, and cognitive avoidance (DSM-5; 2013). In addition, PTSD commonly presents with various forms of negative affect, including anger, sadness and guilt. The severity and course of PTSD symptoms also vary across individuals, and a number of studies have been conducted to investigate related factors and exposure variables (Brewin, Andrews, & Valentine, 2000; Cogle, Resnick, & Kilpatrick, 2009; Kessler

et al., 1995; Kilpatrick & Saunders, 1999; Ozer, Best, Lipsey, & Weiss, 2003; Ullman, Filipas, Townsend, & Starzynski, 2007).

### *1.2. Substance consumption and substance use disorders (SUDs)*

Substance consumption is an important public health issue that continues to result in substantial morbidity and significant societal economic costs (Galea, Nandi, & Viahov, 2004). It is associated with a wide range of negative consequences, including health issues, job loss, and risky and criminal behaviours (McGinnis & Foege, 1999). Surveys have consistently found young adults to have the highest rates of substance consumption (Elliott, Huizinga, & Menard, 2012). The use of substances may involve licit (alcohol and cigarettes, and cannabis in some jurisdictions) or illicit substances.

In addition, frequent and excessive use of substances may result in the development of substance use disorders (SUDs). Individuals with SUDs show impaired control over their use of substances. They may experience cravings and use the substance in larger amounts or over a longer period despite a persistent desire to regulate or discontinue use. Furthermore, SUDs are usually accompanied by social impairment, risky use of the substance and symptoms of tolerance and withdrawal (DSM-5, 2013). Nationally representative surveys have demonstrated that lifetime prevalence rates of SUDs across countries ranged from a low of 1.3% (Italy) to a high of 15.0% (Ukraine), with a median of 7.0% (Demyttenaere et al., 2004; Kessler et al., 2007). With similar diagnostic criteria to SUDs, alcohol use disorders (AUDs) involve problematic patterns of alcohol use leading to significant impairment or distress (DSM-5, 2013). The National Epidemiologic Survey on Alcohol and Related

Conditions in the United States showed that 12-month and lifetime prevalences of AUDs were 13.9% and 29.1%, respectively (Grant et al., 2015).

Some research conducted prior to DSM-5's revised classification scheme referred to substance-related problems using other terminology (e.g., substance misuse/abuse/dependence/use, disorder/addiction, etc.) in order to account for different degrees of problem severity. However, there is no such distinction in DSM-5 which aimed for a continuum approach. Specifically, SUDs occur in a broad range of severity, from mild to severe, with severity based on the number of symptom criteria endorsed. Generally, a mild SUD is suggested by the presence of two to three symptoms, moderate by four to five symptoms, and severe by six or more symptoms (DSM-5, 2013). Therefore, for the sake of consistency, the term "SUDs" will be used throughout this current review wherever it is evident that publications were referring to a pattern of substance consumption that is consistent with the definition of SUDs as provided in DSM-5.

### *1.3. The relationship between PTSD and SUDs*

PTSD and SUDs commonly co-occur (Kessler, Chiu, Demler, & Walters, 2005). Research has shown that the prevalence estimate of SUDs is high in individuals with PTSD, with 15.8% reporting AUDs, approximately one-third having nicotine dependence and 10.6% meeting criteria for SUDs of other drugs (Breslau, Davis, & Schultz, 2003). Similarly, 25-42% of individuals seeking treatment for SUDs meet the criteria for PTSD (Brady, Back, & Coffey, 2004). PTSD is comorbid with the use of various types of drugs, for example, heroin, cocaine, and amphetamines (Blumenthal

et al., 2008; Mills, Teesson, Ross, & Peters, 2006), and most commonly with alcohol and nicotine use (Sareen, Chartier, Paulus, & Stein, 2006; Smith, Blumenthal, Badour, & Feldner, 2010). In addition, patients with concurrent PTSD and SUDs show higher symptom severity and poorer treatment outcomes compared to patients with either disorder alone (Back et al., 2000; Brady, 2001).

The relationship between PTSD and SUDs is complex and bidirectional (Blumenthal et al., 2008; Feldner, Babson, & Zvolensky, 2007; McFarlane, 1998). Extensive research has focused on delineating this relationship (McFarlane, 1998; Stewart, Pihl, Conrod, & Dongier, 1998; Steward & Conrod, 2003). According to the current literature, the following theoretical accounts of the relationship between PTSD and SUDs have been posited.

#### *1.3.1. Self-medication model*

The self-medication model proposes that trauma survivors' excessive use of substance is an attempt to alleviate PTSD symptoms (Khantzian, 2003). This model suggests that the use of substances is maintained and reinforced due to its effect in temporarily reducing the negative affect and other aversive symptoms associated with trauma. According to this model, the use of substance functions to manage the emotional pain resulting from trauma in order to achieve emotional homeostasis (Khantzian, 1985). It posits a degree of psychopharmacological specificity in that the specific substance used is expected to psychophysiologically alleviate aversive affects. Specifically, cocaine is used to regulate low energy and depression, nicotine to remedy dysphoria, and alcohol to relieve anxiety (Khantzian, 1985, 1997). In PTSD,

furthermore, corticotropin-releasing hormone and noradrenergic systems may interact such that the stress response is progressively augmented. Patients may use a range of substances in an effort to interrupt this progressive augmentation (Koob, 1999; Post, Weiss, Smith, & McCann, 1997). Evidence from epidemiological and longitudinal studies, provides support for the self-medication model, such that young adults with early-life trauma tend to use drugs to self-medicate troubling trauma-associated memories, nightmares, or painful hyperarousal symptoms (Reed, Anthony, & Breslau, 2007).

### *1.3.2. Negative reinforcement model*

The negative reinforcement model is a general theory of problematic substance consumption. It suggests that withdrawal-driven negative affect is the fundamental motivator for the use of substances and that PTSD may lead to a greater sensitivity to such effects, hence indirectly augmenting an individual's potential to develop and maintain ongoing problematic substance consumption (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004). In contrast to the self-medication model, this model makes no prediction about psychopharmacological specificity between the substance of choice and the state of psychological distress. Evidence from several laboratory-based studies supports this model (for review, see Smith, Feldner, & Badour, 2011), highlighting the role of withdrawal symptoms (Feldner, Vujanovic, Gibson, & Zvolensky, 2008) and a lack of substance and affective specificity (Beckham et al., 2007; McClernon et al., 2005).

### *1.3.3. Mutual maintenance model*

An extension of the self-medication model, the mutual maintenance model posits a reflexive relationship between SUDs and PTSD symptoms (Kaysen et al., 2011; McFarlane et al., 2009). This model suggests that repeated use of substances not only helps temporarily suppress PTSD symptoms but may also impede natural recovery from PTSD. For example, while exposure to trauma reminders can trigger substance consumption (Baker et al., 2004), withdrawal symptoms from substances, such as palpitations, sweating and shivering, are similar to fear responses during the traumatic event and can evoke traumatic memories and trigger PTSD symptoms (Jacobsen, Southwick, & Kosten, 2001; Stewart & Conrod, 2003). This may in turn exacerbate and maintain PTSD symptoms over time. Neuroendocrine research also provides some evidence for this model, as the acute and chronic stress in PTSD negatively affects hippocampal function, which can be further impaired by chronic alcohol exposure and especially alcohol withdrawal (Conrod & Stewart, 2003; McEwen, 2000).

#### *1.3.4. High-risk and susceptibility hypotheses*

The high-risk and susceptibility hypotheses are other potential pathways between PTSD and SUDs (Chilcoat & Breslau, 1998a, 1998b). The high-risk hypothesis suggests that engaging in substance consumption and related “high-risk” activities (e.g., being intoxicated in dangerous situations) increases the probability of experiencing a traumatic event, and hence of developing PTSD. The susceptibility hypothesis posits that excessive use of substances may play a causal role, in that substance users may be more susceptible to PTSD following a traumatic event due to impaired psychological or neurochemical systems resulting from extensive substance

consumption. A number of studies have demonstrated that excessive substance consumption contributes to rape vulnerability and increases susceptibility to the development of PTSD (Messman-Moore, Ward, & Brown, 2009; Testa, Livingston, Vanzile-Tamsen, & Frone, 2003). In addition, multiple studies with female substance abusers also demonstrate high rates of revictimisation in the form of partner violence, as well as stranger rape and physical assault in adulthood and subsequent development of PTSD (Classen, Palesh, & Aggarwal, 2005; Hien, Nunes, & Levin, 1995; Hien & Scheier, 1996; Messman-Moore et al., 2009; Ullman, Najdowski, & Filipas, 2009).

#### *1.3.5. Third variable model*

The third variable model postulates that concurrent PTSD and SUDs may be due to an unknown shared third variable, such as biological vulnerability and/or personality factors (Ducci et al., 2008; Haller & Chassin, 2013; Miller, Vogt, Mozley, Kaloupek, & Keane, 2006; Sartor et al., 2011). In addition, several research studies suggest that the relationship between PTSD and SUDs may be mediated by other factors, such as poor coping skills, self-regulatory deficits and trauma-related cognitions (Hien, Cohen, & Campbell, 2005; Stewart & Conrod, 2003; Thompson & Kingree, 2010). For example, several studies showed that high anxiety sensitivity appears to partially mediate the relationship between PTSD and SUDs (Lubman, Allen, Rogers, Cementon, & Bonomo, 2007; Stewart, Conrod, Samoluk, Pihl, & Dongier, 2000).

#### *1.4. The relationship between PTSD and SUDs in interpersonal violence*

Interpersonal violence refers to violence between individuals, including within families and between acquaintances and strangers (World Health Organisation, 2014).

Interpersonal violence is further differentiated into sexual and non-sexual assault. Non-sexual assault takes place when an individual or a group provokes and attacks a person physically without overt sexual contact. Non-sexual assault includes physical assault (i.e., physical attacks with or without the use of a weapon), threats or menacing and unwanted contact, such as shoving, pushing, tripping, without necessarily resulting in physical harm (Berenson, San Miguel, & Wilkinson, 1992). In this review, the term ‘sexual assault’ refers to an act in which a person sexually touches, coerces or physically forces a person to engage in a sexual act against their will. This broad category of sexual violence includes rape (forced vaginal, anal or oral penetration or drug-facilitated sexual assault), groping, child sexual abuse, sexual torturing, and sexual harassment (Berenson et al., 1992). Physical assault and sexual assault may also co-occur in certain situations (Sullivan, McPartland, Armeli, Jaquier, & Tennen, 2012; Wang, Iannotti, Luk, & Nansel, 2010).

Many studies have demonstrated the co-occurrence of PTSD and SUDs in victims of interpersonal violence, including both sexual and non-sexual assaults (Griffing et al., 2006; Resnick, Acierno, & Kilpatrick, 1997) and focused on investigating their temporal relationship. Generally, these studies describe a complex temporal relationship between PTSD and SUDs in the context of interpersonal violence (Hedtke et al., 2008; Kilpatrick et al., 2003). Substance consumption can occur pre- and post-assault and may result in peri-assault intoxication. The types of relationship are broadly summarised in the following three categories, which will focus on the broad issue of the relationship between the development of PTSD and acute intoxication,

chronic pre-assault problematic substance use and post-assault SUDs.

#### *1.4.1. The effect of acute substance intoxication on PTSD*

A number of studies have focused on the effect of acute substance intoxication on the development of PTSD and its recovery. Acute substance intoxication involves the victims' consumption, either voluntarily or involuntarily, of psychoactive substances immediately or shortly before interpersonal violence, which can lead to various levels of intoxication and/or incapacitation prior to and during the incident (i.e., pre- and peri-assault intoxication). Overall, inconsistent evidence has been found on the role of acute substance intoxication on PTSD. Some studies have suggested an increased risk of PTSD diagnosis and more chronic and severe course of symptoms in victims of interpersonal violence with acute intoxication (Abbey, Zawacki, Buck, Clinton, & McAuslan, 2004; Kaysen et al., 2010; Richmond & Kauder, 2000; Zatzick et al., 2002), whereas others indicate a protective effect of acute substance intoxication against PTSD (Maes, Delmeire, Mylle, & Altamura, 2001; Mellman, Ramos, David, Williams, & Augenstein, 1998). In addition, a number of studies have demonstrated that sexual assault victims with acute substance intoxication may further develop chronic substance use problems comorbid with PTSD and depression after an assault (Burnam et al., 1988; Kilpatrick, Acierno, Resnick, Saunders, & Best, 1997; Yuan et al., 2003).

#### *1.4.2. The effect of chronic pre-assault problematic substance use on PTSD*

The effect of chronic pre-assault problematic substance use on PTSD has also been investigated. This includes victims who have developed long-term SUDs and/or had excessive use of substances that led to negative consequences such as hangover and

loss of interest in activities and hobbies during the month prior to the occurrence of interpersonal violence. It should be noted that victims with chronic pre-assault problematic substance use patterns may have been either intoxicated or sober during the index incident of interpersonal violence. Similar to studies investigating the effect of acute intoxication on PTSD, findings are mixed. Some studies have suggested the aversive effect of chronic pre-assault problematic substance use on the development and maintenance of PTSD (Kaysen et al., 2006; McFarlane et al., 2009), while others have failed to find any relationship (Mason, Turpin, Woods, Wardrope, & Rowlands, 2006; Zatzick et al., 2002, 2006)

#### *1.4.3. The relationship between PTSD and post-assault SUDs*

In addition, many studies have been conducted to investigate the relationship between PTSD resulting from interpersonal violence and subsequent development of SUDs. These studies take into consideration victims who did not have chronic problematic substance use or acute intoxication prior to and/or during the assault incident but went on to develop SUDs afterwards. Evidence regarding the onset and development of SUDs after assaults has been mixed. Some studies have shown that neither trauma exposure nor the presence of PTSD significantly predicts the onset of SUDs (Breslau et al., 2003; Testa, Livingston, & Hoffman, 2007), while others demonstrated a greater likelihood of subsequent development of SUDs in people meeting criteria for PTSD (Flood, McDevitt-Murphy, Weathers, Eakin, & Benson, 2009; Kessler et al., 2005; Ray et al., 2009; Read et al., 2012). Acierno and his colleagues (1999) also showed that post-assault AUDs are one of the risk factors for

the development of PTSD following rape, but not following physical assault.

### *1.5. The purpose of current review*

In sum, the relationship between PTSD and SUDs in interpersonal violence appears complex and inconsistent. A number of authors have suggested models to account for the relationship between PTSD and SUDs (McFarlane, 1998; Steward et al., 1998; Stewart & Conrod, 2003), but none has recently been systematically reviewed in the context of interpersonal violence. The current review will primarily focus on the effect of acute substance intoxication and chronic pre-assault problematic substance use on the development of PTSD symptoms specifically amongst victims of sexual assault occurring in adolescence and adulthood. The focus was chosen because many studies and reviews have been conducted to investigate the relationship between PTSD and post-assault SUDs (e.g., Jacobsen et al., 2001; Norman et al., 2012; Ullman, Relyea, Peter-Hagene, & Vasquez, 2013), but only a limited number of studies have focused on the effect of acute substance intoxication and chronic pre-assault problematic substance use on PTSD. Therefore, this needs further exploration and clarification. In addition, in the extant relevant research, the sample population, the type of substances and the type of sexual assaults differ, which in turn may contribute to mixed results. It is thus important to systematically review and integrate data from these studies to determine if any systematic pattern of results emerges.

The current review therefore aims to provide an overview of the role of pre-assault substance consumption, namely acute substance intoxication and chronic pre-assault problematic substance use, in the development of PTSD following sexual assault and

to summarise the existing evidence in order to address two questions:

- 1) What are the effects of acute substance intoxication and chronic pre-assault problematic substance use on the development of PTSD symptoms amongst victims of sexual assault?
- 2) Which mediators have been described in the literature that might modulate the effects of acute substance intoxication and chronic pre-assault problematic substance use on PTSD symptoms amongst victims of sexual assault?

Several past reviews have reported the effect of acute alcohol intoxication and chronic pre-assault problematic alcohol use on PTSD symptoms (e.g., Langdon et al., 2017). However, this current review will be broader and cover various types of substances. Studies that investigate sexual assault that co-occur with physical assault will also be considered. In addition, the current review will include both female and male victims of sexual assault. The majority of past studies and reviews have targeted the population of female victims only (e.g., Campbell et al., 2009; Ullman, 2003; Langdon et al., 2017). However, there is a growing recognition of the effects of sexual assault in males, and it is therefore important to address the above questions with regards to both genders. Acute substance intoxication and chronic pre-assault problematic substance use are limited in victims of childhood sexual assault. Because of this, only sexual assault that occurred in adolescence and adulthood is included here.

## **2. Method**

### *2.1. Search strategy*

A systematic literature search was carried out using three electronic databases (PsycINFO, EMBASE, and MEDLINE). Search terms related to PTSD were combined with terms associated with substance consumption and sexual assault (see Figure 1 for details of search terms). The search terms selected were intentionally inclusive and included multiple synonyms in order to ensure that studies considering a wide range of outcomes would be identified. The databases were searched for articles published on or before 6<sup>th</sup> September 2017.

### *2.2. Inclusion criteria*

Studies meeting the following inclusion criteria were included: a) the effect of substance consumption was being investigated; b) the study reported sexual assault in adolescence and adulthood (i.e., age 14 years or older); c) the study included measures of PTSD symptoms; d) the study assessed acute substance intoxication and chronic problematic substance use prior to and during sexual assault; e) the study was published in a peer-reviewed journal; f) the study was published in English; and g) the study was published after January 2000, as Ullman's (2003) review on the link between substance consumption and adult sexual assault covered most relevant studies prior to this date. Studies meeting these criteria were subjected to formal quality and relevance assessment.

Once duplicates were removed, the database search yielded 2004 unique studies. Titles and abstracts of these studies were retrieved for more detailed evaluation. In the first round of selection, if an abstract appeared to represent a relevant article

considering the relationship between substance consumption and PTSD, the full article was read to determine if the study met the inclusion criteria ( $n = 262$ ). In the second round, 187 of the 262 references were excluded from this review because they did not address the impact of substance consumption on PTSD but instead focused on other aspects of the relationship (e.g., treatment for PTSD and SUDs; the prevalence of co-occurrence). Of the remaining 75 articles, 52 articles were further excluded because they focused on the development of SUDs as a result of childhood sexual abuse. In the last round, 12 articles were excluded for lack of clarity as to whether they considered pre- or post-assault substance consumption. As a result, 11 studies remained. Two additional articles within the date range were identified from Campbell, Dworkin, and Cabral's (2009) review, giving a total of 13 articles meeting the inclusion criteria. Figure 1 illustrates the selection process for the relevant articles.

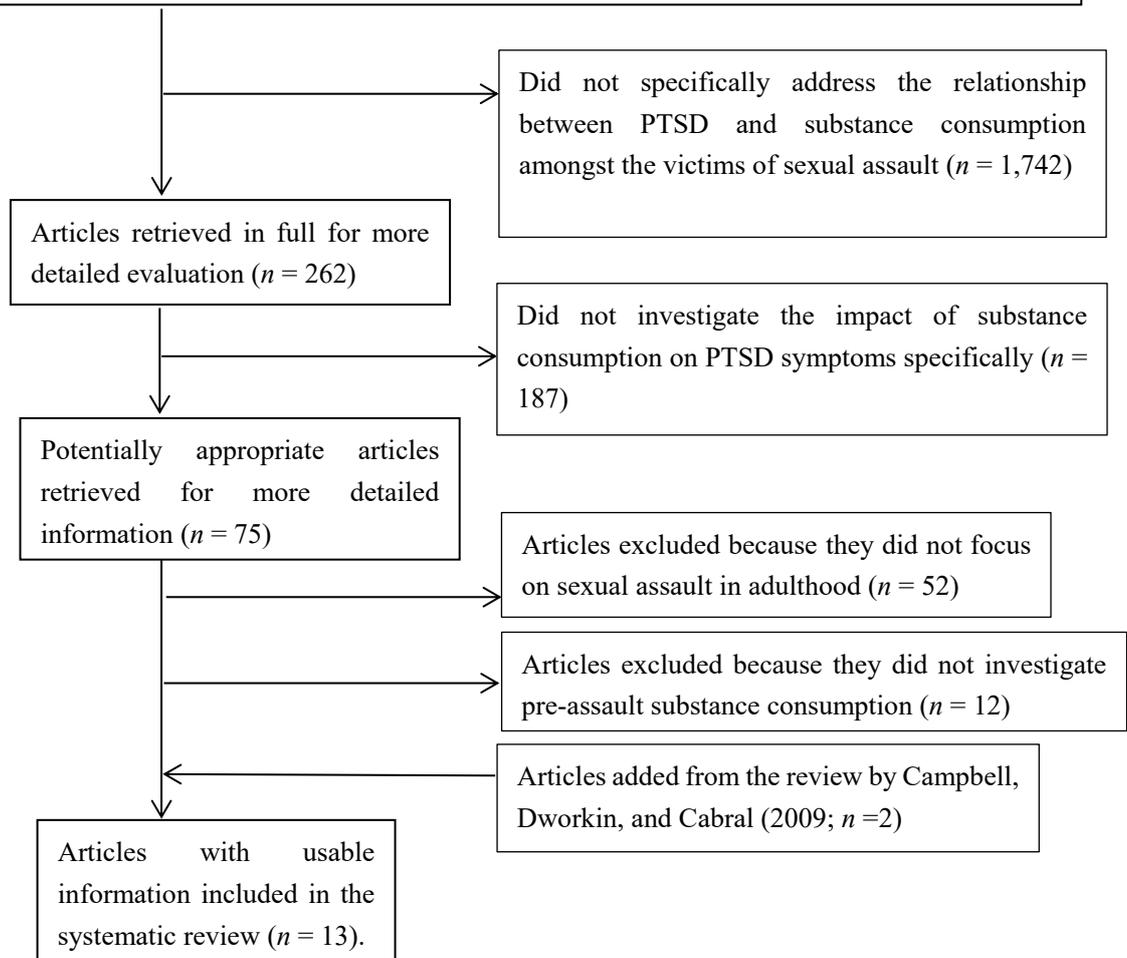
### *2.3. Critical appraisal of articles*

Most researchers agree that systematic reviews should take into account the quality of the included studies. However, methods for critically appraising studies vary according to the nature and methodology of the studies (Pope, Mays, & Popay, 2007). There is a proliferation of checklists and protocols in the literature (Katrak, Bialocerkowski, Massy-Westropp, Kumar, & Grimmer, 2004; Kmet, Lee, & Cook, 2004; Sanderson, Tatt, & Higgins, 2007), meaning that researchers must determine the best procedure for their particular needs.

Many tools are available to assess the quality of intervention studies and studies with randomised designs (e.g., Cahill, Barkham, & Stiles, 2010; Downs & Black,

1998), but fewer options exist for evaluating longitudinal/cohort or cross-sectional studies (studies included in the current review). The Newcastle-Ottawa Scale (NOS; Wells et al., 2011) was developed for assessing quality of non-randomised studies for the purpose of systematic reviews and meta-analyses. Therefore, it was chosen as the most appropriate scale to adapt for this review. The NOS offers a star rating system modified for cohort/longitudinal and cross-sectional studies respectively specific to this review (see Appendix 1). Using the NOS, each study is judged on multiple items, categorised into three groups. Firstly, ‘selection’ items refer to the representativeness and selection of the study groups and the ascertainment of experimental groups. Secondly, ‘comparability’ items examine the comparability of the study groups on the basis of design and/or analysis. Thirdly, ‘outcome’ items assess the determination and quality of outcomes. The overall rating system of quality for the current review was developed based on NOS star ratings. The highest quality studies are awarded up to 10 stars for cohort/longitudinal studies and eight stars for cross-sectional studies. Studies earning seven or more stars were rated as “high” in both relevance and quality, studies scoring five to six were rated as “medium”, and studies scoring less than five were rated as “low”.

<b>Search term</b>	
PTSD: Posttraumatic Stress Disorder or PTSD or Trauma* or Imager* or (Intrus* or emotion*) adj5 (memor* or thought*)	
Substance misuse: Drug or Substance or Alcohol or SUD or AUD or ((drug* or alcohol* or substance*) adj5 (us* or abuse* or misuse* or consum*) adj5 (disorder* addict*))	
SA: rape or (sex*) adj5 (abuse* or offen* or assault* or crime* or victim* or harass* or coercion*) or (interperson*) adj5 (trauma* or violen*)	
<b>Databases</b>	<b>Number of potentially relevant articles identified</b>
PsycINFO	<i>n</i> = 651
MEDLINE	<i>n</i> = 261
EMBASE	<i>n</i> = 1092
<b>Total number of articles (without duplicates)</b>	<b><i>n</i> = 2004</b>



**Figure 1. Flow chart for the selection of relevant articles.**

### 3. Result

#### 3.1. *Relevant articles*

Table 1a and 1b display basic details of the 13 articles retrieved by the search strategy described above. Twelve of these studies included only female victims, while one included both females and males (Blayney et al., 2016). Eleven studies examined sexual assault victims, and two studies investigated victims of both sexual and physical assault (Kaysen et al., 2010, 2011). The samples in these studies were wide ranging in terms of size ( $n = 64$  to 3,001), setting (community, college, criminal justice system, hospital, health and human services, and victims' service agencies), and socio-economic status. All studies were conducted in the United States. Six studies were cross-sectional; seven were longitudinal. These studies utilised (semi-)structured and/or diagnostic interviews, surveys and questionnaires for data collection.

Quality and relevant ratings for the 13 articles included in this review are summarised in Table 2. As can be seen from the table, all studies were judged to be of medium to high quality. In general, the 'comparability' item of the appraisal tool was consistently scored low.

Table 1a

*Details of Longitudinal/Cohort Studies Included in the Current Review*

Study	Year	N	Population	Age (years) mean (range)	Gender	Substance type	Substance consumption	Assault type	PTSD measure	Substance consumption measure	Data analysis method
Blayney et al.	2016	116	College students	23.04 (18-24)	19% M; 81% F	Alcohol	Drinking frequency; HED; alcohol-related negative consequences; alcohol intoxication	SA*‡	PCL-C <sup>c</sup>	R-SES <sup>c</sup> ; DDQ <sup>c</sup> ; YAACQ <sup>c</sup>	SEM
Peter-Hagene & Ullman	2015	877	Community	34.51 (18-69)	F	Alcohol	Alcohol intoxication	SA*	PDS <sup>c</sup>	MSES <sup>c</sup>	Cluster analysis
Kaysen et al.	2010	47	Community, hospitals, health and human services	35.6 (19-53)	F	Alcohol/ drug	Alcohol/drug intoxication; peak alcohol use	SA/PA *	CAPS <sup>a</sup>	STI <sup>a</sup> ; TLFB <sup>b</sup>	HLM
Kaysen et al.	2006	108	Criminal justice system, hospitals, victims' service agencies	31.48 (18-55)	F	Alcohol	Pre-assault AUDs	SA/PA *	CAPS <sup>a</sup>	SCID-NP- III-R-AUD <sup>b</sup>	MANOVA
Kaysen et al.	2011	64	Community, hospitals, victims' service agencies	35.6 (19-53)	F	Alcohol	Pre-assault AUDs; peak alcohol use; alcohol-related negative consequences	SA/PA *	CAPS <sup>a</sup>	TLFB <sup>b</sup> ; SCID-IV- SUD <sup>b</sup> ; DrInC-2R <sup>c</sup>	HLM
Peter-Hagene & Ullman	2016	1013	Community	37.89 (18-71)	F	Alcohol	Alcohol intoxication	SA*	PDS <sup>c</sup>	R-SES <sup>c</sup>	HLM

*Note.* F = female; M = male; SA = sexual assault; PA = physical assault; PTSD = post-traumatic stress disorder; AUD = alcohol use disorders; CAPS = Clinician-Administered PTSD Scale (Blake et al., 1995); PDS = Post-traumatic Stress Diagnostic Scale (Foa, 1995); PCL-C = PTSD Checklist-Civilian Version (Weathers, Litz, Herman, Huska, & Keane, 1993); TLFB = Timeline Follow-Back Interview (Sobell & Sobell, 1992); SCID-IV-SUD = Structured Clinical Interview for DSM-IV, substance use disorder module (First, Spitzer, Gibbon, & Williams, 2001); DrInC-2R = Drinker Inventory of Consequences (Project MATCH Research Group, 1997); SCID-NP-III-R-AUD = Structured Clinical Interview for DSM-III-R Non-Patient Version, alcohol abuse and dependence module (Spitzer, Williams, Gibbon, & First, 1989); R-SES = revised Sexual Experiences Survey (Testa, VanZile-Tamsen, Livingston, & Koss, 2004); HED = Heavy episodic drinking; DDQ = Daily Drinking Questionnaire (Collins, Parks, & Marlatt, 1985); YAACQ = Young Adult Alcohol Consequences Questionnaire (Read, Kahler, Strong, & Colder, 2006); MSES = Modified Sexual Experiences Survey (Messman-Moore, Walsh, & DiLillo, 2010); STI = Standardised Trauma Interview (Resick, Jorden, Girelli, Hutter, & Marhofer-Dvorak, 1988); HLM = hierarchical linear model (Raudenbush & Bryk, 2002); SEM = structural equation modeling (Kline, 1996); MANOVA = multivariate analysis of variance.

<sup>a</sup> Diagnostic interview. <sup>b</sup> (Semi-)structured interview. <sup>c</sup> Surveys/questionnaires

‡ Assault experiences during the college years were assessed. \* Most recent rape experience in adulthood and adolescence was assessed. For individuals with multiple rapes, first incident of rape was assessed. \* The most distressing assault experience in adulthood and adolescence was assessed.

Table 1b

*Details of Cross-sectional Studies Included in the Current Review*

Study	Year	N	Population	Age (years) mean (range)	Gender	Substance type	Substance consumption	Assault type	PTSD measure	Substance consumption measure	Data analysis method
Zinzow et al.	2012	3001	Community	46.58 (18-76)	F	Alcohol/drug	Alcohol/drug intoxication	SA*	NSW- PTSD <sup>b</sup>	REI <sup>b</sup> ; NSW- AA/DA <sup>b</sup>	LRA
Littleton et al.	2009	340	College students	21.6 (18-54)	F	Alcohol/drug	Alcohol/drug intoxication; pre-assault AUDs	SA*	PSS <sup>c</sup>	ACQ <sup>c</sup> ; AUDIT <sup>c</sup>	ANOVA; linear regression
Zinzow, Resnick, McCauley et al.	2010	2000	College students	20.13	F	Alcohol/drug	Alcohol/drug intoxication	SA*	NSW- PTSD <sup>b</sup>	REI <sup>b</sup>	LRA
Zinzow, Resnick, Amstadter et al.	2010	3001	Community	46.58 (18-76)	F	Alcohol/drug	Alcohol/drug intoxication	SA*	NSW- PTSD <sup>b</sup>	REI <sup>b</sup>	LRA
Jaffe et al.	2017	143	Community	22.00 (18-26)	F	Alcohol	Alcohol/drug intoxication; level of intoxication	SA*	PCL-C <sup>c</sup>	MSES <sup>c</sup>	NBHM; multivariate models
Brown et al. (Study 1)	2009	265	College students	19 (18-22)	F	Alcohol/drug	Alcohol/drug intoxication	SA*	PSS <sup>c</sup>	MSES <sup>c</sup>	MANOVA
Brown et al. (Study 2)	2009	244	Community	24 (18-30)	F	Alcohol/drug	Alcohol/drug intoxication	SA*	NSW- PTSD <sup>c</sup>	MSES <sup>c</sup>	MANOVA
Masters et al.	2015	667	Community	24.78 (21-30)	F	Alcohol/drug	Alcohol/drug intoxication; HED	SA†	TSI <sup>c</sup>	R-SES <sup>c</sup> ; HED questionnaire <sup>c</sup>	LCA

*Note.* F = female; SA, sexual assault; PA = physical assault; PTSD = post-traumatic stress disorder; AUD = alcohol use disorders; TSI = Trauma Symptom Inventory (Briere, 1995); NSW-PTSD = National Women's Study PTSD module (Acierno et al., 1999; Ruggiero et al., 2004); PSS = PTSD Symptom Scale (Foa, Riggs, Dancu, & Rothbaum, 1993); NSW-AA/DA = National Women's Study alcohol/drug abuse module (Kilpatrick et al., 2000; Kilpatrick et al., 1997); PCL-C = PTSD Checklist-Civilian Version (Weathers et al., 1993); REI = rape experience interview; TLFB, Timeline Follow-Back Interview (Sobell & Sobell, 1992); R-SES = revised Sexual Experiences Survey (Testa et al., 2004); HED = Heavy episodic drinking; MSES = Modified Sexual Experiences Survey (Messman-Moore et al., 2010); ACQ = Assault Characteristics Questionnaire (Littleton, Axson, Radecki, Breitung, & Berenson, 2006); AUDIT = Alcohol Use Disorder Identification Test (Babor, Higgins-Biddle, Saunders, & Monteiro, 1992; Miles, Winstock, & Strang, 2001); NBHM = negative binomial hurdle model (Hilbe, 2011); LRA = logistic regression analyses; MANOVA, multivariate analysis of variance; ANOVA = univariate analyses of variance; LCA, latent class analyses (Collins & Lanza, 2010)

<sup>a</sup> Diagnostic interview. <sup>b</sup> (Semi-)structured interview. <sup>c</sup> Surveys/questionnaires

\* Most recent rape experience in adulthood and adolescence was assessed. For individuals with multiple rapes, first incident of rape was assessed. \* The most distressing assault experience in adulthood and adolescence was assessed. † Assault experiences in adolescence and adulthood (i.e., at age 14 years or older) were assessed.

Table 2

*Quality and Relevance Ratings*

Study	Year	Selection	Comparability	Outcome	Overall rating
<i>Longitudinal/cohort studies</i>					
Blayney et al.	2016	***	*	**	Medium
Peter-Hagene & Ullman	2015	***	*	**	Medium
Kaysen et al.	2010	****	**	***	High
Kaysen et al.	2006	***	**	*	Medium
Kaysen et al.	2011	***	*	***	High
Peter-Hagene & Ullman	2016	***	*	*	Medium
<i>Cross-sectional studies</i>					
Zinzow et al.	2012	****	**	**	High
Littleton et al.	2009	**	**	**	Medium
Zinzow, Resnick, McCauley et al.	2010	****	*	**	High
Zinzow, Resnick, Amstadter et al.	2010	****	*	**	High
Brown et al. (Study 1)	2009	***	*	*	Medium
Brown et al. (Study 2)	2009	***	*	**	Medium
Masters et al.	2015	****	**	**	High
Jaffe et al.	2017	***	*	**	Medium

### *3.2. Synthesis of articles*

In the literature on pre-assault substance consumption, an important distinction is commonly made between acute substance intoxication and chronic pre-assault problematic substance use. In the current review, the presentation of the studies is therefore structured according to this distinction. Overall, 13 studies reported the effects of pre-assault substance consumption on PTSD symptoms amongst victims of sexual assault. Two studies assessed the effects of chronic pre-assault problematic substance use on PTSD (Kaysen et al., 2006, 2011), while 11 studies investigated the effects of acute substance intoxication on the development of PTSD amongst victims of sexual assault.

Specifically, studies examining the effects of acute substance intoxication varied in their designs: four studies investigated PTSD symptoms in assault victims with and without acute substance intoxication (Kaysen et al., 2010; Peter-Hagene & Ullman, 2016; Blayney et al., 2016; Jaffe et al., 2017); five studies categorised sexual assault experiences into types and compared their unique effects on PTSD symptoms (Brown et al., 2009; Littleton et al., 2009; Zinzow et al., 2012, Zinzow, Resnick, Amstadter et al., 2010; Zinzow, Resnick, McCauley et al., 2010); two studies used a person-centred approach to identify subgroups of victims based on reported sexual assault characteristics and compare these subgroups with one another to investigate effects on PTSD symptoms (Masters et al., 2015; Peter-Hagene & Ullman, 2015). The presentation of these 11 studies is thus structured according to their designs. Due to the advantages of longitudinal over cross-sectional studies in more effectively

examining the effect of pre-assault substance consumption on the development, especially the course, of PTSD symptoms, longitudinal studies are given more weight and hence are presented in advance of cross-sectional studies in the review. More emphasis is placed on studies with higher quality and relevance ratings which are presented in advance of studies with lower ratings.

Of these 13 studies, in addition, three studies investigated factors mediating the effect of acute substance intoxication on PTSD (Blayney et al., 2016; Peter-Hagene & Ullman, 2015, 2016). All three studies are longitudinal, with medium quality and relevance ratings. They examined acute alcohol intoxication and identified two mediators: self-blame and social reactions, which will be subsequently elaborated in this review.

### *3.2.1. The effects of acute substance intoxication on PTSD*

Four studies examined PTSD symptoms in assault victims with and without acute substance intoxication. Kaysen et al. (2010) is a longitudinal study which, out of the 13 studies reviewed, has the highest quality and relevance rating. This study compared PTSD symptoms in victims of sexual or physical assault who were intoxicated as a result of alcohol and/or drug consumption shortly before the assault with victims who were unintoxicated. The PTSD symptoms were assessed at three timepoints: 2-5 weeks post-assault, 3 months post-assault, and 6 months post-assault. After controlling for victims' perceived threat of the assault (i.e., subjective appraisal of risk and certainty of harm) and maximum number of drinks the victim consumed in the month prior to the first assessment, they found that assault victims who were unintoxicated had

significantly more initial intrusive symptoms at 2-5 weeks post-assault than did victims who were intoxicated. Over time, however, the unintoxicated assault victims had a significantly steeper drop-off in intrusive symptoms, suggesting a quicker recovery and shorter course of PTSD symptoms following the assault. There were no significant differences between unintoxicated and intoxicated assault victims in other PTSD symptoms such as avoidance and hyperarousal. This study did not differentiate between victims of physical and sexual assault in their PTSD symptoms.

Similarly, Peter-Hagene and Ullman (2016) examined PTSD symptoms longitudinally in victims of sexual assault who had and had not consumed alcohol shortly before the assault. Participants were assessed annually over the course of three years. Overall, PTSD symptoms declined over time in both groups, indicating recovery from the assault. The intoxicated group had fewer and less intense PTSD symptoms initially, and there was no significant interaction effect between alcohol intoxication and time, suggesting that the differences in PTSD symptoms between intoxicated and unintoxicated victims did not diminish over time. Therefore, the intoxicated group seemed to continue to display fewer PTSD symptoms over time.

Blayney et al. (2016) examined both cumulative and most recent sexual assault experiences during the college years. Cumulative sexual assault refers to the number of times an individual was exposed to sexual assault since starting college. Participants reported their sexual assault experiences, levels of acute alcohol intoxication, baseline PTSD symptoms and baseline drinking behaviours (i.e., drinking frequency, number of binge drinking and alcohol-related negative consequences for the 30 days prior to

the assessment) at the end of their 5th post-matriculation year. After 5 months, at the beginning of the 6th post-matriculation year, they were subsequently assessed on sexual assault revictimisation, PTSD symptoms and drinking behaviours. In examining cumulative experiences of sexual assault, a proportion score (number of assaults during intoxication out of total number of assaults) was calculated to reflect the extent to which alcohol intoxication was potentially implicated in the assault (i.e., the levels of acute alcohol intoxication). In examining the most recent experience of sexual assault, the number of drinks and subjective rating of intoxication at the time of assault were recorded to represent the levels of acute alcohol intoxication. In terms of both cumulative and most recent experiences of sexual assault, the findings suggested that greater levels of acute alcohol intoxication predicted more problematic post-assault drinking behaviours, but not PTSD symptoms. However, after controlling for participants' baseline drinking behaviours and baseline PTSD symptoms, the relationship between acute alcohol intoxication and post-assault drinking behaviours was no longer significant.

Jaffe et al. (2017) assessed the role of acute alcohol intoxication in relation to use and non-use of alcohol shortly before sexual assault, as well as in relation to the level of acute alcohol intoxication at the time of the assault. This cross-sectional study showed that intoxication at the time of the assault was associated with a greater probability of reporting any PTSD symptoms even after controlling for the severity of coercion during the assault. Unlike Blayney et al. (2016), they found a dose-dependent U-shaped effect of acute alcohol intoxication on PTSD symptoms. Specifically,

participants were asked to indicate their level of intoxication at the time of the assault: 0 (*not at all intoxicated*), 1 (*a little*), 2 (*somewhat*), 3 (*quite*), and 4 (*very intoxicated*). Results showed that when controlling for coercion severity, participants who reported an intoxication score of 4 had significantly greater PTSD symptoms than participants who reported a lower score. In addition, there was a trend that predicted PTSD severity was lower at scores of 1, 2 and 3 when compared to score 0, but these differences were not significant. Overall, this study suggested that greater levels of intoxication were associated with more severe PTSD symptoms, whereas low-to-moderate levels of intoxication were associated with less severe PTSD symptoms when compared to no intoxication. This dose-dependent effect of acute alcohol intoxication on PTSD was particularly strong for re-experiencing symptoms.

Five cross-sectional studies categorised sexual assault experiences into types and compared their unique effects on PTSD symptoms. Zinzow et al. (2012) categorised sexual assault experiences into three different types: a) forcible rape in which the perpetrator used force or threat of force; b) drug-or-alcohol-facilitated/incapacitated rape in which victims were intoxicated and incapacitated via voluntary or involuntary consumption of drugs and/or alcohol during an adulthood sexual assault incident; c) ‘combined type’ rape which is defined as sexual assault experiences in which both force and incapacitation were used in the same incident. PTSD outcomes of victims of forcible, drug-or-alcohol-facilitated/incapacitated and ‘combined type’ rape were thus compared with those of nonvictims who had no history of sexual assault. All types of sexual assault experiences were significantly related to the development of PTSD, with

the ‘combined type’ rape exhibiting the highest risk, followed by forcible rape and drug-or-alcohol-facilitated/incapacitated rape. Specifically, victims reporting ‘combined type’ assaults were found to have over four times the likelihood of developing PTSD compared to nonvictims. Victims reporting drug-or-alcohol-facilitated/incapacitated rape or forcible rape were more than two times as likely to develop PTSD as nonvictims.

In the studies by Zinzow, Resnick, Amstadter, et al. (2010) and Zinzow, Resnick, McCauley, et al. (2010), however, sexual assault experiences were categorised differently: a) forcible rape in which the perpetrator used force or threat of force; b) incapacitated rape in which the victim was intoxicated or impaired via *voluntary* intake of drugs or alcohol; and c) drug- or alcohol-facilitated rape if the perpetrator deliberately attempted to produce incapacitation by administering drugs or alcohol to the victim. Both studies showed that forcible rape was associated with the highest risk of PTSD in comparison to incapacitated and drug- or alcohol-facilitated rape. Specifically, in Zinzow, Resnick, Amstadter, et al.’s (2010) study, victims of various types of sexual assault experiences were compared with nonvictims without any history of sexual assault. The findings revealed that women who reported forcible rape were over 3 times as likely as nonvictims to meet lifetime criteria for PTSD, even after controlling for other rape experiences and revictimisation history. Victims who reported drug- or alcohol-facilitated rape were almost twice as likely as nonvictims to meet criteria for PTSD. Victims who reported incapacitated rape, however, did not differ from nonvictims in terms of displaying PTSD symptoms. In addition, a statistical

comparison of odds ratios showed that the risk of PTSD was significantly higher for victims reporting forcible rape in comparison to victims reporting incapacitated rape. The odds ratio for victims reporting drug- or alcohol-facilitated rape did not differ from those reporting forcible or incapacitated rape.

Despite these findings, Zinzow, Resnick, McCauley, et al. (2010) indicated that all three types of sexual assault were positively associated with PTSD. Comparisons were made amongst victims of sexual assault. Specifically, victims reporting a history of forcible rape were 4 times as likely to meet criteria for PTSD as victims without a history of forcible rape. Victims reporting drug- or alcohol-facilitated rape were associated with more than three times the likelihood of meeting PTSD criteria in comparison to victims without such a history. Lastly, victims reporting incapacitated rape were approximately two times as likely to develop PTSD as victims who had not experienced incapacitated rape.

Taking a slightly different approach, Brown et al. (2009) compared forcible rape with incapacitated rape and with verbally coerced sexual assault experiences. Verbal coercion was defined as victims responding to unwanted sexual experiences because they were “overwhelmed by someone’s continual arguments and pressure” or because someone used a position of authority to coerce them. They defined incapacitated rape differently from the studies cited above as victims reporting that they had unwanted sex because they were “incapable of giving consent or resisting due to alcohol or drugs”. Two studies were reported in the Brown et al. (2009) article. Study 1 assessed the most severe unwanted sexual assault experiences in a college sample and found all

three groups differed significantly from one another on PTSD symptom scores. Consistent with the prior studies, forcible rape victims reported the highest number of PTSD symptoms, followed by incapacitated rape and verbal coercion victims, after controlling for the number of unwanted sexual assault experiences. Study 2 investigated the most recent experiences of a more diverse community sample. Victims who reported experiencing multiple methods of coercion were categorised according to the most coercive method (e.g., victims experiencing both verbal coercion and force were classified as forcible rape victims). Findings showed that victims of verbal coercion had significantly fewer PTSD symptoms than did forcible rape victims. Incapacitated rape victims reported an intermediate number of PTSD symptoms that was not significantly different from that of either of the other groups.

Littleton et al. (2009) investigated sexual assault experiences of impaired, incapacitated and nonimpaired victims. To be classified as impaired or incapacitated, victims needed to report impairment due at least in part to substance use. Victims who recounted being unconscious during the assault were classified as incapacitated, while those reporting less severe forms of impairment (e.g., asleep, having trouble walking) were classified as impaired. To be classified as nonimpaired, victims had to have experienced sexual assault that was not preceded by any type of impairment or incapacitation. No significant difference in PTSD symptoms was found amongst these groups. It should be noted that the lack of significant difference in this study may be related to its methodological weaknesses (rated as medium in quality and relevance rating) and relatively smaller sample size than other studies with the similar design.

In addition, two studies used a person-centred approach to identify subgroups of victims based on reported sexual assault characteristics. These subgroups were subsequently compared with one another to investigate effects on PTSD symptoms. Peter-Hagene and Ullman (2015) is a longitudinal study that used cluster analysis to create composite variables that encompassed both alcohol and violence information. They also included assault characteristics identified by previous research to be most relevant to (poor) recovery from PTSD, including victim and perpetrator's use of alcohol, highest levels of violence and severity, victims' perceived life threat and peritraumatic distress, and perpetrator identity. Three significantly different categories of sexual assault emerged from the data: a) alcohol-related assaults (cluster encompassing alcohol-related assault and moderate levels of violence, fear and distress); b) high-violence assaults (cluster with the most violent experiences and severe assaults); and c) moderate sexual-severity assaults (cluster containing the lowest levels of sexual assault severity and physical violence). Peter-Hagene and Ullman (2015) subsequently used these resultant clusters to predict a range of post-assault outcomes, including PTSD symptoms. These outcomes were assessed at a one-year interval, and findings indicated a significant difference amongst three clusters in post-assault PTSD symptoms. Alcohol-related assault victims experienced lower PTSD symptoms than high-violence assault victims but more severe symptoms than moderate-severity assault victims. However, the difference between high-violence and alcohol-related assault victims in PTSD symptoms decreased over time, resulting in no significant difference one year later.

Masters et al. (2015), on the other hand, is a cross-sectional study that used latent class analyses (LCA) to identify subgroups of sexual assault victims based on multiple characteristics of their assault experiences. The subgroup structure was subsequently validated in a second cohort recruited in an identical manner to the first cohort. They identified three substantially different subgroups: a) contact or attempted assault (victims of contact sexual assault or attempted rape, with no act of victimisation by penetration); b) incapacitated assault (victims of rape reporting prior incapacitation by a substance); and c) forceful severe assault (victims of completed rape who were not incapacitated reporting force as the predominant characteristic of the assault). The results indicated that in terms of post-assault psychological distress, women in the forceful severe assault subgroup, compared with the other two subgroups, had significantly higher levels of symptoms of various mental health issues, including PTSD symptoms (e.g., intrusive thoughts and defensive avoidance) over the past six months. Moreover, victims in this group also reported more episodes of binge drinking in the past year than did victims in the incapacitated group.

### *3.2.2. The effects of chronic pre-assault problematic substance use on PTSD*

Kaysen et al. (2011) examined longitudinally the effects of AUDs, self-reported maximum number of drinks and alcohol-related negative consequences for 30 days prior to the assault on different clusters of PTSD symptoms respectively. The victims of sexual or physical assault were assessed within 5 weeks of the assault as well as 3 months and 6 months post-assault. Alcohol-related negative consequences were divided into two variables: a) severity of baseline drinking consequences experienced

during the 30 days prior to the assault; and b) changes in consequences from baseline to 3 months and from baseline to 6 months. Findings suggested that AUDs and alcohol-related negative consequences (e.g., hangover, loss of interest due to drinking) were associated with significantly lower reports of PTSD symptoms immediately post-trauma exposure, even after controlling for demographics, trauma and psychological variables. There was no significant decrease in PTSD symptoms over time amongst victims with AUDs. Likewise, changes in alcohol-related negative consequences over time did not significantly interact with changes in PTSD symptoms. For those reporting high levels of alcohol-related negative consequences during the 30 days pre-assault, their PTSD symptoms did not decrease significantly over time. It was also shown that no individual cluster of PTSD symptoms accounted for this association, and the association of PTSD symptoms with maximum number of drinks was not significant. Similar to the previous study, this study did not differentiate between victims of physical and sexual assault in their PTSD symptoms.

In addition, Kaysen et al. (2006) assessed victims' PTSD symptoms 2-4 weeks and 3 months after the experience of sexual or physical assault longitudinally. They reported that victims with pre-assault AUDs showed significantly worse intrusion and avoidance symptoms of PTSD, but not hyperarousal symptoms, than those without pre-assault AUDs. They also found that victims who had pre-assault AUDs continued to have higher PTSD symptoms over time than victims without such histories, thus experiencing less symptom improvement over time. This interactive effect between pre-assault AUDs and time was only significant for hyperarousal symptoms, not for

avoidance or intrusion symptoms, suggesting that only hyperarousal symptoms improved over time in victims with pre-assault AUDs. This study did not differentiate between victims of physical and sexual assault in their PTSD symptoms.

### *3.2.3. Mediators of the relationship between acute alcohol intoxication and PTSD: Self-blame*

Three longitudinal studies examined the mediating role of post-assault self-blame in the relationship between acute alcohol intoxication and PTSD symptoms. Peter-Hagene and Ullman (2015) measured self-blame using the Self-Blame Attribution Questionnaire (Frazier, 2003), which is composed of two 5-item subscales assessing both characterological and behavioural self-blame. Characterological self-blame attributions are dispositional beliefs about one's own character, reflecting beliefs that the assault was a result of who the victim was as a person or that the assault was deserved. Behavioural self-blame attributions, on the other hand, are situational, specific beliefs about one's actions (e.g., drinking) before the assault. This study showed that although assault characteristics predicted both behavioural and characterological self-blame, high-violence and alcohol-related assault types were related to increased PTSD via characterological self-blame as a mediator. Overall, characterological self-blame was positively related to PTSD, and its indirect effect on the difference in PTSD symptoms between alcohol-related and moderate-severity types was significant.

In a similar vein, Peter-Hagene and Ullman (2016) found that victims who were intoxicated as a result of pre-assault drinking tended to report more behavioural and

characterological self-blame than those who were not. Although the effect of drinking on characterological self-blame was less strong than its effect on behavioural self-blame, it was more consistent over time and was maintained over time. The effect of behavioural self-blame, however, has been demonstrated to diminish over time. Although the total effect of acute alcohol intoxication on PTSD was negative (i.e., acute alcohol intoxication was associated with fewer PTSD symptoms), the overall findings suggested a positive indirect effect of acute alcohol intoxication on PTSD via characterological self-blame, but not behavioural self-blame (i.e., intoxicated victims with characterological self-blame reported increased PTSD symptoms).

In contrast, Blayney et al. (2016) reported inconsistent findings. They examined post-assault cognitions on three scales: a) self; b) world; and c) self-blame. The “self” scale includes cognitions about one’s character, such as “I am inadequate” and “I have permanently changed for the worse”. The “world” scale represents beliefs about the external world, such as “I can’t rely on others” and “I have to be on guard at all times”. The “self-blame” scale includes beliefs that one is responsible for the assault, for example, “the event happened because of the way that I acted”. All three scales were tested as potential mediators for the association between acute alcohol intoxication and PTSD symptoms in relation to both cumulative sexual assault experiences since the start of college and the most recent experience during the college years. Results indicated a lack of significant indirect effect of these cognitions on the relationship between acute alcohol intoxication at the time of the assault and PTSD symptoms.

### 3.2.4. Mediators of the relationship between acute alcohol intoxication and PTSD:

#### *Social reactions*

One longitudinal study examined the mediating role of post-assault social reactions. Peter-Hagene and Ullman (2015) used the Social Reaction Questionnaire (SRQ: Ullman, 2000) to measure how often victims received positive and/or negative social reactions since the assault on a rating scale ranging from 0 (*never*) to 4 (*always*). This questionnaire further separated negative social reactions into acknowledgement-without-support social reactions (i.e., acknowledging the assault happened, but failing to give adequate support; misplaced efforts to control the victim's decisions) and turning-against social reactions (i.e., blaming the victim, not believing her story) based on confirmatory factor analyses (Relyea & Ullman, 2015). The findings indicated that high-violence and alcohol-related assault types were related to increased PTSD via turning-against social reactions specifically. Namely, turning-against social reactions mediated the difference in PTSD symptoms between high-violence and alcohol-related versus moderate-sexual-severity assaults.

## **4. Discussion**

### *4.1. Summary*

The purpose of this review was to provide an overview of the effects of acute substance intoxication and chronic pre-assault problematic substance use on the development of PTSD symptoms in the context of sexual assault. In total, seven studies

showed initial lower levels of PTSD symptoms in intoxicated victims compared to unintoxicated victims (Kaysen et al., 2010; Masters et al., 2015; Peter-Hagene & Ullman, 2015, 2016; Zinzow et al., 2012; Zinzow, Resnick, Amstadter, et al., 2010; Zinzow, Resnick, McCauley, et al., 2010). Two of these studies further showed a more chronic course of PTSD symptoms with less improvement over time in intoxicated victims than unintoxicated ones (Kaysen et al., 2010; Peter-Hagene & Ullman, 2015). One study indicated a dose-dependent effect of acute substance intoxication, showing its positive association with PTSD severity only at high levels of intoxication (Jaffe et al., 2017). All of these studies showed that the effects of acute substance intoxication were particularly strong for re-experiencing PTSD symptoms such as intrusive memories. Three studies found no evidence of effects of acute substance intoxication on PTSD (Blayney et al., 2016; Brown et al., 2016; Littleton et al., 2009).

In addition, two studies showed a more chronic course of PTSD in victims with chronic pre-assault problematic substance use, such as pre-assault AUDs, one of which showed initial lower levels of PTSD symptoms (Kaysen et al., 2016), whereas the other showed initial higher levels (Kaysen et al., 2011). Two studies identified characterological self-blame as a significant mediator of the effect of acute substance intoxication on PTSD (Peter-Hagene & Ullman, 2015, 2016), and one of them also suggested negative post-assault social reactions as a significant mediator (Peter-Hagene & Ullman; 2015). One study, however, failed to find any mediator (Blayney et al., 2016).

#### *4.2. Interpretation of findings*

Based on the results from the current review, it appears that overall acute substance intoxication is associated with initially decreased PTSD symptoms but a more chronic course of residual symptoms. The initial lower level of PTSD symptoms may be because acute substance administration can dampen stress responses and impair acquisition of fear memories (Faingold, N’Gouemo, & Riaz, 1998; Nomura & Matsuki, 2008), which may in turn result in lower perceived severity of the assault and less posttraumatic distress (Abbey, Clinton-Sherrod, McAuslan, Zawacki, & Buck, 2003). However, in more severe sexual assaults, psychoactive drugs are unlikely to have an appreciable stress dampening effect (Brown et al., 2009; Kahn, Jackson, Kully, Badger, & Halvorsen, 2003; Layman, Gidycz, & Lynn, 1996; Peter-Hagene & Ullman, 2015). Therefore, it is unsurprising that higher levels of PTSD symptoms were found in forcible sexual assaults compared to substance-involved sexual assaults.

In addition, the effects on PTSD symptoms may be attributed to the impact of acute substance intoxication on memory and extinction learning. For instance, research suggested that alcohol may elicit retrograde facilitation and anterograde impairment for emotional materials, such that it may facilitate memory for the events occurring prior to but impair memory for the events after its administration, which in this case is the memory for the incident of sexual assault. Therefore, information about sexual assault might not be well-recalled after alcohol consumption, resulting in less psychological distress and an initial decrease in PTSD symptoms (Knowles & Duka, 2004). Furthermore, both human and animal studies showed that extinction learning

under alcohol is slower, weaker and less context-specific, possibly resulting in persistent distress and fear following sexual assault during alcohol intoxication (Bisby et al., 2015; Lattal, 2007; Normura & Matsuki, 2008). Therefore, alcohol may be associated with reduced extinction of the learned associations over time (Stephens et al., 2005), resulting in greater chronicity of PTSD symptoms. However, it should be noted that it is unclear whether effects seen with alcohol can generalise to other drugs, such as cannabis, benzodiazepines or GHB, that have similar amnesic effects (the latter two are commonly used in the case of “date rape”; Elsohly, Lee, Holzhauser, & Salamone, 2001).

However, the particularly strong effect of acute substance intoxication on re-experiencing and intrusive memories, cardinal symptoms of PTSD, may be explained by the dual representation theory (DRT; Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010). According to DRT, memory for an event is supported by contextual and sensation-based memory systems. Contextual memory representations (C-reps) are the basis for narrative memory, can be voluntarily retrieved, and are contextually bound. Sensory memory representations (S-reps) include low-level, sensation-based information pertaining to sensory and affective experiences. Typical memory encoding involves interconnected and equally salient C-reps and S-reps, whereas pathological encoding may occur during traumatic events, resulting in salient and enduring S-reps that are disconnected from corresponding C-reps without contextualising sensory memories (Brewin et al., 2010). As a result, the reactivation of S-reps (e.g., through reminders) can trigger perceptual re-experiencing

of the event without information regarding the encoding context (e.g., intrusive memories and flashbacks). Research has found that substance intoxication, such as in the case of alcohol, may selectively impair contextual memories (Söderlund, Parker, Schwartz, & Tulving, 2005), so that intoxication at the time of sexual assault may intensify re-experiencing and intrusion symptoms by further increasing the disconnection between C-reps and S-reps. In turn, more frequent intrusive memories and re-experiencing symptoms may foster a sense that the world is unsafe, potentially increasing hyperarousal or avoidance symptoms (Jaffe et al., 2017), further hindering recovery (Brewin et al., 2010).

In addition, research evidence suggests that substances, such as alcohol and benzodiazepine (Manconi et al., 2017; Roehrs & Roth, 2001), can lead to disturbances in rapid eye moment (REM) sleep, which, in turn, can suppress memory consolidation via dreaming and result in a long-term impact on PTSD symptoms (Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002). Insufficient memory consolidation may lead the traumatic memory trace to stay primarily located in subcortical and primary perceptual areas (S-reps), leaving it tightly coupled to its autonomic and perceptual markers, without appropriately integrating in autobiographical, cortical memory networks (C-reps). Exposure to a trauma trigger subsequently results in the involuntary retrieval of traumatic memory that is not contextualised and that is fragmented in time (i.e., intrusive memories), consisting of primary sensory information (images, smell, sounds) that is linked to physiological fear symptoms (Brewin, 2011; van Marle, 2015).

The U-shape dose-dependent effect of acute alcohol intoxication shown in Jaffe et al.'s (2017) study might be related to the effect of amnesia resulting from high levels of acute intoxication. A number of research studies show that the consumption of high-level amnesic substances can sometimes result in amnesia for trauma, especially in some cases of involuntary intoxication. Due to the lack of recall of the traumatic experience, victims with amnesia tend to wonder about what has happened and imagine the worst-case scenario, which, in turn, can lead to negative interpretations of the assault and hence various anxiety and PTSD symptoms, including fear, avoidance, nightmares and intrusive thoughts (McNeil, 1996; Mechanic, Resick, & Griffin, 1998). In addition, despite alcohol-related memory impairment at high levels of intoxication, victims are likely to retain memory from before and after the trauma (Ehlers et al., 2002) that also contributed to the development of intrusive memories. However, Jaffe et al.'s findings differs from those of Bisby and his colleagues (2009). They conducted experimental studies examining the effects of acute alcohol intoxication on intrusive memories following trauma video scenarios relating to road traffic accidents rather than interpersonal violence. They found an inverted U-shape effect of alcohol on intrusive memories, with a low dose increasing memory intrusions and a high dose decreasing intrusive symptoms. Differences in study methodology and sample likely contributed to these differing results. For instance, it is likely that the levels of intoxication achieved in the controlled laboratory environment are lower than those that would be experienced personally in a real-world setting.

The reviewed studies assessing mediating factors showed that characterological,

but not behavioural, self-blame, mediated the effects of acute substance intoxication, contributing to the chronic course of PTSD symptoms over time. Previous studies have reported similar findings that characterological self-blame is related to poorer recovery outcomes (Frazier, 2003; Koss, Figueredo, & Prince, 2002; Ullman, Filipas, Townsend, & Starzynski, 2007). Blame that is related to one's behaviour (e.g., drinking or taking drugs) might not have the same degree of detrimental effect on recovery as blame that is generalised to one's character (e.g., "I am a bad person"; "it's my fault"), which is more inherent and less modifiable (Macy, Nurius, & Norris, 2007). Although the use of substances is a specific behaviour, its links to characterological self-blame might be driven by strong societal stereotypes about the use of alcohol and drugs, especially among women who tend to be viewed as more sexual, "loose," or "bad", and deserving punishment (George, Cue, Lopez, Crowe, & Norris, 1995; Norris & Cubbins, 1992). As a result, individuals tend to blame themselves for the assault and identify with these societal stereotypes if they had been drinking or taking drugs, resulting in characterological self-blame, which is more strongly related to PTSD over time.

Post-assault social reactions also play a role in the chronicity of PTSD symptoms. Sexual assault victims with acute substance intoxication tended to experience more blame and disbelief from others and hence receive more negative social support than victims without intoxication (Ullman & Filipas, 2001; Ullman & Najdowski, 2011). There is ample evidence that negative social reactions contribute to PTSD symptoms (Littleton, 2010; Ullman et al., 2007), although positive social support does not appear to protect against PTSD (Elklit & Christiansen, 2013; Littleton, 2010; Peter-Hagene &

Ullman, 2014; Ullman & Peter-Hagene, 2016). In addition, due to the aversive social responses, these victims are less likely to seek help or talk about the assault with others, leading to more maladaptive individual and social coping strategies, such as avoidance, denial and social withdrawal. This, in turn, hinders the recovery of PTSD symptoms (Relyea & Ullman, 2015).

Due to the limited number of studies and inconsistent findings (Kaysen et al., 2016; Kaysen et al., 2011), it is difficult to draw any conclusion regarding the effects of chronic pre-assault problematic substance use on PTSD symptoms. The inconsistent findings may be attributed to the different sample sizes (both relatively small) and the course and onset of pre-assault substance problems. The time for the follow-up PTSD assessments also varies between studies, and PTSD symptoms were examined either in clusters or as a whole, which may lead to differential outcomes. In addition, two studies examining the effects of chronic pre-assault problematic substance use included both physical and sexual assault victims, so the outcomes may not be generalisable to studies with sexual assault victims only. Lastly, these two studies both investigated AUDs, possibly leading to different results from the effects of other drugs.

#### *4.3. Limitations*

The limitations of this review should be kept in mind when considering the findings. Although the review was designed to include both male and female sexual assault victims, there was only one study comprising both genders (with only 19% male college victims in a total sample of 116; Blayney et al., 2016). Previous research suggested gender differences in that women appear more vulnerable to alcohol-related

consequences at lower levels of alcohol exposure than men (Nolen-Hoeksema, 2004). In general, women tend to have more fatty tissue than men as a percentage of their body weight. Fat is inversely related to body water. As alcohol is more soluble in water than in fat, it is distributed throughout a lower water volume, resulting in less alcohol dilution in women. In addition, women usually have lower gastric dehydrogenase activity in the stomach to metabolise alcohol, so that after an equivalent dose of alcohol, women have higher blood ethanol levels than men and hence greater vulnerability to the consequences of drinking alcohol (Jones & Jones, 1976; Lieber, 1997). Therefore, the findings in this current review, which mostly consisted of female victims, may not be generalisable to male victims.

In addition, most reviewed studies reported the impact of pre-assault alcohol consumption, whereas there was little extant information on the impact of other types of substances, limiting the generalisability of these findings. Research also highlighted that the vast majority of victims who use drugs also consume alcohol (Wood & Sher, 2002), so the co-occurrence may bring challenges in separating the outcomes. In addition, the reviewed studies did not report the type of drugs involved in the assault. Research studies show that stimulant drugs (e.g., nicotine, cocaine, methamphetamine) and depressant drugs (e.g., heroin, GHB, benzodiazepine) affect the body and brain functions differently (e.g., Hindmarch, 2004; Meyer & Quenzer, 2013) and may result in different effects on the development of PTSD symptoms.

The inclusion of diverse designs (cross-sectional and longitudinal) might be considered a limitation of the current review. However, this was necessary to obtain a

comprehensive understanding of the impact of pre-assault substance consumption on PTSD. Although the quality of studies was gauged, the author was the sole evaluator, which may have introduced bias.

This review included community and college samples and samples from specific agencies with mostly large samples over multiple time points. Despite this breadth, there remained some variation in methodological strengths across the reviewed studies. Methodologically weaker studies, including those with lower quality and relevance ratings, smaller sample sizes and shorter follow-up periods, should be given less weight in this review.

Similarly, there were variations in the use of different measures for assessing PTSD symptoms and sexual assault experiences, resulting in a lack of consistency in variable definitions. In addition, some studies took baseline measures shortly after the assault, whereas others collected the data long after the assault had occurred. This may lead to problems in comparing results across studies due to potential confounding variables.

As shown in Jaffe et al.'s (2017) study, there may be a dose-dependent effect of acute substance intoxication. The levels of acute substance intoxication were not reported in most of the reviewed studies, and it was possible that they varied across studies, contributing to inconsistent findings that for instance, low levels of substances would impact PTSD symptoms differently from high levels. Furthermore, it is reasonable to hypothesise that the effects of chronic pre-assault problematic substance use may also be dose-dependent, possibly leading to different degrees of PTSD

symptoms depending on the severity of pre-assault substance problems. Therefore, further studies need to be conducted to explore this hypothesis.

#### *4.4. Clinical implications*

The findings reported in this review have a number of clinical implications. They suggest that lower initial PTSD symptoms following trauma exposure amongst substance consumers may not necessarily indicate reduced risk for PTSD over time. Given that early interventions for victims of sexual assault may not be offered to those who initially present with lower PTSD symptoms, it is possible that these particular individuals may be less likely to receive early interventions for PTSD (Roberts, Kitchiner, Kenardy, & Bisson, 2009). Moreover, because of shame, stigma and negative social reactions, including the tendency to “blame the victim”, even victims with severe PTSD symptoms may not receive early help as a result of their failure to seek it. Therefore, the findings from this review suggest a need for routinely assessing both pre-assault and post-assault substance consumption (Resnick, Acierno, Amstadter, Self-Brown, & Kilpatrick, 2007) in order to effectively detect potential victims who might develop chronic PTSD development and provide appropriate early interventions. In addition, previous research supports providing a brief PTSD intervention for trauma-exposed individuals who are also endorsing difficulties with drinking in order to facilitate natural recovery from drinking problems. Conversely, reducing the degree of problems associated with alcohol use could, in turn, encourage PTSD recovery over time (Zatzick et al., 2004). Therefore, interventions addressing one of the problems in an acute trauma-exposed sample could be helpful in alleviating the other.

Furthermore, the findings of the review help identify mediators for PTSD development following sexual assaults, which is key in appropriately targeting the focus of interventions and hence developing effective prevention programmes for the victims (Litz, Gray, Bryant, & Adler, 2002). Specifically, the findings suggested that early interventions should target and focus on areas of self-blame and the development of social support to help victims recover from the trauma effectively.

#### *4.5. Future directions*

This review highlights some gaps in this field of research. Little is known about the impact of substances other than alcohol on PTSD development amongst victims of sexual assault. In addition, very limited research has been conducted with male victims of sexual assault. Therefore, future research should be carried out in these areas. Additionally, since all studies were conducted in the US, this clearly limits generalisability to low- and middle-income countries. Given differences in attitudes towards sexual behaviour and the use of substances between the US and, for example, European countries (Karam, Kypros, & Salamoun, 2007; Kuntsche, Rehm, & Gmel, 2004), the results might not be applicable for other high-income countries.

Longitudinal studies with prolonged follow-up periods would also be helpful in understanding the development of post-assault PTSD symptoms and investigating the outcomes of different levels of acute substance intoxication and chronic pre-assault problematic substance use. More laboratory-based studies were recommended to establish the causal relationship between pre-assault substance consumption and PTSD.

Lastly, as PTSD and SUDs have been shown to be closely associated, it would be invaluable to design and evaluate intervention programmes that address these problems concurrently within the trauma-exposed population.

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## Part 2: Empirical Paper

Intrusive Memories Following a Single Dose of Hydrocortisone: Examining the  
Effect of Hydrocortisone on Intrusive Memories in Healthy Volunteers

## **Abstract**

### **Aim**

Recent studies suggest that pharmacological strategies targeting the human stress system may play a role in modulating intrusive memories, a canonical symptom of post-traumatic stress disorder (PTSD). Hydrocortisone that is administered in the critical memory consolidation period shortly after the traumatic event seems to reduce the risk of PTSD. However, the findings of relevant clinical studies in this area have so far been inconsistent, thus requiring further investigation and clarification. Therefore, the current study aimed to examine the effects of a single dose of hydrocortisone administered shortly post-film on intrusive and declarative memories using the trauma film paradigm.

### **Method**

Healthy female participants were randomly allocated to a hydrocortisone (oral, 30mg) or matched placebo control group. Trait, state and psychophysiological measures (heart rate, blood pressure and salivary cortisol level) were taken before and after a film containing distressing content. Some of these measures were repeated after drug administration. Participants recorded film-related intrusive memories for the next 7 days, before their declarative memory was assessed via free and cued recall tasks.

### **Results**

Compared to the placebo group, the frequency and vividness (but not distress) of intrusive memories were significantly reduced in the hydrocortisone group. In contrast, indices of declarative memory were unaffected by hydrocortisone treatment.

## **Discussion**

The findings provide experimental evidence that hydrocortisone, when administered within a critical window of opportunity post-trauma, can reduce the occurrence of a clinically important memory-related symptom in a model of PTSD. Such findings suggest that a single dose of hydrocortisone can provide protective effects, and this is clinically important for the development of early preventive interventions for PTSD.

## **1. Introduction**

### *1.1. Emotional memories*

Emotional information and events have a privileged status in human cognition. Due to their salience, they enhance new learning and adaptive behaviours. The human brain has evolved to respond effectively to emotional stimuli for survival and reproductive benefits. Extensive research has suggested the significant yet inconsistent effects of emotion on the quality and durability of memory recall (Kensinger, 2009; Schaefer & Philippot, 2005).

Emotional stimuli can have an important adaptive function for memory enhancement, making emotional events easier to recall and hence ensuring that one can identify and strive for rewarding events and avoid threatening events in the future. For instance, emotions can enhance the richness and vividness of subjective details of a memory. Experimental studies have shown that people are more likely to remember emotional than neutral pictures or words (Dewhurst & Parry, 2000; Ochsner, 2000). The emotional intensity of an autobiographical memory has also been shown as a predictor of how well these memories are recalled (Talarico, LaBar, & Rubin, 2004). Similarly, eyewitness research has demonstrated that people who attended to an emotional event report detailed and vivid memories for this event with more clarity than for neutral events (Christianson & Hubinette, 1993).

On the other hand, intensely emotional events or chronic exposure to stressful experiences can result in maladaptive consequences for memory processes (McEwen,

2007; Sheline, 2003), ultimately leading to maladaptive memory, as shown in a wide range of emotional disorders (Williams, 1996; Wilhelm, McNally, Baer, & Florin, 1997). For example, people who witness highly distressing events or have aversive experiences often have poor recall of the details (Christianson & Safer, 1996; Steblay, 1992), with memories that are more general and autobiographical than memories with specific spatio-temporal details.

### *1.2. Intrusive memories in PTSD*

Severe life stressors and emotional experiences can result in post-traumatic stress disorder (PTSD) in vulnerable individuals. Reviews suggest lifetime prevalence rates of PTSD in the population as approximately being between 5% and 12% (Breslau et al., 1998; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; World Health Organisation, 2003). PTSD symptoms include avoidance of reminders of the traumatic event, emotional numbing, high arousal, and the re-experiencing of the traumatic event in the form of intrusive memories, nightmares or repetitive flashbacks (American Psychiatric Association, 2013).

Intrusive memories, one of the cardinal symptoms of PTSD, involve the fragmented involuntary recall of autobiographical information which is distorted in terms of contextual, spatial and temporal details. Therefore, individuals experiencing intrusive memories usually feel as if the traumatic event is happening again at their present time and location (Ehlers, Hackmann, & Michael, 2004; Hackmann, Ehlers, Speckens, & Clark, 2004). These memories can be easily triggered by sensory cues and re-experienced spontaneously without conscious recollections of the traumatic

event (Ehlers & Clark, 2000; Ehlers et al., 2010). Intrusive memories have been the focus for a variety of empirical and theoretical work over the past decades (reviewed in Marks, Franklin, & Zoellner, 2018), as such investigations may provide important insight into the study of emotional memories and the understanding of memory processes in the general population.

### *1.3. Dual Representation Theory (DRT)*

The dual representation theory (DRT) was developed to account for the intrusive memories in PTSD (Brewin, Dalgleish, & Joseph, 1996) and subsequently expanded to describe the occurrence and neural mechanisms of intrusive memories in the general context of healthy episodic memory (Brewin, Gregory, Lipton, & Burgess, 2010). According to the DRT, an event is represented in two parallel systems, namely contextual representations (C-reps) and sensory representations (S-reps). C-reps involve a subset of sensory input that is voluntarily and deliberately retrieved and recorded into an abstract structural description, which is integrated with both contextual and spatial information and personal semantic memory over time. In contrast, S-reps are low-level representations including sensory and perceptual inputs and affective states that are mainly accessed involuntarily.

The DRT also proposes the corresponding neural mechanisms underpinning these representations. Sensory association areas support the allocentric sensory information in C-reps, while the hippocampus and other areas in the medial temporal lobe (MTL) support the allocentric contextual and spatial information in C-reps. The insula supports internal autonomic markers of affective values in S-reps (Craig, 2002;

Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004), which, via the amygdala (LeDoux, 1996), become associated with the low-level sensory characteristics of the event, supported by early sensory cortical and subcortical areas. The required process of egocentric-alloentric translation is supported by the retrosplenial and posterior parietal cortices, with higher-level imagery incorporating S-reps with corresponding C-reps supported in the precuneus (Brewin et al., 2010). Finally, Papez's circuit supports the viewpoint orientation for which the egocentric representation is generated (Bird, Bisby, & Burgess, 2012; Taube, 1998).

In normal memory processing, although S-reps decay quickly and become relatively inaccessible (Brewin et al., 2010), they can be retrieved by their close association with corresponding C-reps via higher-level representations. This association allows the S-rep represented event to be correctly integrated with its semantic and autobiographical context, forming declarative memory and thereby preventing it from being re-experienced in the present. This association also allows for heightened conscious control over retrieval via the connections from prefrontal cortex to the MTL, such as directed attention, the provision of specific retrieval cues, verification of the products of retrieval (Burgess & Shallice, 1996; Fletcher & Henson, 2001), strategies for disambiguating it from events with similar contexts (King et al., 2005), and deliberate suppression of retrieval if required (Anderson et al., 2004).

However, extreme stress, as in the case of traumatic events, can potentiate amygdala functioning while impairing hippocampal functioning, producing stronger S-reps but weaker or impoverished C-reps and poor connections between them

(Elzinga & Bremner, 2002; Metcalfe & Jacobs, 1998; Payne et al., 2006; Vyas, Mitra, Rao, & Chattarji, 2002). The over-encoding of S-reps with insufficient C-reps results in a memory that is not contextualised but instead experienced as happening again in the present, ultimately leading to intrusive memories.

In addition, the extinction process of fear responses learned from a traumatic event occurs via top-down inhibitory control of the prefrontal cortex over the amygdala and the integration of now emotionally neutral contextual information via the hippocampal consolidation. Therefore, fear extinction becomes difficult due to the upregulated amygdala functioning in S-reps and downregulated hippocampal functioning in C-reps.

#### *1.4. The stress response*

Neuroendocrine research has also reported the role of the stress response in emotional memories, and this sheds light on the development of intrusive memories. In particular, exposures to emotionally arousing stimuli or occurrences activate two bodily stress systems releasing different types of adrenal hormones (Roozendaal, McEwen, & Chattarji, 2009). One is the sympathetic nervous system, which is involved in the release of noradrenaline and adrenaline from the adrenal medulla, leading to the rapid behavioural, metabolic and cognitive adaptation known as the fight-or-flight response. The other is the hypothalamic-pituitary-adrenal (HPA) axis, which mediates the release of glucocorticoids from the adrenal cortex, as a slower and longer-lasting process responsible for a return to physiological equilibrium and homeostasis.

These hormones are implicated in the mechanism by which the privileged status

of emotional memories is maintained. They contribute to the stabilisation of memory traces and other memory functions by influencing limbic brain structures (Roosendaal, 2002).

### *1.5. The effect of glucocorticoids*

The current research focuses on the effects of glucocorticoids on various memory processes. Stress leads to enhanced activity of the HPA axis, resulting in an increased release of glucocorticoids from the adrenal cortex (McEwen, 2000). Cortisol (pharmaceutical form: hydrocortisone; rodent form: corticosterone) is the most important endogenous human glucocorticoid, also acting as a biomarker for stress. The effect of glucocorticoids on memory may be memory-phase-dependent, with enhancing effects on memory consolidation and impairing effects on memory retrieval (Dominique, Aerni, Schelling, & Roosendaal, 2009; Roosendaal, 2002; Wolf, 2009).

#### *1.5.1. Memory consolidation*

Following encoding, there is a period of consolidation during which memories are transferred into long-term storage and are subject to emotional effects and neurohormonal modulation (McGaugh, 2000). It has been posited that memory consolidation is reflected at a cellular level by the process of hippocampal long-term potentiation (LTP) as an enduring form of synaptic plasticity (Guzowski et al., 2000; Lynch, 2004). During this period, memories are malleable within a “window of opportunity” lasting up to approximately 6 hours, raising the possibility of various types of manipulation, including pharmacological interference of glucocorticoids (Zohar et al., 2011; Zohar, Sonnino, Juven-Wetzler, & Cohen, 2009). Evidence from

both human and animal studies indicates that glucocorticoids administered shortly post-learning enhances the consolidation of memories, especially emotional in comparison with neutral memories (Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Maheu, Joover, Beaulieu, & Lupien, 2004; Roozendaal, Williams, & McGaugh, 1999; Smeets, Otgaar, Candel, & Wolf, 2008).

Glucocorticoid hormones modulate memory consolidation by entering the brain and binding to two intracellular types of adrenal steroid receptors (de Kloet, 1991; Reul & de Kloet, 1985;). Glucocorticoid receptors (GRs) have low affinity for corticosterone, whereas mineralocorticoid receptors (MRs) have a much higher affinity for glucocorticoids (Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2016). Most of the enhancing effects of glucocorticoid on memory consolidation have been attributed to GR function, but more recent studies have highlighted the importance of MR function (Cornelisse, Joel, & Smeets, 2011; Oitzl & de Kloet, 1992; Otte et al., 2007; Rimmele, Besedovsky, Lange, & Born, 2013; Roozendaal, Portillo-Marquez, & McGaugh, 1996).

The hippocampus has a high density of GRs (Reul & de Kloet, 1985). Post-training infusions of corticosterone or other GR agonists into the hippocampus enhance memory consolidation in animal studies involving various types of tasks and training (Roozendaal & McGaugh, 1997b; Roozendaal, 2002). Glucocorticoids also help activate the amygdala (Roozendaal, 2000) to receive and process affective stimuli,

and elevated cortisol levels in humans are associated with increased amygdala activity in response to emotional stimuli (van Stegeren et al., 2007; van Stegeren, Wolf, Everaerd, & Rombouts, 2007). Infusions of specific GR agonists into the basolateral complex of the amygdala (BLA) in rodents immediately after inhibitory avoidance training seem to enhance memory retention performance (Roozendaal & McGaugh, 1997a). In addition, the BLA activation facilitates consolidation processes in other brain regions, including the hippocampus and medial prefrontal cortex (mPFC; McGaugh, Cahill, & Roozendaal, 1996; McGaugh, Ferry, Vazdarjanova, & Roozendaal, 2000). Researchers have examined these BLA-hippocampus interactions in mediating glucocorticoid effects on memory consolidation (Roozendaal, Okuda, van der Zee, McGaugh, 2006; van Stegeren, Wolf, Everaerd, Scheltens, et al., 2007; van Stegeren, Wolf, Everaerd, & Rombouts, 2007), and the stimulatory influence of mPFC on BLA activity via a loss of inhibitory control (McDonald, 1991; Rosenkranz & Grace, 2002; de Quervain et al., 2009).

The effect of glucocorticoids on memory consolidation follows an inverted U-shape dose-response relationship (de Kloet, Oitzl, & Joëls, 1999; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; Lupien & McEwen, 1997). Excessively high or low levels of glucocorticoids can negatively interfere with memory consolidation, while their optimal level at the peak of the Yerkes-Dodson curve can lead to memory enhancement (Kuhlmann & Wolf, 2006; Patel et al., 2000). For instance, in a study investigating the effect of administering 20mg and 40mg hydrocortisone, memory facilitation for both negative and neutral information was only observed in the 20mg group (Abercrombie,

Kalin, Thurow, Rosenkranz, & Davidson, 2003). Similarly, a 30mg dose of hydrocortisone produced memory enhancement for emotional stimuli (Kuhlmann & Wolf, 2006), whereas a 10 mg dose of hydrocortisone administration impaired recall and recognition for both neutral and pleasant words (Top et al., 2003). In animal studies, moreover, high doses of corticosteroids negatively affect memory consolidation following a stressful event, whereas low doses facilitate memory consolidation (Cohen, Matar, Buskila, Kaplan, & Zohar, 2008).

In addition, glucocorticoid levels can vary with circadian rhythms, along with fluctuations in response to external stressors (Chung, Son, & Kim, 2011). Endogenous cortisol levels peak in the early morning and then fall to their lowest levels approximately 3-5 hours following sleep onset (Kalsbeek et al., 2012; Sahdev & Reznick, 2015). This pattern is in line with findings from a meta-analysis that exogenous hydrocortisone administration in the morning is associated with memory impairment due to excessive levels of circulating glucocorticoid, whereas its administration in the late afternoon is associated with memory enhancement as a result of mildly elevated level of glucocorticoids (Het, Ramlow, & Wolf, 2005).

### *1.5.2. Memory retrieval*

Following successful encoding and consolidation, memories can be later retrieved. Evidence exists from animal and human studies employing traditional declarative and autobiographical memory tasks indicating that stress and stress-induced release of glucocorticoids impair memory retrieval (de Quervain, Roozendaal, & McGaugh, 1998; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Wolf, Schommer,

Hellhammer, McEwen, & Kirschbaum, 2001). The impairing effects of glucocorticoids on memory retrieval are especially pronounced for emotionally arousing materials independent of their valence (i.e., both positive and negative materials), compared to neutral materials (Kuhlmann, Piel, & Wolf, 2005). Patients with rheumatoid arthritis showed impaired memory retrieval after being treated with the synthetic glucocorticoid prednisone one hour before delayed retrieval testing of materials that they had learned one day prior. Impairment was observed although they had also learned the materials under prednisone treatment (Coluccia et al., 2008). In addition, the impairing effect of glucocorticoids has also been observed in studies testing memory recall shortly after learning or training. For example, in a study by Wolf and his colleagues (2001), participants learned a word list before 0.5mg/kg hydrocortisone administration and then were asked to recall this list 2 hours later. Compared to the placebo group, the hydrocortisone group showed poorer word list recall.

Furthermore, studies have also demonstrated that this glucocorticoid-induced memory retrieval impairment depends largely on GR activation in the hippocampus. Infusion of GR agonists administered into the hippocampus of rats 1 hour before retention testing induces similar selective memory retrieval impairment in a water maze task (Roozendaal, Griffith, Buranday, Dominique, & McGaugh, 2003). Glucocorticoids block hippocampal-dependent influence on memory retrieval by reducing the hippocampal firing rate with a delay of approximately 30-60 minutes (Joels, 2001). Further studies in animals have indicated that the BLA interacts with the

hippocampus in mediating glucocorticoid effects on the retrieval of emotionally arousing information. Lesions of the BLA or the infusion of a  $\beta$ -adrenoceptor antagonist into the BLA block the impairing effect of a GR agonist infused into the hippocampus on memory retrieval of spatial information (Roozendaal et al., 2003; Roozendaal, Hahn, Nathan, Dominique, & McGaugh, 2004). In addition, it should be noted that 'stress levels' of glucocorticoids may impair short-term memory retrieval (i.e., working memory) via influences on the prefrontal cortex (Arnsten, 2000; Lupien, Gillin, & Hauger, 1999). A number of fMRI studies observed decreased activation in the prefrontal cortex after cortisol treatment (Oei et al., 2007).

The effects of glucocorticoids on memory retrieval may be time-dependent, as they do not permanently block the memory (Roozendaal, 2002). Retention performance was not impaired when rats were tested either 2 minutes or 4 hours after exposure to stress, whereas stress doses of corticosterone injected 30 minutes before retention testing have been found to impair memory retrieval (Dominique, Roozendaal, & McGaugh, 1998). This time course for retention impairment is correlated with plasma corticosterone levels, which peak 30 minutes after stress exposure and return to baseline within four hours. Therefore, in order to experimentally separate different memory phases, an appropriate retrieval interval is needed so that the experimental manipulations can target a specific memory phase (Wolf, 2009). To observe glucocorticoid effects on memory consolidation, it is important to maintain a long interval (i.e., 24 or 48 hours) between drug treatment and retention testing to allow for memory consolidation and the clearance of glucocorticoids. On the other hand, to test

glucocorticoid effects on memory retrieval, a relatively shorter memory testing interval should be considered (Roozendaal, 2002). However, it should be noted that it is difficult to parse the separate effects of glucocorticoids on memory in relation to retrieval and consolidation. For instance, short-term impairment of retrieval following glucocorticoid administration would tend to reduce rehearsal during the consolidation period, thus indirectly affecting memory consolidation.

### *1.5.3. Intrusive memories*

Fewer studies have focused on the effects of glucocorticoid specifically on intrusive memories. Limited laboratory studies have been conducted to investigate the relationship between glucocorticoid and intrusive memories in non-clinical human populations. Trauma film paradigms, recognised as a valid model (Bisby, King, Brewin, Burgess, & Curran, 2010; Brewin & Saunders, 2001; Holmes & Bourne, 2008; Soni, Curran, & Kamboj, 2013), are often used to examine the formation of intrusive memories by successfully inducing short-lasting intrusions and psychological distress associated with films with traumatic content in non-clinical participants (Holmes & Bourne, 2008; James et al., 2016).

For instance, a study used trauma film paradigm to investigate the relationship between endogenous cortisol level, intrusive memories and sympathetic reactions (Chou, La Marca, Steptoe, & Brewin, 2014). A positive correlation was found between post-film salivary cortisol levels and intrusion frequency in healthy participants with increased saliva alpha-amylase (sAA) activity, an indicator of enhanced noradrenergic activation in the sympathetic nervous system (Sahu, Upadhyay, & Panna, 2014; van

Stegeren et al., 2006). In addition, some experimental studies examined the effects of hydrocortisone on modulating various stages of trauma memory processing by administering it before, during or after viewing the trauma film. Specifically, a recent study examined the influence of pharmacologically increased cortisol levels during encoding and consolidation of a trauma film on the consecutive development of intrusive memories (Rombold et al., 2016). Healthy female participants were administered 20mg hydrocortisone prior to film viewing and subsequently asked to record their intrusive memories in a paper diary for the following 7 days. Results showed a lack of significant effect of hydrocortisone on the number of intrusions, their vividness and the degree of distress evoked by the intrusions. Furthermore, another study examined the influence of repeated cortisol administration during memory retrieval on intrusive memories (Graebener, Michael, Holz, & Lass-Hennemann, 2017). In this study, 20mg hydrocortisone was administered twice a day for 3 days following the presentation of trauma film. Participants were asked to record the number of intrusive memories and rate the distress caused by each intrusive memory over these 3 days. The findings showed that there was no significant effect of hydrocortisone on intrusion frequency or distress.

There were also studies using clinical samples to examine the effect of hydrocortisone on intrusive memories during various memory processes. In a recent meta-analysis, hydrocortisone was the only early pharmacological intervention to have a large effect in reducing the risk of PTSD (Sijbrandij, Kleiboer, Bisson, Barbui, & Cuijpers, 2015). Clinical studies are limited in examining the effect of hydrocortisone

on intrusive memories during memory encoding as it is difficult to administer hydrocortisone prior to the occurrence of a traumatic event. There were, nevertheless, a number of studies examining the effect of hydrocortisone on intrusive memory during memory consolidation. For instance, trauma victims of work or traffic accidents who received 100–140mg hydrocortisone within 6 hours post-trauma showed a decreased risk for subsequent PTSD 3 months post-trauma (Zohar et al., 2011). In addition, compared to placebo, patients who received stress doses of hydrocortisone during various kinds of medical treatments within the period of memory consolidation showed reduced intrusive memories and other PTSD symptoms related to their medical procedures in the long run (Schelling et al., 1999, 2001, 2004, 2006). Similarly, patients who had received a loading dose of hydrocortisone intravenously during cardiac surgery reported fewer intrusive memories and other PTSD symptoms at 6-month post-surgery follow-up assessments (Weis et al, 2006).

With regards to the effect of hydrocortisone on intrusive memories during memory retrieval, Aerni and his colleagues (2004) conducted a study that required trauma victims to take 10mg hydrocortisone orally on a daily basis for 3 months, and to daily report their PTSD symptoms. The findings suggested that hydrocortisone could reduce the frequency and intensity of intrusive memories, effectively inhibiting retrieval of daily-rated traumatic memories. Furthermore, in Delahanty et al.'s (2013) study, patients with physical injuries following a traumatic event received 20mg hydrocortisone within 12 hours post-trauma (outside the critical period of memory consolidation) and every 12 hours for the following 10 days. The results suggested that

patients who had received hydrocortisone treatment reported fewer intrusive memories at 1-month and 3-month follow-ups. These findings suggested that hydrocortisone might lead to retrieval impairment that further impact on memory retention in the long term. In another recent study, nonetheless, PTSD patients were randomly assigned to one of two treatment conditions; they received either 1) 1 week placebo followed by 1-week hydrocortisone (10mg/day), followed by 1-week placebo, followed by 1-week hydrocortisone (30mg/day) or 2) 1-week hydrocortisone (30mg/day), followed by 1-week placebo, followed by 1-week hydrocortisone (10 mg/day), followed by 1-week placebo (Ludäscher et al., 2015). Intrusive memories were assessed three times per day over the course of the treatment. The findings showed that overall, there was no significant difference in the frequency and intensity of intrusive memories between these two conditions.

#### *1.6. The current study*

As noted above, few studies have examined the effect of glucocorticoids specifically on the development of intrusive memories. Additionally, amongst the studies focusing on intrusive memories, there may also be some potential confounds arising from variations in patient and trauma characteristics that weakened the validity of the observational studies conducted with clinical populations. Recently, a number of laboratory studies were carried out in non-clinical human samples, but results were inconsistent.

This current study, therefore, addresses these conceptual and methodological limitations by investigating the effect of a single dose of hydrocortisone following an

'analogue trauma' on Day 1 on intrusive memories in the following week (Day 1-7) and declarative memories (Day 8) in a healthy population using the trauma film paradigm. It focuses on the effect of hydrocortisone administered shortly after the trauma film (within the consolidation window) in the afternoon when there is a relatively lower level of endogenous cortisol. This mimics treatment of real-world PTSD more closely than pre-encoding administration. In addition, there has thus far been a lack of explanation for the distinct mechanisms of action of hydrocortisone on intrusive and declarative memories in terms of well-established theoretical models such as the DRT. This current study aims to fill this gap. Extensive research on the actions of sex hormones on brain structures has shown gender differences in response to acute and chronic stressors (Eiland, Ramroop, Hill, Manley, & McEwen, 2012; McEwen, Nasca, & Gray, 2016; Soni et al., 2013). This current study will therefore focus on the female population taking a hormone-based contraceptive in an effort to minimise confounding effects of gender and ovarian hormone fluctuations on memory processes.

### **Hypotheses**

- 1) Given the enhancing effect of hydrocortisone on memory consolidation via the hippocampus, an important area supporting C-reps, participants who are administered hydrocortisone will perform better on declarative memory tasks than participants who are administered placebo.
- 2) Due to the top-down effects of well-consolidated C-reps, participants who are administered hydrocortisone will experience fewer intrusive memories than

participants who are administered placebo. As such, declarative memory performance will be expected to be negatively correlated with the frequency of intrusive memories.

- 3) Participants will show an increase in subjectively experienced distress and negative states immediately after the presentation of trauma film, indicating a successful induction of traumatic memories.
- 4) Post-film salivary cortisol levels will be positively correlated with the frequency of intrusive memories, if there is an increase in mean heart rate as an indicator of sympathetic activation during film viewing.

## **2. Method**

### *2.1. Design*

This current study was part of a larger project investigating stress-modulating drugs and memories, using three independent groups (hydrocortisone, propranolol and placebo). A randomised, double-blind, placebo-controlled and between-subject design was used to examine the effect of a single dose of hydrocortisone (30mg) and propranolol (80mg), compared to matched placebo, on intrusive and declarative memories following an analogue trauma. This study was carried out jointly with another trainee from University College London (UCL; Sim, 2018), who focused on the effects of propranolol (see appendix 2). In the current study, however, only the results from the placebo and hydrocortisone groups will be reported. All procedures

were approved by the UCL research ethics committee (see appendix 3).

## *2.2. Participants*

A convenience sample was recruited from UCL and the surrounding locale via online research recruitment websites and posters and flyers put up around the campus. In the recruitment advertisement, participants were briefly informed about the process and purpose of the study and also cautioned regarding the intake and side effects of drugs and the graphic nature of the trauma film. Interested participants were provided with the study information sheet and consent form and subsequently underwent a telephone screening (approximately 15 minutes) to assess and confirm their eligibility for the study.

Female participants aged 18-35 years old were recruited. In order to limit the potential effect of variations in circulating ovarian hormone levels at specific menstrual cycle stages on intrusive memories and to reduce the cortisol response to stressors (Roche, King, Cohoon, & Lovallo, 2013), they were required to have been taking an oral hormone-based contraceptive for more than one month (Bryant et al., 2011; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Soni et al., 2013). Other inclusion criteria included fluency in English, normal physical health, normal or corrected-to-normal colour vision, normal blood pressure, body mass index (BMI) between 18.5 and 30 kg/m<sup>2</sup>, weekly alcohol consumption (i.e., ≤ 14 units/112g, the UK standard for women), daily reliable access to Internet to facilitate data collection, and ability and willingness to complete an online memory monitoring diary daily for 7 days.

Exclusion criteria included self-reported historical or current diagnosis of mental health issues requiring treatment, history of significant interpersonal violence or trauma such as being assaulted or witnessing violent assault, injury or death, known memory impairments, asthma, diabetes, chronic obstructive pulmonary disease (COPD), significant sleep problems, cardiac pacemaker implant or other cardiovascular conditions, history of epilepsy or neurosurgery, impaired liver or kidney function, history of severe anaphylactic reaction to a variety of allergens, and history of fainting. Medication-specific exclusion criteria include hypersensitivity to hydrocortisone, intolerance to lactose, inability to swallow capsules, pregnancy or breastfeeding, currently taking cardiovascular or psychiatric medication or beta-blockers, and regular ( $\geq$  twice per month) recreational or medical use of drugs other than alcohol and caffeine.

Power analysis for this current study was informed by previous studies examining pharmacological and behavioural manipulations on intrusive memories (e.g. Holmes, James, Coode-Bate, & Deepro, 2009; Soni et al., 2013; Das et al., 2016). A large effect ( $f = 0.04$ ) was used with  $\alpha = 0.05$ , and power  $1-\beta = 0.8$ . Based on a power calculation performed using G\*Power version 3.1.9.2 (Faul, Erdfelder, Buchner, & Lang, 2009), the total minimum sample size was estimated to be  $n = 66$ .

In total, 186 participants were screened, and 111 met inclusion and exclusion criteria. Of these, 92 participants attended the study on Day 1. Two withdrew on Day 1 due to their initial reactions to the trauma film and two were withdrawn either due to misreporting of oral contraceptive use (only 2-week continuous use rather than  $\geq 1$

month) and one due to undisclosed depressive symptom at screening. Therefore, the final sample constituted 88 participants (hydrocortisone  $n = 29$ ; propranolol  $n = 30$ ; placebo  $n = 29$ ; see Figure 1). All participants provided written informed consent and received £25 remuneration for completing the study.

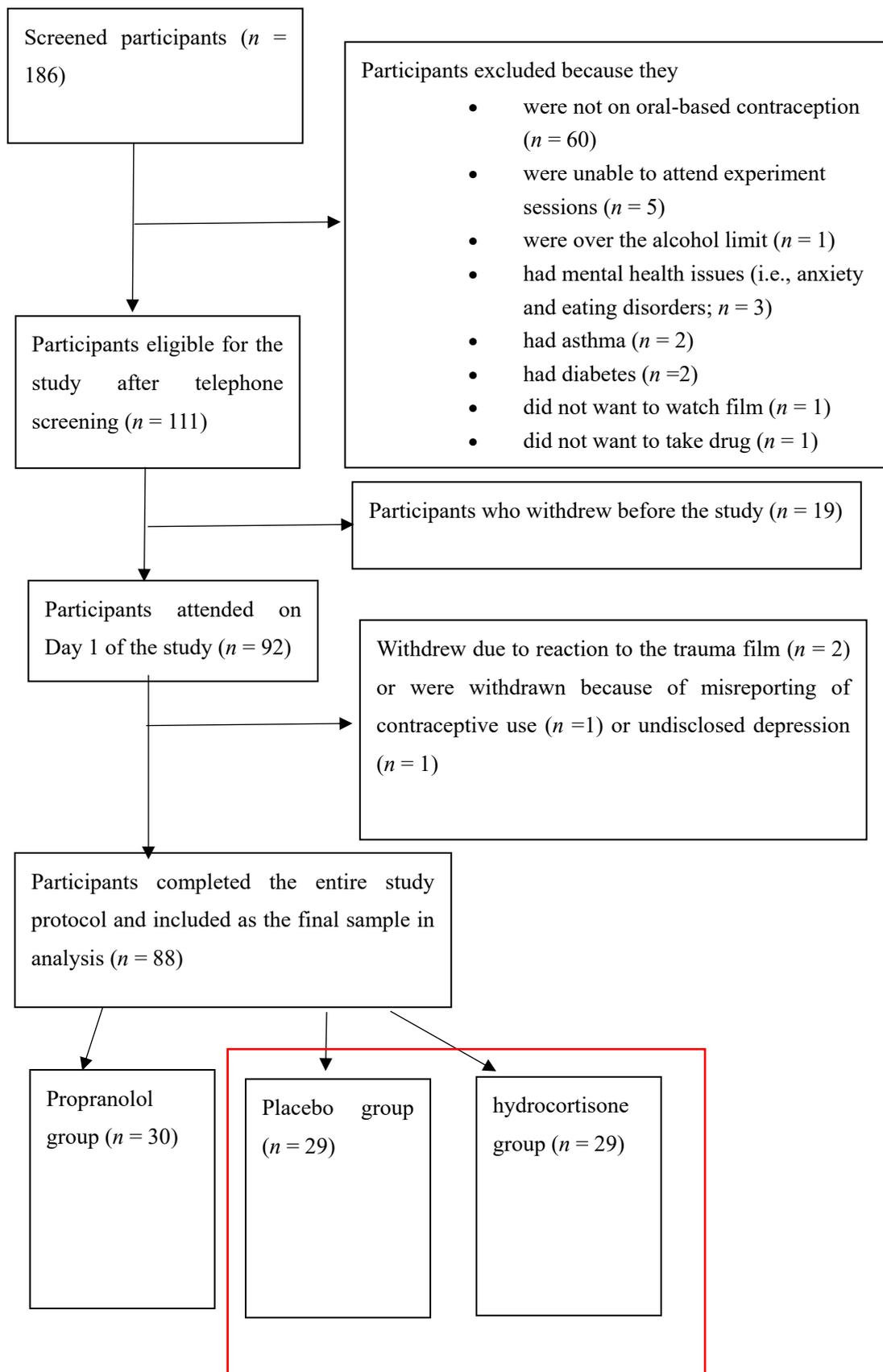


Figure 1. Participant flowchart.

### 2.3. Materials

*Trauma Film.* The emotional video consisted of two video clips taken from the film “*Irreversible*” (Studio Canal, France). The scenes included a violent rape of a female victim by a male perpetrator (scene one, 15 minutes long) and a man being beaten to death in a club (scene two, 4 minutes long). A voiceover preceded each scene to outline the characters and context of the scenes and link the two depicted events, which helped create a single coherent narrative. The use of these clips was based on pilot data showing a greater number of intrusions following these clips than previously used multiple short scenes (Soni et al., 2013). These clips had also been used successfully in previous relevant studies assessing intrusive memories (Das et al., 2016).

All participants were informed of the very graphic nature of the trauma film in the study advert, during the telephone screening and at the start of study on Day 1. They were informed that they could withdraw from the study at any point if they found the scenes too distressing (see appendix 4). Participants watched the film on a 15-inch laptop monitor in a darkened lab. The audio track was played through headphones. A chinrest was used to minimise head movement artefacts during eye movement recordings. An eye-tracker (GP3 eye-tracker, Gazepoint, Vancouver, Canada) was used to continuously monitor participants’ eye movements and measure their level of engagement and attention throughout the film (LaBar & Cadenza, 2006). Gaze duration and number of fixations on pre-defined areas of interest were recorded and analysed offline using Gazepoint software. This was to determine whether the groups

were equivalent at baseline on these attentional parameters.

*Drug administration.* Participants took a single dose of hydrocortisone, propranolol or placebo orally. The 30mg hydrocortisone (1x10mg and 1x20mg; Auden Mckenzie Pharma Division Ltd, Ruislip, UK) tablets were re-formulated in-house. Pairs of tablets (10mg, 20mg) were mechanically crushed and re-encapsulated into two identical opaque gelatin capsules and filled with additional lactose powder. The placebo consisted of two identical capsules containing lactose powder only. One hour after drug administration (before the final physiological and subjective measures), participants and researchers were asked to independently guess which drug participants had received.

## 2.4. Measures

### 2.4.1. Trait measures

*Depression.* Participants' levels of depressed mood were measured using the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Carbin, 1988). This is a psychometrically sound self-report inventory containing 21 multiple-choice questions measuring the severity of depression. It instructed participants to describe the way they have been feeling during the past 2 weeks. A total BDI-II score was calculated for each participant.

*Anxiety.* The State-Trait Anxiety Inventory for adults (STAI; Spielberger, 1983) was used to measure participants' trait levels of anxiety. The inventory includes 20 items, and responses are made using a 4-point Likert scale (*almost never, sometimes, often, almost always*). For each participant, a total STAI score was calculated.

*Dissociation.* The Dissociative Experience Scale-II (DES-II; Carlson & Putnam, 1993) was selected as a measure of participants' naturalistic level of dissociative symptoms. This questionnaire consists of 28 questions about experiences that one may have in daily life. Participants were asked to estimate the percentage of time that they had the described experience. The sub-scores for amnesia, derealisation and absorption were calculated, together with a total DES-II score.

#### 2.4.2. *State measures*

*Acute emotional responses to the film.* This set of six visual analogue scales (VASs; McCormack, David, & Sheather, 1988) was employed to capture participants' levels of disgust, fear, anger, sadness, happiness and distress. They were asked to give their responses according to how they felt "right now". Emotional responses were measured on 10-point numerical rating scales anchored with the descriptors "not at all" and "very". This measure is used extensively in epidemiologic and clinical research to measure the intensity and frequency of various symptoms (Paul-Dauphin, Guillemin, Virion, & Briançon 1999). Responses to the negative items of the VASs (disgust, fear, anger, sadness, and distress) were highly correlated and loaded onto a single factor (average score) along with the positive VAS item (happiness).

*Positive and negative affects.* To assess participants' current positive and negative affective states, the Positive-Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was used. This instrument includes 10 positive and 10 negative items rated on a 5-point Likert scale (*very slightly or not at all, a little, moderately, quite a bit, extremely*). The PANAS negative and positive subscales were calculated.

*Bodily sensations.* The Bodily Symptoms Scales (BSS; Bond & Lader, 1974) were used to gauge a series of bodily sensations, including anxiety, depression, memory impairment, palpitations or increased heart rate, nausea or sickness, emotional numbness, euphoria, drowsiness, muscular tension, headache, loss of concentration, shaking or trembling and confusion. Participants were asked to rate these sensations on a scale from 0-100%.

*Impact of the film.* The revised Impact of Events Scale (IES-R; Weiss & Marmar, 1997) measured the effect, if any, of the trauma film on participants. Participants were provided with a list of difficulties (e.g., poor sleep, emotional numbness, adverse physical reactions) that they might have experienced after watching the film on Day 1. They needed to indicate and rate how much they had been distressed or bothered by each of the listed difficulties for the following 7 days. Sub-scale scores were calculated for intrusion, avoidance and hyperarousal, together with a total IES-R score.

#### 2.4.3. *Physiological measures*

*Heart Rate.* Participants' heart rates were measured to capture the interplay between sympathetic and parasympathetic influences on the heart and the autonomic nervous system's response to threat (Nikolin, Boonstra, Loo, & Martin, 2017; Porges, 1997). Heart rate data were recorded using a BodyGuard 2 ECG device (FirstBeat Technologies, Jyvaskyla, Finland) at a sampling rate of 1000Hz and expressed as the mean heart rate for a targeted event. Ag/AgCl electrodes were attached below the right clavicle and left ribcage. On Day 1, a 5-minute period prior to viewing the trauma film served as pre-film (baseline) indices of autonomic arousal. The period between the

start and end of the film was used to determine heart rate during the film. A final 5-minute period was used to determine heart rate 1-hour post-drug. On Day 8, similarly, the 5-minute period prior to the free recall task served as a baseline. The periods between the start and end of the free recall and of the cued recall tasks were used to determine heart rate during these two tasks.

*Blood Pressure.* A portable blood pressure monitor (BM40 XL; Beurer UK Limited) was used to measure systolic and diastolic blood pressure. A cuff was placed around participants' left wrist and readings taken.

*Saliva samples.* Participants' bodily cortisol levels were collected from their saliva samples. As stated in the *Procedure* section (see below), they were instructed not to consume any food or drinks containing caffeine for the 2 hours prior to the study and required to rinse their mouths with water at the beginning of the study. Passive drool (approximately 500  $\mu$ l) was collected in cryovials via a truncated straw (Shirtcliff, Granger, Schwartz, & Curran, 2001). Saliva samples were frozen immediately and stored at  $-80^{\circ}\text{C}$  until further analysis. The enzyme-linked immunosorbent assay (ELISA) was used to analyse the saliva sample and measure the level of cortisol.

#### 2.4.4. *Memory assessments*

*Intrusive memories.* Each day, participants were asked to record the number of intrusive memories related to the trauma film they had experienced in a diary via an online Qualtrics interface (Qualtrics; Provo, Utah, USA). At the end of the study on Day 1, they were provided with a detailed description of the nature of intrusive memories as follows (refer to Appendix 5.5 and 5.6 for full description):

“By ‘spontaneous’, what we mean is memories of the film that suddenly pop into your mind automatically. We do not mean times when you deliberately think about it or mull it over. The spontaneous memories may pop into your mind when you are doing or thinking about something completely unrelated. Or you may be reminded of the film by things that happen in your environment. The main thing is that you didn’t mean to think about the film, but recall something about it, out of the blue”

Participants were sent email/smartphone prompts at 8pm daily for the 7 days of recording (Day 1 to Day 7) to remind them to record their intrusive memories on the Qualtrics device. The importance of daily completion of memory diary entries was emphasised and mentioned.

Participants needed to report the frequency of intrusive memories each day and briefly describe their contents. They were then asked to classify the type of memory as “verbal” or “sensory” or “both”. In addition, they rated the memory vividness and distress caused by these memories on a 5-point Likert scale (*1 = not at all; 5 = extremely*).

*Declarative memory.* Participants were asked to complete a free recall task on Day 8. They were instructed to write about both scenes of the trauma film “[in as much detail] as possible, including information about where things happen, when they happen, who they happen to, what the people and scenes look like, etc.” Participants typed their responses directly into a text box (see appendix 5.3). Free recall performance was determined by counting the number of recalled idea units (the total

of gist and detail units) as a proportion of all possible accurately recalled units across the entire sample (i.e., maximum possible free recall performance). Participants' written accounts were reviewed by two raters independently blind to drug allocation. Intraclass correlations (ICC) were calculated to evaluate inter-rater reliability ( $ICC_{(\text{scene 1 gist unit})} = 0.945$ ;  $ICC_{(\text{scene 1 detail unit})} = 0.982$ ;  $ICC_{(\text{scene 2 gist unit})} = 0.948$ ;  $ICC_{(\text{scene 2 detail unit})} = 0.971$ ).

Subsequently, a cued recall task was used, involving 19 questions about the events in the trauma film (Das et al., 2016; see appendix 5.4). Participants received a score of 1 for a correct answer, 0.5 for a partially correct answer, and 0 for an incorrect answer to each question, and then a total score was calculated for their recall of the content of the traumatic film after 7 days. Participants' responses were reviewed by two raters independently blind to drug allocation to ensure inter-rater reliability ( $ICC = 0.925$ ).

*Diary compliance.* Participants were asked to self-rate how accurately they completed the online diary for the past 7 days on a scale of 0-10 ( $0 = \text{not at all accurately}$ ,  $10 = \text{extremely accurately}$ ).

#### 2.4.5. Sleep measures

*Sleep habit.* The Adapted Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; see appendix 5.1) was used to measure participants' usual sleep habits. Participants were asked to indicate the most accurate replies for the majority of days and nights in the month prior to Day 1. They needed to report the time that they usually went to bed and got up, average hours of actual sleep at night, and average minutes taken to fall asleep. They were also asked to subjectively

rate their sleep quality on a 4-point Likert scale (*very good, fairly good, fairly bad, very bad*). Sub-scores were calculated for sleep quality, latency, duration and efficiency.

*Sleep survey.* Participants were asked to indicate their sleep quality for the night after Day 1 of the study. Some questions were adapted from the PSQI (see appendix 5.1). Participants also needed to answer questions about their dreams retrospectively, including nightmares, night terrors, affectivity of dreams and dream contents relating to the trauma film. Participants reported this information via the online diary together with their reports on intrusive memories.

## 2.5. Procedure

*Screening.* Participants underwent a telephone screening interview to determine their eligibility for the study after expressing their interest over email (see appendix 4). Eligible participants were briefly informed about the study and reminded of the highly graphic nature of the film clips and involvement of drugs. They were assured that they had the right to withdraw from the study at any stage without needing to give a reason. In addition, prior to Day 1, participants were reminded via email and text message to avoid consuming food or any drinks containing caffeine for 2 hours before the study.

*Day 1.* Following the telephone screening, all eligible participants were asked to attend Day 1 testing, which commenced between 2pm and 5pm. Participants who wished to proceed in the study were given time to read the information sheet and complete the informed consent form. They were then taken to rinse their mouths in preparation for saliva collection. The ECG device was fitted, allowing for a sufficient stabilisation period ( $\geq 10$  minutes before the start of the film). Participants completed

a series of trait questionnaires (in this order: BDI-II, STAI, DES-II, PSQI), followed by pre-film (Time 1) state questionnaires (in this order: VASs, PANAS, BSS). Blood pressure was recorded, and saliva samples were collected immediately pre-film (Time 1). The blood pressure monitor cuff remained on the participant's arm to allow measures to be taken immediately post-film.

Subsequently, participants were asked to rest their chins on a head mount and put on a set of headphones. They were instructed to not move and to try to attend to the film shown on the laptop as much as possible. The lights were turned off. Once the eyetracker was calibrated, participants were shown the trauma film.

Heart rate was assessed continuously, with event markers identifying the 5-minute pre-film period as Time 1 and the period between the start and end of film viewing as Time 2. Blood pressure readings and saliva samples were taken again (Time 2) immediately after viewing the film. Participants were asked to complete post-film (Time 2) state measures (VASs, PANAS, BSS).

According to their allocated group, participants then swallowed the two gelatin capsules with water. After drug administration, they sat quietly and completed 'filler' tasks for one hour. These included a demographic questionnaire (ethnicity, education level, employment status) and a music rating task. They listened to a standard sequence of 25 clips of classical music via headphones and rated their pleasantness after each clip (see appendix 5.2). This task was used to fill the time while the drug was absorbed, so the ratings were not analysed. Participants were asked to report any adverse effects during this hour.

After 1 hour, participants were asked to guess which drug they had received. Researcher also made a guess independently. Post-drug (Time 3) state measures (VASs, PANAS, BSS) were taken, following by blood pressure readings and the collection of saliva samples. Before the ECG device was removed, the end time was marked, identifying the final 5-minute period as Time 3. Lastly, written and verbal instructions on recording intrusive memories in the following week were provided. The time for Day 8 testing was scheduled as close as possible to the start time of Day 1 testing, before each participant left the laboratory.

*Day 1 to Day 7.* Starting on the day of the trauma film (Day 1), participants were required to complete the memory diary on a daily basis from Day 1 to Day 7. The time of diary completion was recorded automatically on Day 1 via Qualtrics, enabling calculation of the potential consolidation or retrieval period (the period between film viewing and intrusive memory recording) on Day 1. Participants followed a link to a Qualtrics webpage to enter relevant information about intrusive memories. On Day 2 only, they were also required to provide information about their sleep during the night after the film viewing.

*Day 8.* One week later, participants returned to the laboratory. Upon arrival, the ECG was fitted, allowing for a stabilisation period of over ten minutes. They completed a series of state measures in the following order: IES-R, VASs, PANAS and BSS. This was followed by a free recall task and subsequently a cued recall task, before asking them to self-evaluate their compliance with completing the diary entries for the past 7 days. Similar to Day 1, heart rate was assessed continuously, with event markers

identifying the 5-minute period pre-free recall task as Time 1, the period between the start and end of the free recall task as Time 2, and the period between the start and end of the cued recall task as Time 3. The ECG device was removed. Upon completion, participants were debriefed and requested to refrain from discussing the study from others. Finally, they were reimbursed for their participation in the study.

## 2.6. Statistical analysis

Statistical analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) version 25. The hydrocortisone ( $n = 29$ ) and placebo ( $n = 29$ ) groups were included in the data analysis. Data were inspected for normality both visually and statistically using the Kolmogorov-Smirnov test. Equality of variance was examined using Levene's test. The majority of data conformed to assumptions of the linear model, except the positively skewed data of cortisol levels, IES measures and the frequency of intrusive memories. Cortisol levels and IES measures were successfully log transformed, while the data of intrusive memories frequency were log+1 transformed.

The state affect and physiological data (cortisol level, heart rate, blood pressure, and state measures) were analysed using repeated measures ANOVA with Time as the within-subject factor and Group as the between-subject data. Similarly, preliminary repeated measures analysis of the data of intrusive memories across seven days (frequency, vividness, and distress) was also conducted using a Repeated ANOVA with Day as the within-subject factor and Group as the between-subjects factor. No *a priori* covariates were specified for any analysis. Since intrusion data consisted of zero-inflated counts, the effect of drug group was re-analysed using Negative Binomial

Regression with estimated values of parameter.

### *2.7. Missing data and outliers*

There were no missing values for the declarative memory and IES measures. The data for frequency, vividness and distress of intrusive memories were virtually complete (0.7% missing; Little's MCAR test:  $\chi^2(76) = 47.95$ ,  $p = 0.995$ ), with complete data on Days 1,4,5, and 6 for frequency and on Days 1,4, 5, 6 and 7 for vividness and distress. Given the declining pattern of frequency, vividness and distress across days, the small number of missing data points were replaced by the next day's values (next observation carried back).

## **3. Results**

### *3.1. Descriptive statistics*

In the final sample ( $n = 58$ ), the mean age was 23.72 years old ( $SD = 3.37$ ; range: 18-32), with mean education of 16.28 years ( $SD = 1.83$ ; range: 13-21). The majority of participants were students ( $n = 44$ , 75.9%) and 24.1% ( $n = 14$ ) were currently employed. In terms of ethnicity, 51.7% ( $n = 30$ ) identified as White, 19.0% ( $n = 11$ ) East Asian, 6.9% ( $n = 4$ ) South Asian, 5.2% ( $n = 3$ ) Black African, 3.4% ( $n = 2$ ) Southeast Asian, 1.7% ( $n = 1$ ) Black Caribbean, 8.6% ( $n = 5$ ) Mixed, and 3.4% ( $n = 2$ ) Other. The mean BMI was 22.41kg/m<sup>2</sup> ( $SD = 2.36$ ; median = 22.35; range: 17.47-27.58). The mean duration on oral contraception was 35.68 months ( $SD = 36.29$ ; range: 1-144). Participant demographics, psychological trait variables, physiological

variables and baseline ratings of sleep quality are given in Table 1. Hydrocortisone and placebo groups did not differ significantly on these variables.

Table 1

*Participant Demographics, Trait Characteristics, Physiological Variables and Baseline Ratings of Sleep Quality by Drug Treatment Group*

Variables	Hydrocortisone ( <i>n</i> = 29) M (SD)	Placebo ( <i>n</i> = 29) M (SD)	Statistics for group difference	<i>p</i> -value	Effect size (Cohen's <i>d</i> )
<b>Demographics</b>					
Age (years)	23.66 (3.12)	23.76 (3.64)	$t(56) = 0.116$	0.908	-0.03
BMI (kg/m <sup>2</sup> )	22.72 (2.09)	22.01 (2.60)	$t(56) = -1.135$	0.261	0.30
Education (years)	16.34 (1.37)	16.24 (2.20)	$t(46.9) = -0.215$	0.83	0.05
Duration of taking contraceptives continuously (months)	31.06 (32.91)	39.90 (38.93)	$t(56) = 0.933$	0.355	0.26
<b>Trait characteristics</b>					
BDI-II	5.10 (4.56)	6.79 (4.09)	$t(56) = 1.485$	0.143	-0.39
STAI	36.34 (9.91)	38.62 (7.82)	$t(56) = 0.971$	0.336	-0.26
<b>DES-II</b>					
Amnesia	1.71 (4.22)	1.72 (2.10)	$t(55) = 0.011$	0.991	<0.01
Derealisation	2.24 (3.97)	1.90 (3.05)	$t(56) = -0.371$	0.712	0.10
Absorption	10.79 (8.86)	10.34 (6.98)	$t(56) = -0.214$	0.831	0.06
Total	9.57 (9.51)	9.37 (6.65)	$t(56) = -0.091$	0.927	0.02
<b>Blood pressure</b>					
Systolic (mmHg)	109.66 (13.58)	110.59 (10.80)	$t(56) = 0.289$	0.774	-0.08
Diastolic (mmHg)	68.45 (8.22)	71.52 (7.93)	$t(56) = 1.447$	0.153	-0.38
<b>Baseline sleep quality</b>					
Sleep quality	0.83 (0.60)	1.07 (0.59)	$\chi^2(2) = 2.360$	0.307	-0.40
Sleep latency	0.86 (0.69)	0.83 (0.76)	$\chi^2(2) = 0.624$	0.732	0.04
Sleep duration	0.55 (0.74)	0.63 (0.68)	$\chi^2(3) = 1.926$	0.588	-0.11
Sleep efficiency	0.31 (0.54)	0.38 (0.68)	$\chi^2(2) = 1.333$	0.513	-0.11

Note. BMI = Body Mass Index; BDI-II = Beck Depression Inventory-II (Beck et al., 1988); STAI = State-Trait Anxiety Inventory (Spielberger, 1983); DES-II = Dissociative Experience Scale-II (Carlson & Putnam, 1993).

### *3.2. Manipulation checks: Response to the film*

The specific effects of the trauma film presented before the drug administration was isolated by examining the changes in participants' subjective state and physiological responses between Time 1 and 2 (see Table 2). A significant increase in VAS-negative scale and decrease in VAS-happiness scale from Time 1 to 2 were observed. Likewise, there was a significant increase in PANAS-negative and decrease in PANAS-positive scales. The majority of BSS scores also significantly differed between Time 1 and 2, apart from the scores for memory impairment, loss of concentration and drowsiness. These consistent data with large effect sizes suggested a significant deterioration in positive mood and elevation in negative mood. In terms of physiological indices, systolic blood pressure showed a significant increase from Time 1 to 2. However, there were small but non-significant increase in cortisol levels and heart rate from Time 1 to 2. It should also be noted that in terms of attentional parameters during film viewing, the hydrocortisone and placebo groups did not differ in dwell time represented by average gaze duration and number of fixation (see Table 4).

Table 2

*Physiological and Subjective State Responses at Time 1 and 2*

Measures	Time 1 ( <i>n</i> = 58) M (SD)	Time 2 ( <i>n</i> = 58) M (SD)	Time effect <i>t</i> (57)	<i>p</i> -value	Effect size (Cohen's <i>d</i> )
VASs					
Negative scale	0.48 (0.73)	5.89 (2.07)	-20.829	<0.001***	-3.49
Happiness	5.29 (2.42)	1.67 (1.68)	12.067	<0.001***	1.74
PANAS					
Positive	27.90 (7.46)	19.45 (5.87)	11.850	<0.001***	1.26
Negative	12.71 (3.35)	25.72 (7.60)	-13.385	<0.001***	-2.22
BSS					
Anxiety	12.33 (14.73)	41.81 (23.71)	-10.056	<0.001***	-1.49
Depression	5.34 (6.94)	18.47 (18.95)	-5.972	<0.001***	-0.92
Memory impairment	3.95 (6.83)	7.31 (15.86)	-1.639	0.107	-0.28
Palpitation	3.41(7.54)	30.47 (25.52)	-8.726	<0.001***	-1.44
Nausea	2.21 (5.79)	20.90 (23.70)	-6.550	<0.001***	-1.08
Emotional numbness	9.62 (19.86)	23.09 (26.67)	-3.740	<0.001***	-0.57
Euphoria	8.57 (17.63)	1.17 (3.44)	3.342	0.001**	0.58
Drowsiness	13.82 (18.77)	10.48 (19.44)	1.095	0.278	0.17
Muscular tension	8.98 (14.24)	25.24 (23.29)	-6.742	<0.001***	-0.84
Headache	2.28 (5.77)	6.72 (11.56)	-3.230	0.002**	-0.49
Loss of concentration	5.88 (9.26)	5.90 (10.66)	-0.012	0.991	<0.01
Shaking	2.00 (7.14)	16.84 (21.34)	-5.436	<0.001***	-0.93
Confusion	1.91 (5.47)	11.07 (19.50)	-3.705	<0.001***	-0.64
Physiological measures					
Systolic BP (mmHg)	110.12 (12.17)	116.12 (16.11)	-3.580	0.001**	-0.42
Diastolic BP (mmHg)	69.98 (8.15)	71.47 (9.30)	-1.838	0.071	-0.17
Cortisol level (µg/dL)	0.14 (1.11)	1.15 (0.08)	-1.051	0.298	-1.28
Mean HR (beats/min)	78.49 (8.92)	90.10 (11.95)	-1.236	0.222	-1.10

Note. VASs = visual analogue scales (McCormack et al., 1988); PANAS = Positive-Negative Affect Schedule (Watson et al., 1988); BSS = Bodily Symptoms Scales (Bond & Lader, 1974); BP = blood pressure; HR = heart rate

\*\*\**p* < 0.001; \*\**p* < 0.01; \**p* < 0.05.

*Correlations.* There was no significant correlation between post-film cortisol level at Time 2 and the total frequency of intrusive memories in the following week ( $r(55) = 0.042, p = 0.760$ ). Blood pressure change between Time 1 and 2 correlated with post-film PANAS-negative ( $r(58) = -0.265, p = 0.045$ ), BSS heartbeat ( $r(58) = -0.349, p = 0.007$ ), BSS tension ( $r(58) = -0.341, p = 0.009$ ), and BSS shaking ( $r(58) = -0.384, p = 0.003$ ), suggesting that the increase in blood pressure at Time 2 was due to the trauma film rather than spontaneous changes.

### 3.3. Response to drug

During the study, no participant reported any adverse effects. The specific effects of drugs administered after film viewing was isolated by examining the changes in participants' physiological responses between Time 2 and 3. The bio-physiological index relevant to the hydrocortisone group indicated a clear increase in salivary cortisol levels (shown in Figure 2). Results from repeated measure ANOVA showed a robust Drug x Time interaction on cortisol level ( $F(1.6, 84.1) = 26.229, p < 0.001, \eta^2 = 0.340$ ), a main effect of Time ( $F(1.6, 84.1) = 48.794, p < 0.001, \eta^2 = 0.489$ ), and a main effect of Drug ( $F(1, 51) = 13.179, p = 0.001, \eta^2 = 0.205$ ). As expected, follow-up repeated measures at each level of the group showed that this effect was mainly driven by changes in the hydrocortisone group ( $F(1.3, 31.7) = 52.952, p < 0.001, \eta^2 = 0.679$ ). In the hydrocortisone group, there was a significant increase in salivary cortisol level between Time 2 and 3 ( $F(1, 25) = 52.078, p < 0.001, \eta^2 = 0.676$ ), not between Time 1 and 2 ( $F(1, 25) = 1.808, p = 0.191, \eta^2 = 0.067$ ). There was a significant moderate change in cortisol level in the placebo group ( $F(1.5, 39.2) = 4.392,$

$p = 0.028$ ,  $\eta p^2 = 0.145$ ). However, repeated contrasts showed that there was no significant change between Time 1 and 2 ( $F(1, 26) = 3.370$ ,  $p = 0.078$ ,  $\eta p^2 = 0.115$ ), or between Time 2 and 3 ( $F(1, 26) = 1.801$ ,  $p = 0.191$ ,  $\eta p^2 = 0.065$ ).

Table 3 outlines the summary statistics for physiological and subjective state measures on Day 1. Overall, no main effect of Drug or interaction effect of Drug and Time was found on other physiological measures and subjective state and bodily measures. The absence of detectable subjective bodily symptoms was in line with participants' guess on the receipt of drug, indicating successful blinding ( $\chi^2(2) = 0.262$ ,  $p = 0.877$ ,  $V = 0.068$ ). Similarly, researchers remained blind ( $\chi^2(2) = 1.309$ ,  $p = 0.520$ ,  $V = 0.149$ ).

Table 3

## Summary Statistics for Physiological and Subjective State Measures on Day 1

Measures	Time effect			Drug effect			Drug x Time interaction			
	Statistics	<i>p</i> -value	$\eta p^2$	Statistics	<i>p</i> -value	$\eta p^2$	Statistics	<i>p</i> -value	$\eta p^2$	
Physiological measures										
Cortisol level (µg/dL)	$F(1.6, 84.1) = 48.794$	<0.001 ***	0.489	$F(1, 51) = 13.179$	0.001 **	0.205	$F(1.6, 84.1) = 26.229$	<0.001 ***	0.340	
Systolic (mmHg)	$F(1.8, 100.7) = 8.655$	0.001 **	0.134	$F(1, 56) = 0.807$	0.373	0.014	$F(1.8, 100.7) = 0.721$	0.475	0.013	
Diastolic (mmHg)	$F(2, 112) = 1.703$	0.187	0.030	$F(1, 56) = 1.141$	0.290	0.020	$F(2, 112) = 0.834$	0.437	0.015	
Mean (beats/min)	$F(1.4, 77.6) = 3.507$	0.033 *	0.061	$F(1, 54) = 0.881$	<0.001 ***	<0.001	$F(1.4, 77.6) = 0.105$	0.835	0.002	
VASs										
Negative scale	$F(1.7, 94.6) = 317.726$	<0.001 ***	0.850	$F(1, 56) = 1.013$	0.379	0.014	$F(1.7, 94.6) = 1.460$	0.238	0.025	
Happiness	$F(2, 112) = 67.813$	<0.001 ***	0.548	$F(1, 56) = 0.001$	0.979	<0.001	$F(2, 112) = 0.745$	0.477	0.013	
PANAS										
Positive	$F(1.8, 100.8) = 61.574$	<0.001 ***	0.524	$F(1, 56) = 0.315$	0.577	0.006	$F(1.8, 100.8) = 0.537$	0.567	0.010	
Negative	$F(1.6, 90.0) = 163.281$	<0.001 ***	0.745	$F(1, 56) = 0.020$	0.888	<0.001	$F(1.6, 90.0) = 1.261$	0.282	0.022	
BSS										
Anxiety	$F(1.7, 94.4) = 90.416$	<0.001 ***	0.618	$F(1, 56) = 0.502$	0.482	0.009	$F(1.7, 94.4) = 0.458$	0.601	0.008	
Depression	$F(2, 112) = 24.625$	<0.001 ***	0.205	$F(1, 56) = 0.178$	0.675	0.003	$F(2, 112) = 0.662$	0.505	0.012	
Memory impairment	$F(1.6, 90.0) = 1.940$	0.158	0.033	$F(1, 56) = 0.014$	0.907	<0.001	$F(1.6, 90.0) = 0.386$	0.635	0.007	
Palpitation	$F(1.3, 70.1) = 73.037$	<0.001 ***	0.566	$F(1, 56) = 0.126$	0.723	0.002	$F(1.3, 70.1) = 0.375$	0.590	0.007	
Nausea	$F(1.1, 61.2) = 40.535$	<0.001 ***	0.420	$F(1, 56) < 0.001$	0.997	<0.001	$F(1.1, 61.2) = 0.063$	0.824	0.001	
Emotional numbness	$F(2, 112) = 8.703$	<0.001 ***	0.135	$F(1, 56) = 0.015$	0.901	<0.001	$F(2, 112) = 0.271$	0.763	0.005	
Euphoria	$F(1.7, 95.8) = 6.037$	0.005 *	0.097	$F(1, 56) = 0.050$	0.924	0.001	$F(1.7, 95.8) = 0.685$	0.485	0.012	
Drowsiness	$F(1.7, 97.4) = 14.8$	0.001 **	0.209	$F(1, 56) = 0.035$	0.825	0.001	$F(1.7, 97.4) = 0.861$	0.425	0.015	
Muscular tension	$F(1.2, 73.8) = 42.722$	<0.001 ***	0.433	$F(1, 56) = 0.777$	0.382	0.014	$F(1.2, 73.8) = 1.118$	0.311	0.020	
Headache	$F(2, 112) = 5.138$	0.007 **	0.084	$F(1, 56) = 0.068$	0.796	0.001	$F(2, 112) = 0.155$	0.857	0.003	
Loss of concentration	$F(1.5, 81.2) = 10.555$	<0.001 ***	0.159	$F(1, 56) = 0.594$	0.444	0.011	$F(1.5, 81.2) = 0.902$	0.381	0.016	
Shaking	$F(1.5, 85.1) = 23.267$	<0.001 ***	0.311	$F(1, 56) = 0.011$	0.915	<0.001	$F(1.5, 85.1) = 0.459$	0.580	0.008	
Confusion	$F(1.5, 81.2) = 10.666$	<0.001 ***	0.160	$F(1, 56) = 0.008$	0.929	<0.001	$F(1.5, 81.2) = 0.375$	0.620	0.007	

Note. BP = blood pressure; HR = heart rate; VASs = visual analogue scales (McCormack et al., 1988); PANAS = Positive-Negative Affect Schedule (Watson et al., 1988); BSS = Bodily Symptoms Scales (Bond & Lader, 1974);  $\eta p^2$  = partial eta squared

\*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$ ; \*  $p < 0.05$ .

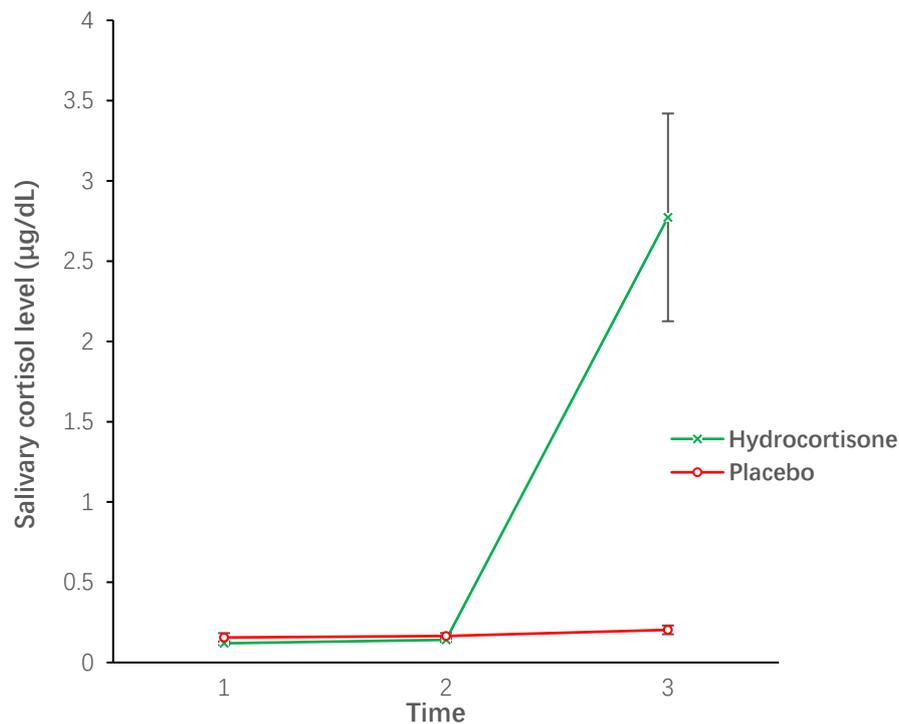


Figure 2. Salivary cortisol level on Day 1. Error bars represent standard errors.

### 3.4. Intrusive memories Day 1

Critically, the number of hours between film viewing and diary completion on Day 1 did not differ significantly between groups (see table 4). Groups also did not differ in their ratings of sleep quality on Day 1. Therefore, any observed group differences on memory-related outcomes were not attributable to difference in these variables.

As the drug group differences were evident on Day 1, the sub-acute effects of hydrocortisone versus placebo on the frequency, vividness and distress of intrusive memories on Day 1 were examined separately. There was a significant difference between drug groups in the frequency of intrusive memories on Day 1 ( $t(56) = 3.264$ ,  $p = 0.002$ ,  $d = -0.94$ ), indicating higher frequency in the placebo than hydrocortisone group. Similarly, there was a significant difference in vividness on Day 1 ( $t(56) = 2.655$ ,

$p = 0.010$ ,  $d = -0.64$ ), suggesting higher level of vividness in the placebo than hydrocortisone group. However, there was no significant difference in distress on Day 1 ( $t(55) = 1.686$ ,  $p = 0.097$ ,  $d = -0.45$ ).

Table 4

*Diary Completion Time, Attentional Parameters, and Ratings of Sleep Quality on Day 1 by Drug Treatment Group*

Variables	Hydrocortisone ( <i>n</i> = 29) M (SD)	Placebo ( <i>n</i> = 29) M (SD)	Statistics for group difference	<i>p</i> -value	Effect size (Cohen's <i>d</i> )
Diary completion time	7.64 (5.47)	7.90 (4.79)	$t(56) = 0.046$	0.963	-0.05
Attentional parameters					
Average gaze duration	2.59 (2.35)	2.54 (1.89)	$t(54) = -0.078$	0.938	0.02
Number of fixation	7.72 (6.33)	8.61 (5.77)	$t(56) = -0.184$	0.855	-0.15
Ratings of sleep quality					
Sleep quality	0.89 (0.69)	1.24 (0.79)	$\chi^2(3) = 3.952$	0.267	-0.47
Sleep latency	0.89 (0.99)	1.17 (1.07)	$\chi^2(3) = 1.477$	0.688	-0.27
Sleep duration	0.82 (0.77)	0.72 (0.70)	$\chi^2(3) = 1.223$	0.747	0.14
Experience of dream	0.32 (0.48)	0.41 (0.50)	$\chi^2(1) = 0.522$	0.470	-0.18
Experience of nightmare	0.18 (0.39)	0.17 (0.38)	$\chi^2(1) = 0.004$	0.951	0.03
Experience of night terror	<0.001*	0.03 (0.19)	$\chi^2(1) = 0.983$	0.322	-0.22

\* Only one participant reported in the hydrocortisone group reported experience of night error on Day 1, resulting in a very small value of mean and standard deviation.

### 3.5. Intrusive memories on Day 1-7

Intrusive memories across Day 1-7 were examined. Figure 3 shows the frequency of intrusive memories across Day 1-7, indicating a steady decline overall. This is consistent with the results of repeated measure ANOVA that there was a significant main effect of Drug on the frequency of intrusive memories ( $F(1, 56) = 8.073, p = 0.006, \eta p^2 = 0.126$ ). There was also a main effect of Time on the frequency of intrusive memories ( $F(5.0, 280.4) = 33.446, p < 0.001, \eta p^2 = 0.374$ ). However, there was a lack of significant interaction effect, showing that the rate of decline did not differ between drug groups ( $F(5.0, 280.4) = 0.825, p = 0.533, \eta p^2 = 0.015$ ).

In addition, Helmert contrasts were used to compare daily intrusive memories with the mean of intrusive memories on the subsequent days. They showed that for the placebo group, intrusive memories on Day 1, Day 2 and Day 3 were more frequent than subsequent days (Day 1:  $F(1, 28) = 52.689, p < 0.001, \eta p^2 = 0.657$ ; Day 2:  $F(1, 28) = 31.632, p < 0.001, \eta p^2 = 0.530$ ; Day 3:  $F(1, 28) = 7.930, p = 0.009, \eta p^2 = 0.221$ ). For the Hydrocortisone group, similarly, intrusive memories on Day 1, Day 2 and Day 3 were more frequent than subsequent days (Day 1:  $F(1, 28) = 34.565, p < 0.001, \eta p^2 = 0.552$ ; Day 2:  $F(1, 28) = 17.273, p < 0.001, \eta p^2 = 0.382$ ; Day 3:  $F(1, 28) = 11.231, p = 0.002, \eta p^2 = 0.286$ ).

Negative binomial regression, furthermore, confirmed the main effect of Drug and showed that across Day 1-7, relative to the hydrocortisone group, the placebo group experienced 2.25 times as many total number of intrusive memories (95% CI: 1.43-3.55;  $p = 0.001$ ). The incident rate ratio (IRR) remained virtually unchanged (Exp(B)

= 2.210; 95% CI: 1.40-3.50;  $p = 0.001$ ) when baseline BDI, STAI and DES total scores were added to the model. The covariates did not significantly improve the model (BDI:  $\text{Exp(B)} = 0.983$ ; 95% CI: 0.91-1.07;  $p = 0.685$ ; STAI:  $\text{Exp(B)} = 1.021$ ; 95% CI: 0.99-1.06;  $p = 0.258$ ; DES:  $\text{Exp(B)} = 0.990$ ; 95% CI: 0.95-1.03;  $p = 0.585$ ).

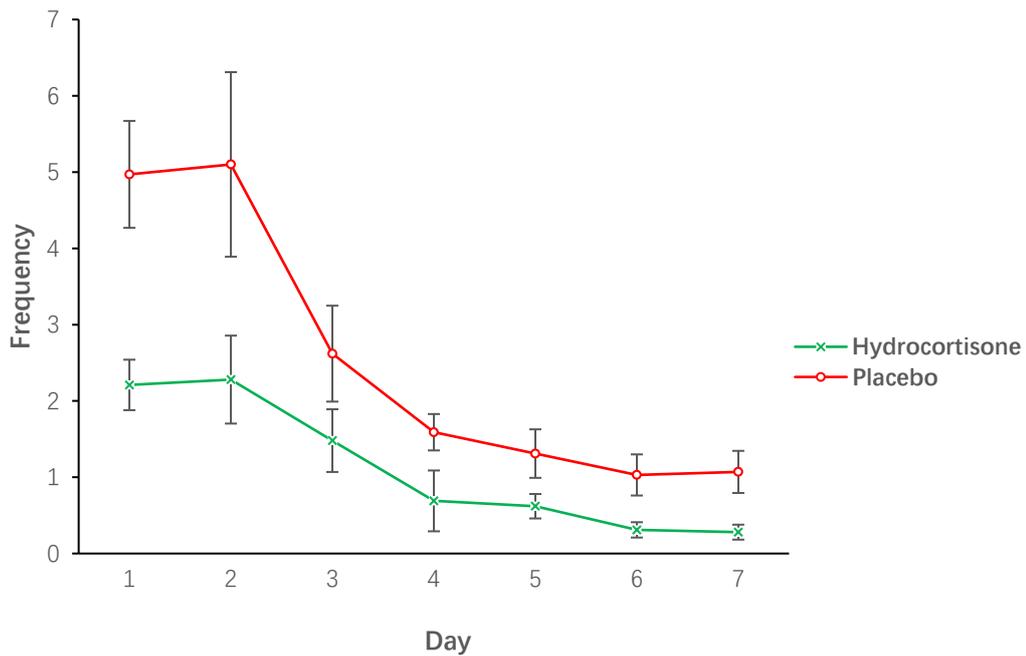


Figure 3. The frequency of intrusive memories across Day 1-7. Error bars represent standard errors.

Figure 4 shows a steady decline in the vividness of intrusive memories across Day 1-7. There was a main effect of Drug ( $F(1, 54) = 5.905, p = 0.018, \eta p^2 = 0.099$ ) and a main effect of Time ( $F(6, 324) = 29.862, p < 0.001, \eta p^2 = 0.356$ ) on the frequency of intrusive memories. However, there was a lack of significant interaction effect, showing that the rate of decline did not differ between drug groups ( $F(6, 324) = 0.653, p = 0.687, \eta p^2 = 0.012$ ).

Helmert contrasts showed that for the placebo group, intrusive memories on each of Day 1, Day 2 and Day 3 were more vivid than subsequent days (Day 1:  $F(1, 28) = 87.730, p < 0.001, \eta p^2 = 0.758$ ; Day 2:  $F(1, 28) = 32.088, p < 0.001, \eta p^2 = 0.534$ ; Day 3:  $F(1, 28) = 11.440, p = 0.002, \eta p^2 = 0.290$ ). For the Hydrocortisone group, intrusive memories on each of Day 1, Day 2 and Day 3 were also more vivid than subsequent days (Day 1:  $F(1, 26) = 26.757, p < 0.001, \eta p^2 = 0.507$ ; Day 2:  $F(1, 26) = 9.577, p = 0.005, \eta p^2 = 0.269$ ; Day 3:  $F(1, 26) = 7.021, p = 0.014, \eta p^2 = 0.213$ ).

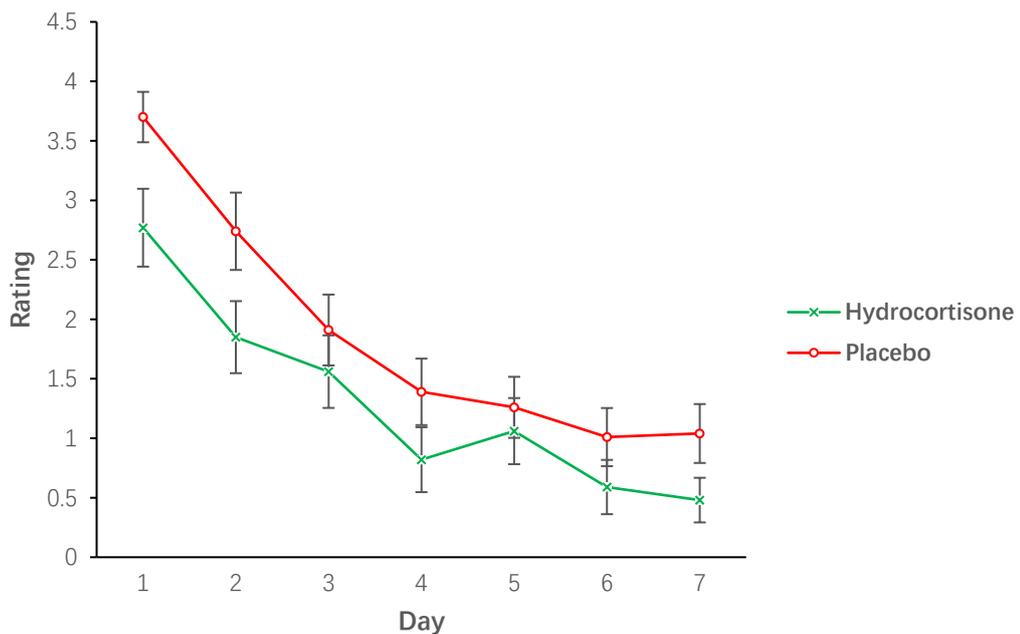


Figure 4. The vividness of intrusive memories across Day 1-7. Error bars represent standard errors.

Figure 5 shows a steady decline in the distress of intrusive memories across Day 1-7. There was a main effect of Time ( $F(6, 324) = 31.294, p < 0.001, \eta p^2 = 0.367$ ) and

no significant main effect of Drug ( $F(1, 54) = 3.613, p = 0.063, \eta p^2 = 0.063$ ) or interaction effect ( $F(6, 324) = 0.578, p = 0.722, \eta p^2 = 0.011$ ) on the distress of intrusive memories. Therefore, the distress of intrusive memories and the rate of decline in distress did not differ between drug groups.

Helmert contrasts showed that for the placebo group, intrusive memories on each of Day 1, Day 2 and Day 3 were more distressing than subsequent days (Day 1:  $F(1, 28) = 65.445, p < 0.001, \eta p^2 = 0.700$ ; Day 2:  $F(1, 28) = 40.488, p < 0.001, \eta p^2 = 0.591$ ; Day 3:  $F(1, 28) = 9.375, p = 0.005, \eta p^2 = 0.251$ ). For the Hydrocortisone group, intrusive memories on each of Day 1, Day 2 and Day 3 were also more distressing than subsequent days (Day 1:  $F(1, 26) = 31.176, p < 0.001, \eta p^2 = 0.545$ ; Day 2:  $F(1, 26) = 13.741, p = 0.001, \eta p^2 = 0.346$ ; Day 3:  $F(1, 26) = 6.608, p = 0.016, \eta p^2 = 0.203$ ).

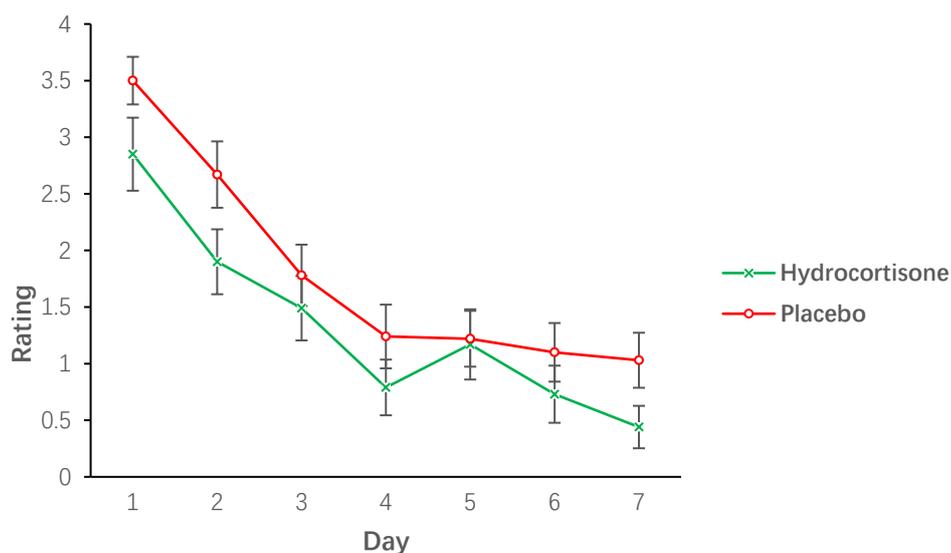


Figure 5. The distress of intrusive memories across Day 1-7. Error bars represent standard errors.

### 3.6. Declarative memory on Day 8

There were no group differences in subjective state measures and IES-R on Day 8 (see Table 5). In addition, there was no group difference in self-reported diary compliance ratings. Participants' performance on free and cued recall tasks on Day 8 is given in Table 6. Overall, there were no drug group differences in any measure of free or cued recall performance. Considering declarative memories for both scenes of the trauma film together, there was no significant difference in free recall (gist:  $t(56) = -0.695$ ,  $p = 0.490$ ,  $d = 0.21$ ); detail:  $t(56) = -0.952$ ,  $p = 0.345$ ,  $d = 0.25$ ; idea information:  $t(56) = -0.891$ ,  $p = 0.377$ ,  $d = 0.22$ ) or cued recall ( $t(56) = -0.172$ ,  $p = 0.864$ ,  $d = 0.04$ ).

*Correlations.* In the placebo group, there was a strong positive correlation between the number of intrusive memories on Day 1 and all measures of free recall (average of both scenes) on Day 8 (gist:  $r = 0.679$ ,  $p < 0.001$ ; detail:  $r = 0.460$ ,  $p = 0.012$ ; total:  $r = 0.534$ ,  $p = 0.003$ ). However, there was no significant correlation between Day 1 frequency and Day 8 cued recall (average of both scenes;  $r = 0.038$ ,  $p = 0.843$ ). Similarly, there was a positive correlation between total number of intrusive memories across 7 days and all measures of free recall (gist:  $r = 0.615$ ,  $p < 0.001$ ; detail:  $r = 0.391$ ,  $p = 0.036$ ; total:  $r = 0.467$ ,  $p = 0.011$ ), but not on cued recall on Day 8 ( $r = -0.038$ ,  $p = 0.845$ ). In the hydrocortisone group, however, there was no significant correlation between the frequency of intrusive memories on Day 1 and cued recall ( $r = 0.168$ ,  $p = 0.384$ ) or all measures of free recall (gist:  $r = 0.196$ ,  $p = 0.307$ ; details:  $r = 0.251$ ,  $p = 0.189$ ; total:  $r = 0.240$ ,  $p = 0.211$ ). In addition, there was no correlation between the

total number of intrusive memories across 7 days and free recall of gist units ( $r = 0.263$ ,  $p = 0.168$ ) or cued recall on Day 8 ( $r = 0.201$ ,  $p = 0.295$ ). Nonetheless, there was a positive correlation between the total number of intrusive memories across 7 days and free recall of detail units ( $r = 0.441$ ,  $p = 0.017$ ) and total units ( $r = 0.395$ ,  $p = 0.034$ ). Therefore, in the placebo group, a higher number of intrusive memories was associated with better declarative memories, suggesting frequent intrusive memories supporting long-term declarative memory. In the hydrocortisone group, nonetheless, the lack of correlations suggested that declarative memory performance was not associated with the frequency of intrusive memories on Day 1 but might be associated with overall frequency of intrusive memories.

In addition, there was a general decrease in mean heart rate from Time 1 ( $M = 83.4$ ,  $SD = 10.8$ ) to Time 2 ( $M = 80.6$ ,  $SD = 10.8$ ) to Time 3 ( $M = 78.0$ ,  $SD = 10.9$ ) on Day 8. There was a main effect of Time on mean heart rate ( $F(1.5, 79.7) = 21.302$ ,  $p < 0.001$ ,  $\eta p^2 = 0.287$ ), but no main effect of Drug ( $F(1, 53) = 1.074$ ,  $p = 0.305$ ,  $\eta p^2 = 0.020$ ), or interaction of Drug and Time ( $F(1.5, 79.7) = 0.499$ ,  $p = 0.556$ ,  $\eta p^2 = 0.009$ ). Therefore, there was no evidence of increased sympathetic arousal during free or cued recall tasks on Day 8.

Table 5

*Diary Compliance Rating, Subjective State Measures and IES-R Scores by Drug Treatment Group*

Measures	Hydrocortisone ( <i>n</i> = 29) M (SD)	Placebo ( <i>n</i> = 29) M (SD)	Statistics	<i>p</i> -value	Effect size (Cohen's <i>d</i> )
Diary compliance rating	8.72 (1.13)	8.48 (1.70)	<i>t</i> (56) = -0.636	0.527	0.17
IES-R					
Intrusion	6.27 (4.62)	8.52 (6.13)	<i>t</i> (56) = 1.573	0.121	-0.41
Avoidance	7.28 (6.16)	8.17(6.30)	<i>t</i> (56) = 0.548	0.586	-0.16
Hyperarousal	1.93 (2.28)	3.10 (3.63)	<i>t</i> (47.2) = 1.473	0.147	-0.39
Total	15.48 (10.93)	19.93 (15.0)	<i>t</i> (56) = 1.292	0.202	-0.34
VASs					
Negative scale	0.48 (0.77)	0.32 (0.42)	<i>t</i> (43.6) = -1.019	0.314	0.26
Happiness	5.21 (1.84)	5.10 (2.43)	<i>t</i> (56) = -0.183	0.855	0.05
PANAS					
Positive	24.59 (6.58)	25.45 (7.50)	<i>t</i> (56) = 0.465	0.644	-0.12
Negative	11.72 (1.75)	12.0 (2.28)	<i>t</i> (56) = -0.453	0.652	-0.14
BSS					
Anxiety	12.52 (14.89)	8.93 (9.42)	<i>t</i> (56) = -1.096	0.278	0.29
Depression	3.86 (6.47)	4.14 (5.44)	<i>t</i> (56) = 0.176	0.861	-0.05
Memory impairment	1.86 (4.18)	4.34 (11.18)	<i>t</i> (56) = 1.120	0.267	-0.29
Palpitation	4.03 (7.45)	3.07 (4.30)	<i>t</i> (44.8) = -0.604	0.549	0.16
Nausea	2.21 (5.58)	5.72 (14.51)	<i>t</i> (36.1) = 1.218	0.231	-0.32
Emotional numbness	5.66 (11.56)	5.48 (9.01)	<i>t</i> (56) = -0.063	0.950	0.02
Euphoria	9.45 (18.43)	11.10 (19.78)	<i>t</i> (56) = 0.330	0.743	-0.09
Drowsiness	11.14 (16.41)	11.9 (14.41)	<i>t</i> (56) = 0.179	0.859	-0.05
Muscular tension	5.10 (11.01)	5.07 (7.27)	<i>t</i> (56) = -0.014	0.989	<0.01
Headache	2.79 (6.73)	5.52 (9.91)	<i>t</i> (56) = 1.225	0.226	-0.32
Loss of concentration	4.55 (9.13)	5.79 (8.63)	<i>t</i> (56) = 0.532	0.597	-0.14
Shaking	2.24 (6.84)	1.41 (3.51)	<i>t</i> (56) = -0.580	0.564	0.15
Confusion	1.38 (4.25)	2.52 (4.15)	<i>t</i> (56) = 1.033	0.306	-0.27

Note. IES-R = The revised impact of Events Scale (Weiss & Marmar, 1997); VASs = visual analogue scales (McCormack et al., 1988); PANAS = Positive-Negative Affect Schedule (Watson et al., 1988); BSS = Bodily Symptoms Scales (Bond & Lader, 1974).

\*\*\* *p* < 0.001; \*\* *p* < 0.01; \* *p* < 0.05.

Table 6

*Free Recall and Cued Recall Scores by Drug Treatment Group*

Memory scores	Hydrocortisone ( <i>n</i> = 29) M (SD)			Placebo ( <i>n</i> = 29) M (SD)		
	Scene 1	Scene 2	Average	Scene 1	Scene 2	Average
FR gist (%)	23.85 (9.17)	28.08 (11.12)	25.96 (8.52)	23.92 (9.89)	24.63 (12.60)	24.28 (9.93)
FR detail (%)	5.78 (2.95)	12.10 (5.22)	8.94 (3.70)	6.45 (3.56)	9.53 (4.70)	7.99 (3.91)
FR total (%)	9.59 (4.16)	13.85 (5.59)	11.72 (4.37)	10.13 (4.72)	11.18 (5.27)	10.66 (4.70)
CR total	4.43 (1.53)	3.43 (1.60)	3.93 (1.30)	4.53 (1.08)	3.22 (1.52)	3.88 (0.95)

Note. FR = free recall; CR = cued recall.

## 4. Discussion

### *4.1. Findings of the current study*

This study examined the effect of administering hydrocortisone shortly after an experimentally induced trauma on subsequent intrusive memories in healthy women using a trauma film paradigm. The findings provided partial support for the proposed hypotheses. Participants showed an increase in subjectively experienced negative states post-film and hydrocortisone and placebo groups differed in their cortisol levels after drug intake, indicating a successful induction of traumatic memories and hydrocortisone administration. Moreover, the frequency and vividness of intrusive memories throughout the course of the week after the trauma film significantly differed between the hydrocortisone and placebo groups. As predicted, the administration of a single dose of hydrocortisone within the memory consolidation window reduced intrusive memories, with a sub-acute effect on the day of film viewing. However, contrary to predictions, after one week, performance on free- and cued-recall tasks related to the trauma film did not differ between these two groups. Furthermore, declarative memory performance was not negatively correlated with the frequency of intrusive memories.

Consistent with the hypothesis, there was a significant reduction in the frequency and vividness of intrusive memories in the hydrocortisone group. One explanation for such a reduction could be the improved consolidation of C-reps via hydrocortisone treatment during the critical period of memory consolidation and hence top-down,

down-regulation of intrusive memories (S-reps) that ultimately led to the overall lower rate of intrusive memories in the hydrocortisone condition. Alternatively, another explanation for the decrease in intrusive memories could be the initially impaired retrieval of trauma memory via hydrocortisone administration that further impeded subsequent memory retention as there was less information to be rehearsed during the consolidation period, resulting in a continuously lower number of intrusive memories for the rest of the week (Day 2-7).

In this study, there was a short time interval between drug administration and memory recording (approximately 8 hours on average). On the one hand, it was possible that hydrocortisone disrupted the formation of intrusive memories by weakening the memory retrieval process while the consolidation process was not yet completed and the cortisol level was still elevated. This explanation could be supported by the finding that there was a sub-acute difference between drug groups on Day 1 that the hydrocortisone group showed significantly lower frequency and vividness of intrusive memories than the placebo group. Past research suggested that PTSD symptoms develop over time after trauma because of positive feedback mechanisms in which the traumatic memories are constantly retrieved and restored (Pitman, Orr, & Shalev, 1993). Hydrocortisone might prevent chronic stress symptoms and incidence of PTSD in patients with traumatic memories through interference with memory retrieval. On the other hand, the effect of hydrocortisone on retrieval impairment is related to plasma corticosterone levels that can return to baseline within a few hours (i.e., fewer than 8 hours) post-administration due to its short duration of action

(Dominique et al., 1998). It was possible that plasma corticosterone levels have returned to the baseline by the time of intrusion recording, limiting its effect on memory retrieval. Therefore, both explanations for the reduction in intrusive memories need to be explored further, given that the timescale of this study did not permit testing the difference between memory consolidation and retrieval.

Contrary to predictions, the findings of the current study only showed a reduction in intrusive memories but not in declarative memories. Although a number of studies showed that stress and stress-induced elevations of cortisol can improve declarative memories, it should be noted that these studies differ from the current one in that they administered mostly psychosocial stressors (Domes, Heinrichs, Reichwald, & Hautzinger, 2002; Smeets et al., 2008) and/or administered exogenous hydrocortisone *prior* to stimulus presentation, usually at the time of encoding (Abercrombie et al., 2003; Buchanan & Lovallo, 2001; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Maheu et al., 2004). Therefore, the findings of the aforementioned studies may have been affected by other factors as a result of differences in design from the current study.

Additionally, in the previous study demonstrating that induced stress and/or hydrocortisone administered shortly after learning negatively affected memory retention, declarative memory was tested within a relatively short period of time (i.e., < 24 hours; Diamont, Fleshner, Ingersoll, & Rose, 1996; Wolf et al., 2001). However, in the current study, declarative memory was tested after one week, so that there was a relatively long interval between learning and recall. During this long interval, a

number of events might have happened to interfere with memory of the trauma film and natural forgetting from Day 1 to Day 8 might have occurred in both groups, which hence contributed to the lack of significant difference between drug groups in declarative memory performance.

Alternatively, the lack of enhancing effect on declarative memory performance might be linked to stress at the time of retrieval on Day 8. Stress might have been created as a result of the demand of the surprise memory tasks, which in turn impaired memory performance (de Quervain et al., 2009). However, there was no indication of increased heart rate as an indicator of sympathetic arousal during memory tasks, making this alternative explanation unlikely.

In addition, inconsistent with the hypothesis that declarative memory performance is negatively correlated with intrusive memories, a significant positive correlation between total frequency of intrusive memories across 7 days and free recall of the trauma film (especially its detail units) was found in the hydrocortisone group. There seemed to be a positive relationship between intrusive and declarative memory, suggesting that a lower number of intrusive memories (possibly as a result of initially impaired retrieval via hydrocortisone administration) might be associated with worse declarative long-term memories.

Despite a reduction in frequency and vividness, there was no significant impact of hydrocortisone on the degree of distress evoked by intrusive memories. In addition, there was a lack of significant differences between the hydrocortisone and placebo groups on IES-R measures, so that, similar to the findings in Rombold et al.'s (2016)

study, post-film hydrocortisone treatment did not seem to influence emotional responses or subjective interpretations of the impact of trauma (Brewin, 2001). The lack of effect on intrusion distress was inconsistent with some of the previous studies suggesting that emotional aspects of PTSD, such as anxiety and depression, could be improved by the administration of hydrocortisone (Delahanty et al., 2013; Zohar et al., 2011). It might have been that the current study was underpowered to detect effects on distress, as the effect sizes for frequency ( $\eta p^2 = 0.126$ ), vividness ( $\eta p^2 = 0.099$ ), and distress ( $\eta p^2 = 0.063$ ) were not too dissimilar and when examining the difference between drug groups in the degree of distress, the calculated  $p$ -value was equal to 0.063.

In this study, the lack of significant change in heart rate during the trauma film seemed to indicate no noradrenergic activation in the sympathetic nervous system amongst participants (Sahu, Upadhyay, & Panna, 2014; van Stegeren et al., 2006). In addition, there was no correlation between total frequency of intrusive memories and participants' post-film salivary cortisol levels. These findings were consistent with the hypothesis that a positive correlation between post-film salivary cortisol level and frequency of intrusive memories only in participants with increased sympathetic activation, which also concurred with Chou et al.'s (2014) research findings. Furthermore, endogenous cortisol level increase and sympathetic activation had previously been considered essential for inducing an emotional effect on intrusive memories (Chou et al., 2014; Keyan & Bryant, 2017; Winter et al., 2007). The lack of change in these physiological reactions suggests that the non-significant reduction in

distress might be related to the absence of sufficient emotional effects on intrusive memories in the first place. Interestingly, the reduction of intrusive memories in the hydrocortisone group was still found in spite of a lack of increase in these physiological reactions, indicating that the effect of hydrocortisone administered shortly after the trauma film might be independent of emotional influences.

#### *4.2. Limitations*

Some limitations of the current study should be recognised. Intrusive memories were examined in healthy participants following a relatively mild stressor, which lacks the intensity of real-life traumatic events that potentially lead to PTSD. Therefore, it is uncertain whether these effects on reducing intrusive memories would be applicable to the intrusive memories in patients with PTSD. In addition, vulnerable populations, such as individuals with previous traumatic experiences, might respond differently to hydrocortisone during consolidation and retrieval of traumatic events (de Quervain et al., 2009; Rombold et al. 2016; Yehuda, 2002).

It has also been suggested in past studies that patients with established PTSD can show low endogenous cortisol levels, depending on trauma type (Meewisse, Reitsma, Vries, Gersons, & Olf, 2007; Pitman & Orr, 1990; Young & Breslau, 2004). Different at-risk groups may have distinctly different physiological reactions to trauma despite being classified under a single diagnosis of PTSD (Aerni et al., 2004). The lack of universal patterns makes the findings less generalisable. Therefore, patients with previous traumatic experiences of various types may have different baseline endogenous cortisol levels and other physiological responses, affecting the formation

of intrusive memories and resulting in responses to hydrocortisone treatment that differ from those in this current study using healthy participants.

In addition, emotional memory consolidation differs between men and women (Felmingham, Tran, Fong, & Bryant, 2012), and female sex hormones have an impact on the formation of intrusive memories (Ferree, Kamat, & Cahill, 2011). For instance, salivary estrogen in women is associated with increased intrusive memories (Cheung, Chervonsky, Felmingham, & Bryant, 2013). As a result, the results from a female sample might not be transferable to men. Emotional memory consolidation also differs between women with a natural cycle and women taking oral contraception (Nielsen, Barber, Chai, Clewett, & Mather, 2015). Research has suggested that changes in sex hormones as a result of taking oral contraception might also affect sleep and hence memory (Baker et al., 2017). In addition, past research has also indicated that hydrocortisone has differential impacts on memory consolidation and retrieval in young and old samples (Wolf et al., 2001). Therefore, this sample, consisting solely of young females taking oral contraceptives, may limit generalisability.

In this study, drug was administered within the window of opportunity for memory consolidation, but the intrusive memories on Day 1 were retrieved within a short post-drug time interval. Orally administered hydrocortisone is highly bioavailable, but it is short-acting in terms of the duration of action and time of maximum concentration. For example, 20mg hydrocortisone has a plasma and biological half-life of approximately 100 minutes and 8-12 hours respectively (Cevc & Blume, 2004; Liapi & Chrousos, 1992; Meikle & Tyler, 1977; Webb & Singer, 2005). Therefore, the

duration of action and the time of administration of hydrocortisone in the current study did not allow for discrimination between the effects on the formation of intrusive memories of hydrocortisone during consolidation and retrieval of the trauma film. This also made it difficult to interpret the findings in terms of the mechanisms by which the drug has an impact. Future studies would benefit from ensuring a long interval (i.e., 24 hours) post-drug before the recording of intrusive memories in order to examine the effect of hydrocortisone on memory consolidation alone.

In addition, the filler task used in this current study consisted of 1-hour classical music clips, which may have had differential effects on individuals depending on their appraisal of the music. Research has supported the association between relaxing music and lower post-stressor cortisol levels, so participants who particularly enjoyed or were aroused by the music may have experienced different changes in their cortisol levels (Khalifa, Bella, Roy, Peretz, & Lupien, 2003). Future studies should include subjective ratings of how relaxing or arousing participants found the music clips in order to control for endogenous cortisol changes.

Lastly, the 1-hour post-oral hydrocortisone assessment of cortisol levels might not have given an accurate indication of peak concentrations as these occur closer to 2 hours post-administration (Jung et al., 2014). However, it might be difficult to have participants remained at the study centre for a longer time period. In addition, although BDI-II was used in this current study to measure participants' trait levels of depressed mood, it may not represent trait depression generally as it only asked participants to report their mood over the past 2 weeks. It might be a good idea to use other trait

measures such as the State-Trait Depression Scales (STDS; Spielberger, 1995; Krohne, Schmukle, Spaderna & Spielberger, 2002), in which some items instruct people to report how they feel generally.

#### *4.3. Clinical implications and future directions*

A strength of this current study lies in the use of the trauma film paradigm that can induce intrusive memories within a randomised controlled design. The study ensured equivalent baseline characteristics, attentional parameters during film viewing, and timestamped recording of intrusive memories across participants to minimise the effect of confounding variables. Even though the induced intrusive memories are discrepant from real-life trauma, the findings of the current study shed an important light on the effect of hydrocortisone administered shortly after trauma on intrusive and declarative memories in a young female sample. This study adds to a wealth of literature that reports the relationship between emotional memories and glucocorticoid. In addition, although floor-level results have often been a concern when investigating subclinical symptoms, the current study found that the use of online diaries is a feasible method of collecting data of intrusive memories in healthy individuals. This was reflected in the 0% drop-out rate and low levels of missing data, showing participants' good compliance with the study.

Furthermore, this study involves the administration of hydrocortisone post-learning within the window of memory consolidation. This is an important step to identifying possible preventative treatment for emotional disorders such as PTSD, as it is very unlikely that the practitioners would have the opportunity to administer

hydrocortisone prior to a traumatic event. Moreover, a pharmacological treatment that can be administered immediately as a single dose rather than repeatedly following a traumatic event (Graebener et al., 2017) may help to impede the formation of intrusive memories in the first place, thus alleviating the potentiated suffering of an individual who not only experienced a traumatic event, but who may also potentially be forced to relive it via intrusions and flashbacks. Future advances in screening methods may also allow practitioners to identify risk factors and ascertain a patient's baseline cortisol response to a traumatic event, then to subsequently make decisions as to whether or not the individual requires further pharmacological interventions.

In terms of future directions, research should focus on the time-dependent effects of hydrocortisone to clarify its effect at each stage of the memory process, namely encoding, consolidation, retrieval and reconsolidation. It may be useful to conduct studies in which hydrocortisone is given after a delay (e.g., 30 minutes - 1 hour) which is more clinically realistic as most people cannot be treated directly after traumatic events. In addition, studies should be carried out to examine both genomic and non-genomic effects of hydrocortisone on the formation of intrusive memories. The endocannabinoid system, along with genetic and epigenetic mechanisms within the HPA axis, have all been suggested to be involved in the formation and development of intrusive memories, hence requiring more explorations and investigations. The interactional influence of the HPA axis and noradrenergic systems should be examined by blocking or activating one system while conversely activating or blocking the other. Lastly, neuroimaging techniques may be helpful in uncovering neural mechanisms of

S-reps and C-reps consolidation with theoretical reference to DRT, as researchers may be able to discover differences in activation of the hippocampus and amygdala in response to emotional stimuli following hydrocortisone administration.

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### Part 3: Critical Appraisal

## **Introduction**

This critical appraisal considers conceptual and practical issues raised during the process of the current research project. Firstly, this appraisal comprises my personal assumptions and how they have been challenged and modified throughout the project. Next, it will reflect on the methodological and analytical choices and the feelings of anxiety and frustration that have raised in me. Lastly, this critical appraisal will set out insights gained from research results and their implications for future work. The strengths, limitations and implications of the current research project that were discussed in the empirical paper in Part 2 will not be repeated in this critical appraisal.

### **1. Personal assumptions**

Researchers usually carry their own assumptions during the process of research that reflect their experiences, values and beliefs, which in turn inevitably influence their research (Willig, 2013). The consideration and presentation of a researcher's influences upon their work, known as the process of reflexivity, generates richer findings that the reader can more easily assess in relation to their own settings (Finlay, 1998; Mantzoukas, 2005; Willig, 2013). It is impossible to exclude bias in research studies (Kaptchuk, 2003; Mantzoukas, 2005; Norris, 1997; Soeken & Sripusanapan, 2003), and bias is not by definition counterproductive for research studies. It has been argued that biased studies do not necessarily constitute invalid research, and acknowledging and reflecting on one's biases and assumptions can improve the

validity of research findings and lead to more objective evaluations of one's research (Endacott, 1994; Mays & Pope, 2000; Moseley & Mead, 2004; Whittemore, Chase, & Mandle, 2001). During the process of this current research, I held several assumptions that might have emerged from my personal as well as professional experiences. These assumptions were challenged and modified as my research progressed.

Firstly, before conducting this research, I believed that stress is disadvantageous and always brings about negative consequences in our daily lives. This assumption emerged from a range of personal experiences; for example, stress can negatively affect my concentration and performance in work and study. However, while reading relevant literature on the relationship between stress hormones and memory, I realised that a number of studies have suggested that either extremely high or low levels of stress can lead to harmful effects on memory, whereas a reasonable level of stress actually has a beneficial effect on memory (Kuhlmann & Wolf, 2006; Patel et al., 2000). In addition, the impact of stress on memory is also dependent on memory phase (Dominique, Aerni, Schelling, & Roozendaal, 2009; Roozendaal, 2002; Wolf, 2009). The supporting evidence from this current research also consolidated these findings. I then reflected on this information in relation to my daily experiences. For instance, an appropriate amount of stress during exam revision can help me remember and revise more efficiently, while stress prior to an exam can harm my memory of study materials. Therefore, my negative view of stress was shifted, and this research helped me update my knowledge and have a neutral view of the functions of stress.

In addition, I began my research with an assumption that psychological

interventions outweigh pharmacological interventions in the treatment of trauma-related symptoms. This assumption stemmed from my professional experience as a trainee clinical psychologist, where I was equipped with more knowledge of trauma-related therapies, such as trauma-focused cognitive-behavioural therapy (CBT; Fitzgerald & Cohen, 2012), compassion-focused therapy (CFT; Gilbert, 2010), and eye movement desensitization and reprocessing (EMDR; Shapiro & Solomon, 1995) than pharmacological treatments. The significant findings from the current research allowed me to gain more knowledge of the impact of pharmacological interventions on the treatment of psychological trauma and realise the importance of both types of interventions and their complementary effects in the treatment of trauma. These findings helped me have greater awareness that pharmacological and psychological interventions for trauma are not mutually exclusive and that using them complementarily can be more effective in reducing trauma-related symptoms (Hetrick, Purcell, Garner, & Parslow, 2010; Jonas et al., 2013; McHugh, Whitton, Peckham, Welge, & Otto, 2013).

## **2. Reflections on the research process**

On reflection, I experienced feelings of anxiety and frustration at various stages of my research. Firstly, although I found myself interested in the field of trauma and trauma-related symptoms, I was relatively unfamiliar with research studies in the area of psycho-pharmacology and brain functions that are important parts of the current research project. Therefore, I was initially not confident and did not believe that I had

a sufficient body of knowledge for carrying out this research. Furthermore, most of my previous research experiences had involved the use of retrospective questionnaires and surveys, whereas the current research project is experiment-based, involving the use of various research and technical equipment (e.g., eye-tracker, BodyGuard 2 ECG device and the collection and analysis of saliva sample) in a laboratory setting. My lack of relevant experience or knowledge created many challenges for me, and much time was spent familiarising myself with the research equipment before the start of testing. These self-doubts fostered anxiety and made me question whether it was wise to have chosen this research project. In addition, as this was a joint project in which I worked with a colleague who was another trainee from the same doctoral course at University College London (UCL; Sim, 2018), I was concerned that my lack of knowledge and confidence would impede the overall progress of the project and hence affect the progress of my colleague's work. However, my supervisors and colleagues from the same research project offered me support and demonstrated patience while helping me make sense of new and complicated ideas. I also received encouragement from my supervisors in the process of writing my research proposal, which set a good direction for my research project. In addition, I realised that my lack of previous experience in these areas of research actually helped me become more open and curious about different ideas and more able to generate new and creative ideas. Therefore, as my research project progressed, I gained more confidence, certainty and interest in my research.

Due to the graphic nature of the trauma film and the use of medications in this

current research, I was initially concerned about potential negative effects on healthy participants involved in the study. I discussed my concerns with my supervisors, who directed me to some relevant papers in which the effects of hydrocortisone were elicited, a similar study design was used, and the trauma film paradigm was validated (e.g., Holmes & Bourne, 2008; Rombold et al., 2016; Soni, Curran, & Kamboj, 2013; Zohar et al., 2011; Zohar, Sonnino, Juven-Wetzler, & Cohen, 2009). As I became more familiar with the literature, I began to realise that my initial concerns were mainly related to my lack of relevant knowledge, so that it was important to ensure that I gained a good understanding of this area of research. In addition, my anxiety led me to become warier when explaining the study process to the research participants, highlighting to them their right to withdraw from the study at any point and gaining their consent before they started the experiment. During the experiment, furthermore, no participants reported any negative drug effects. After they were debriefed, many participants were interested in the research findings and asked to be updated about our findings after our project is finalised. Participants' interests were rewarding and encouraging.

In addition, as part of the inclusion criteria, participants needed to be taking oral-based contraceptives for at least one month in order to be eligible for the current study. This brought about challenges for our recruitment, as many participants expressed interest in the study but later realised that they were ineligible because they did not take oral-based contraceptives. As a result, our recruitment was slowed, creating much anxiety in me and my colleague, thinking that we might not be able to recruit enough

participants on time and hence not have sufficient power for the result analysis. The current study was advertised on various research platforms, and I constantly explored different types of online and offline platforms in order to promote our research. This was an opportunity to learn which platforms were more efficient. Eventually, our recruitment was a success, and we managed to recruit more participants than we originally planned. After we had recruited enough participants, they were still a number of participants getting in touch with us and would like to take part. Participants who were interested but unable to take part in our research project were informed that if they were interested, they would be kept on our contact list and would be contacted for similar research studies in the future. Recruitment strategies were also shared with other researchers. As noted in the empirical paper in Part 2, this current study only involved young female participants, limiting the research findings. Research has suggested that although approximately 74% of reproductive age women use some form of contraception on a regular basis (Alkema, Kantorova, Menozzi, & Biddlecom, 2013; Rowlands, 2007; Taylor, Keyse, & Bryant, 2006), only a small proportion of women in some non-western cultures use contraception (Gueye, Speizer, Corroon, & Okigbo, 2015; Joshi, Khadilkar, & Patel, 2015). As a result, the sample diversity was limited, making it difficult to generalise the current findings to other cultural contexts. The current research findings need to replicate in other cultural contexts in order to examine their generalisability.

This current research was designed as a joint study divided between me and my colleague. I focused on the effects of hydrocortisone, while my colleague focused on

the effects of propranolol. We worked collaboratively in designing the study, recruiting participants, running the experiments and analysing the data, which increased the efficiency of our work via consistent mutual support. By working in pairs, inter-rater reliability can be reinforced. However, there was some confusion about how we should present the research findings in our respective research dissertations. We determined that there were two ways of presenting our work, but we were not sure which would be most suitable. Specifically, as we shared the same placebo group, we could compare the hydrocortisone, propranolol and placebo groups altogether, or, alternatively, we could compare our respective drug groups with the placebo group individually. After evaluating the pros and cons of each method and consulting our supervisors, we decided to resort to the latter as the former might lead to our research dissertations being similar to each other and lacking in originality, although it would be more scientifically valid and consistent with the study design. We also decided to combine and present our overall research findings in a published paper in the future, comparing all three groups with each other as a whole.

### **3. Implications for future work**

More work is required to understand the effect of hydrocortisone on intrusive and declarative memories following the experience of trauma. The empirical paper in Part 2 discussed the implications of the current research for future work. This critical appraisal will instead focus on its implications for my personal clinical and professional work and its implications beyond clinical psychology.

Firstly, the findings from the current research project have implications for my clinical work. Although the current research examined intrusive memories relating to sexual assault, these findings may shed important light on intrusive memories relating to other types of traumatic experiences. For instance, I am currently working as a trainee clinical psychologist at a clinical health setting with cancer patients. Many of my patients have reported that they experience intrusive memories, images and thoughts after their cancer treatment. Research has suggested that cancer patients may experience intrusive imagery and thoughts post-surgery, which negatively affect their psychological well-being and quality of life and result in mental health issues during remission (Chan et al., 2001; Kazak, & Noll, 2015; Monti et al., 2017; Vickberg, Bovbjerg, DuHamel, Currie, & Redd, 2000). It is important to take into consideration patients' physical as well as psychological well-being in the treatment of cancer (de Vibe, Bell, Merrick, Omar, & Ventegodt, 2009; Epstein, Fiscella, Lesser, & Stange, 2010). As shown by the current research findings, the beneficial effects of administering hydrocortisone within the memory consolidation window on reducing the frequency and vividness of intrusive memories suggested that pharmacological treatment following cancer treatment may potentially be an effective intervention for alleviating intrusive memories and hence reducing mental health issues after cancer treatment in these patients. Therefore, future work is needed to replicate these results in this clinical population in order to consolidate the research findings.

Furthermore, some intrusive memories in cancer patients are verbal, presented in the form of thoughts and statements. These experiences are sometimes known as

intrusive thoughts, which are considered different phenomena from intrusive images as they are produced by separate memory systems according to the dual representation theory of PTSD (Brewin, Gregory, Lipton, & Burgess, 2010; Hageraars, Brewin, van Minnen, Holmes, & Hoogduin, 2010). In the current study, although participants were asked to report whether their intrusive memories were verbal or sensory or both, the number of intrusive memories was recorded and calculated without any differentiation. It might be helpful to ensure verbal and sensory intrusive memories are analysed separately in future work in an attempt to examine the effects of hydrocortisone on intrusive images and thoughts respectively as well as to determine whether hydrocortisone has a differential effect on these distinct types of intrusive memories.

In addition, this current research project showed that trauma memory can be modulated immediately and shortly following the experience of trauma, usually within 6 hours (Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Zohar et al., 2011). This finding suggests the importance of timing in the treatment of trauma. Intervention needs to be implemented soon after trauma and within the appropriate time frame. In regard to cancer patients, it might be prudent to implement interventions soon after cancer treatment in order to prevent the occurrence of intrusive memories over time.

Moreover, the findings from the current research have implications for other areas as well as for clinical psychology. Through this research project, I have observed that the reduction in trauma-related symptoms extends well beyond the traditional boundaries of clinical psychology into fields such as social psychology, health psychology, sociology and politics. Real progress will emerge only from holistic,

multi-disciplinary work that targets not only the individual level but also community and societal levels. In addition, any efforts to improve the wellbeing of trauma victims (e.g., female victims of sexual assault) depends on the reduction of stereotyping and prejudice in both local communities and wider society (Allport, 1954; Buddie & Miller, 2001; George & Martínez, 2002; McKimmie, Masser, & Bongiorno, 2014). At the community level, specifically, such work might include interventions based on principles of social psychology, which seek to increase positive social reactions to assault victims and reduce relevant stereotyping via encouraging meaningful social interactions and support from families, friends and the community as well as from virtual social interactions online (Allport, 1954; Crisp & Turner, 2009; Kraut et al., 1998; Pettigrew, 1998; Pettigrew & Tropp, 2008; Rutland & Killen, 2015). On a societal level, efforts might include national publicity campaigns to tackle prejudice and discrimination and to support the feminist movement (Donat & D'Emilio, 1992; Franiuk, Seefelt, Cepress, & Vandello, 2008; Johnson, Olivo, Gibson, Reed, & Ashburn-Nardo, 2009; Mardorossian, 2002; Matthews, 2005).

Additionally, assault victims need to be encouraged to voice their opinions in order to increase awareness in the general public (Houston & Kramarae, 1991; Thompson, 2000). Moreover, in some societies where sexual assault victims are stigmatised and blamed, non-discriminatory and destigmatising campaigns should be encouraged (Barnett, Sligar, & Wang, 2016; Deitz, Williams, Rife, & Cantrell, 2015; Lefley, Scott, Llabre, & Hicks, 1993; Trenholm, Olsson, Blomqvist, & Ahlberg, 2016). Research indicates that a non-blaming environment plays a significant role in improving post-

trauma well-being and reducing trauma-related symptoms (Peter-Hagene & Ullman, 2015, 2016; Relyea & Ullman, 2013; van der Bruggen, & Grubb, 2014). Real progress will also depend on the continuation of governmental work to provide social support to trauma victims under the scheme of social welfare via implementing support groups and appropriate services for acute interventions and long-term follow-up (Hazelwood & Burgess, 2016; Neville & Heppner, 1999; Staggs, Long, Mason, Krishnan, & Riger, 2007). Publicity about these available services and support is needed to help victims become aware of them. Self-help guidelines also need to be made available and accessible to the general public (Herbert, 2017; Litz, Williams, Wang, Bryant, & Engel, 2004; McCann & Pearlman, 2015). Finally, police investigation and appropriate legal consequences for perpetrators are essential to provide social justice for the victim (Carbone-Lopez, Slocum, & Kruttschnitt, 2016; Martin & Powell, 1994; Mennicke, Anderson, & Kennedy, 2014).

### **Conclusion**

Through the process of carrying out this research project, I have been struck by the complexity of memory processes, brain areas and the effect of hydrocortisone on memory. There were some challenges in terms of study design, participant recruitments, and result analyses and presentation. Through collaboration with my supervisors and my colleague, however, these dilemmas have been resolved via active discussions. Carrying out the current research project has been a powerful learning experience about pharmacological interventions and brain mechanisms with which I was initially unfamiliar but later became profoundly interested. I have also gained

knowledge regarding how to use a range of research equipment, which is certainly valuable for me in terms of conducting other experiments in the future. Some of my previous assumptions have been challenged and modified through the process of this current research. Conducting this research project has given me a greater awareness of the importance of collaboration and group discussion that can often generate new ideas and insights into the research. Furthermore, the current research findings clarify the effect of hydrocortisone on intrusive memories and have important implications, not only for my personal clinical work as a trainee clinical psychologist, but also for work beyond clinical psychology into areas of social psychology, politics, crime justice, gender equality and social welfare. Overall, I was very pleased to see that this current research experience consolidates my passion and hope of pursuing further research in the realm of trauma.

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## Appendices

## Appendix 1: Quality and relevant assessment scales

**Adapted from Newcastle-Ottawa Quality Assessment Scale  
(cohort study)**

*Italics represent changes from original assessment scale*

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

**Selection (Maximum 4 stars)**

- 1) Representativeness of the exposed cohort
  - a) truly representative of the average *victims of SA* in the community \*
  - b) somewhat representative of the average *victims of SA* in the community \*
  - c) selected group of users (*e.g. using specialist service or with a particular need*)
  - d) no description of the derivation of the cohort
  
- 2) Selection of the non-exposed cohort
  - a) drawn from the same community as the exposed cohort \*
  - b) drawn from a different source
  - c) no description of the derivation of the non-exposed cohort
  
- 3) Ascertainment of exposure
  - a) secure record (*e.g. police record or report*) \*
  - b) structured interview \*
  - c) written self-report
  - d) no description
  
- 4) Demonstration that outcome of interest was not present at start of study
  - a) yes \*
  - b) no

**Comparability (Maximum 2 stars)**

- 1) Comparability of cohorts on the basis of the design or analysis
  - a) study controls for *baseline mental health condition (except for SUDs)* \*
  - b) study controls for *demographics (e.g. age, race/ethnicity, sexuality, education background, marital status, employment status, income level etc.)* \*

**Outcome (Maximum 4 stars)**

- 1) Assessment of outcome
  - a) independent blind assessment \*
  - b) record linkage \*
  - c) self-report
  - d) no description
  
- 2) Was follow-up long enough for outcomes to occur

- a) yes (*follow up  $\geq 6$  months*) \*
- b) no (*follow up  $< 6$  months*)

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for \*
- b) subjects lost to follow up unlikely to introduce bias - small number lost -  $\leq 20\%$  follow up, or description provided of those lost \*
- c) follow up rate  $< 80\%$  and no description of those lost
- d) no statement

**Adapted from Newcastle-Ottawa Quality Assessment Scale  
(adapted for cross-sectional studies)**

*Italics represent changes from original assessment scale*

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

**Selection: (Maximum 4 stars)**

1) Representativeness of the sample

- a) truly representative of the average *victims of SA* in the community \*
- b) somewhat representative of the average *victims of SA* in the community \*
- c) selected group of users (*e.g. using specialist service or with a particular need*)
- d) no description of the derivation of the cohort

2) Sample size

- a) Justified and satisfactory \*
- b) Not justified

3) Non-respondents

- a) Comparability between respondents' and non-respondents' characteristics is established, and the response rate is satisfactory. \*
- b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
- c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

- a) Validated measurement tool \*
- b) Non-validated measurement tool, but the tool is available or described
- c) No description of the measurement tool

**Comparability (Maximum 2 stars)**

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

- a) study controls for *baseline mental health condition (except for SUDs)* \*
- b) study controls for *demographics (e.g. age, race/ethnicity, sexuality, education background, marital status, employment status, income level etc.)* \*

**Outcome:(Maximum 2 stars)**

1) Assessment of the outcome:

- a) Independent blind assessment \*

- b) Record linkage \*
- c) Self-report
- d) No description

2) Statistical test:

- a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). \*
- b) The statistical test is not appropriate, not described or incomplete.

## Appendix 2: Trainee contribution to the project

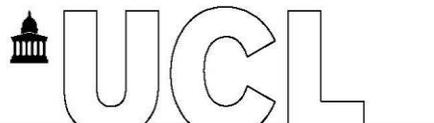
This project was conducted jointly with another Trainee Clinical Psychologist at University College London (UCL). We generated ideas together and designed experiment protocols under the supervision of Dr. Sunjeev Kamboj and Professor Val Curran. We worked collaboratively to recruit participants, and conduct telephone screening and experiments during testing sessions, initially in pairs and subsequently independently after we became more familiar and confident with the experiment protocols and testing materials and equipment. Two Masters students also helped us recruit participants and carry out experiments. We attended research meetings together and contributed to group discussions.

Data for hydrocortisone, propranolol and placebo groups were collected altogether. I focused on the hydrocortisone group, while the other trainee focused on the propranolol group. We shared the placebo group and compared our drug groups with the placebo group respectively. The data analysis was carried out independently. We coded participants' free recall performance independently and subsequently compared our coding in order to ensure inter-rater reliability.

### Appendix 3: Ethical approval documents

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**UCL RESEARCH ETHICS COMMITTEE  
ACADEMIC SERVICES**



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31<sup>st</sup> October 2016

Dr Sunjeev Kamboj  
Research Department of Clinical, Educational and Health Psychology  
UCL

Dear Dr Kamboj

**Notification of Ethical Approval**

**Re: Ethics Application 5583/002: Probing the role of the stress system in consolidation of involuntary and declarative emotional memory using a single dose of cortisol or propranolol in healthy humans**

I am pleased to confirm in my capacity as Chair of the UCL Research Ethics Committee (REC) that your study has been ethically approved by the REC until **30<sup>th</sup> August 2018**. Approval is granted on condition that the follow drug formulations are used, as opposed to 30mg single dose and propranolol capsules, as detailed in the attached letter from Anna Song, Regulatory Manager – Pharmaceuticals, UCL Joint Research Office. In addition, Appendix I to your ethics application should be amended and re-submitted to reflect this change.

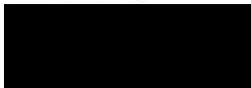
- Hydrocortisone will be given as 10 and 20mg tablets (over-encapsulated) or 2 placebos
- Propranolol 80mg tablets + one placebo or 2 placebos

Approval is also subject to the following conditions.

1. You must seek Chair's approval for proposed amendments (to include extensions to the duration of the project) to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form': <http://ethics.grad.ucl.ac.uk/responsibilities.php>
2. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator ([ethics@ucl.ac.uk](mailto:ethics@ucl.ac.uk)) immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.
3. For non-serious adverse events the Chair or Vice-Chair of the Ethics Committee should again be notified via the Ethics Committee Administrator ([ethics@ucl.ac.uk](mailto:ethics@ucl.ac.uk)) within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Academic Services, 1-19 Torrington Place (9<sup>th</sup> Floor),  
University College London  
Tel: +44 (0)20 3108 8216  
Email: [ethics@ucl.ac.uk](mailto:ethics@ucl.ac.uk)  
<http://ethics.grad.ucl.ac.uk/>

Yours sincerely



**Professor John Foreman**  
**Chair, UCL Research Ethics Committee**

Enc.

Cc: Professor Valerie Curran, Dr Georges Iskandar, An Tong Gong & Zihui Sim



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Email: [a.song@ucl.ac.uk](mailto:a.song@ucl.ac.uk) Tel No. 020 7679 4466  
Web-sites: [www.uclh.nhs.uk](http://www.uclh.nhs.uk); [www.ucl.ac.uk](http://www.ucl.ac.uk)

**Re: Probing the role of the stress system in consolidation of involuntary and declarative emotional memory using a single dose of cortisol or propranolol in health humans  
(Dr. Sunjeev Kamboj, Ethics ID: 5583/002)**

The purpose of this document is to assess the use of **hydrocortisone 10/20mg tablets** and **propranolol 80mg capsules** and their **placebo** for use in the above referenced clinical study.

In order to assess the risk the following will be looked at:

- 1) The formulation quality and licensing status
- 2) The fitness for purpose
- 3) The management of the medicines

**Formulation quality and the licensing status**

*Hydrocortisone*

Hydrocortisone 10 and 20mg are licensed products and will be provided by UCLH pharmacy via local hospital supply. It is a marketed product produced by Auden Mckenzie (Pharma Division) Ltd, who holds the appropriate marketing authorisation for this product.

*Propranolol*

Propranolol 80mg tablets is a licensed product and will be provided by UCLH pharmacy via local hospital supply. It is a marketed product produced by Accord Healthcare Ltd and Actavis UK Ltd, who both hold appropriate marketing authorisation for this product.

*Placebo*

Placebo will be made on site in the clinical psychopharmacology unit at the Research Department of Clinical, Education & Health Psychology, UCL. It has been assured that the active hydrocortisone and propranolol will be overencapsulated to maintain blinding. The opaque capsules for overencapsulation as well as placebo capsules will be sourced from a reputable source within the UK (Boots or Graftons Pharmacy). The placebo capsules will be filled with milk powder, which will also be sourced from the above mentioned venues.

The quality of the materials will not be further investigated.

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**Director UCL SLMS Research Support Centre, Director R&D UCLH – Brian Williams**  
**Managing Director UCL SLMS Research Support Centre – Dr Nick McNally**  
**Co Director of R&D (RFH) – Dr Adele Fielding**

### **Fitness for purpose**

Consideration needs to be given to the pharmacology (both pharmacokinetic and pharmacodynamics) of the investigational material in the formulation proposed for the study with respect to the study's intended use.

As proposed, hydrocortisone is a glucocorticoid that is the principal corticosteroid secreted by the adrenal cortex. It works to supplement cortisol levels and alter amygdala activation by upregulating the glucocorticoid system using exogenous cortisol.

Propranolol is a non-selective  $\beta$ -blocker and works by blocking noradrenaline action within the amygdala by acting at the central  $\beta$ -adrenergic receptors.

This study intends to investigate the effect of hydrocortisone or propranolol or placebo as a single dose on the consolidation of involuntary and voluntary episodic emotional memory in healthy participants.

There have been studies in a clinically relevant population using hydrocortisone or propranolol to show these drugs can improve symptoms of post-traumatic stress disorder if given straight after the event.

The study and its commercial use have shown fluoxetine to have a favourable safety, tolerability and pharmacokinetic profile.

### **Management of the medicines**

Blinding arrangements: This study will be double-blinded. Patients will be randomised using a computer algorithm for treatment assignment to avoid bias and ensure even distribution of treatment. The randomised patient will receive a treatment number and bottle ID to ensure the correct treatment is dispensed to the patient.

The investigator will have an unblinded list for use in scenarios of unblinding. The tablets will be overencapsulated and milk-powder filled opaque capsules used as placebo. Patients will take TWO capsules ONCE only. The combination can be one of the following:

- a. ONE overencapsulated 10mg hydrocortisone + ONE overencapsulated 20mg hydrocortisone
- b. ONE overencapsulated 80mg propranolol capsule + ONE placebo capsules
- c. TWO placebo capsules

Study medicines sourcing and accountability arrangement: As a measure of risk minimisation it is suggested -

1. All medication should be clearly labelled to avoid cross-contamination and accidental unblinding.
2. Staff involved in making up placebo and overencapsulation activity should be suitably trained and make medication in a way that traceability is possible (unblinding purposes or

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audits) by means of keeping batch records or worksheets.

3. Drugs should be clearly segregated from other stock to facilitate management and stored at temperature ranges as specified by supplier. It is recommended that as a minimum a calibrated min/max thermometer is used to record storage temperatures.
4. Hydrocortisone/propranolol/placebo should be dispensed as per valid prescription and per patient randomisation.

28<sup>th</sup> October 2016



Anna Song  
Regulatory Manager - Pharmaceuticals

## Amendment Approval Request Form

<b>1</b>	<b>Project ID Number:</b> 5583/002	<b>Name and Address of Principal Investigator:</b> Sunjeev Kamboj, Reader in Clinical Psychology Research Department of Clinical, Educational and Health Psychology, UCL
<b>2</b>	<b>Project Title:</b> Probing the role of the stress system in consolidation of involuntary and declarative emotional memory using a single dose of cortisol or propranolol in healthy humans	
<b>3</b>	<b>Type of Amendment/s (tick as appropriate)</b> Research procedure/protocol (including research instruments) <input checked="" type="checkbox"/> Participant group <input type="checkbox"/> Sponsorship/collaborators <input type="checkbox"/> Extension to approval needed (extensions are given for one year) <input type="checkbox"/> Information Sheet/s <input type="checkbox"/> Consent form/s <input type="checkbox"/> Other recruitment documents <input type="checkbox"/> Principal researcher/medical supervisor* <input type="checkbox"/> Other <input type="checkbox"/>  <i>*Additions to the research team other than the principal researcher, student supervisor and medical supervisor do not need to be submitted as amendments but a complete list should be available upon request *</i>	
<b>4</b>	<b>Justification</b> (give the reasons why the amendment/s are needed) We would like to recruit an additional 15 participants to this study. Our original power calculation assumed a large effect. However, recent evidence suggests that a more conservative estimate of effect size for the current study is warranted (Sijbrandij et al, 2015, Lancet Psychiatry), especially given recent concerns in the psychological literature about low powered studies. Importantly, a larger sample would also allow us to more reliably investigate the role of individual differences in the response to hydrocortisone or propranolol. We therefore request recruitment of an additional 15 participants to take our sample size to n=30 per group (our current target is n=25 per group).	
<b>5</b>	<b>Details of Amendments</b> (provide full details of each amendment requested, state where the changes have been made and attach all amended and new documentation)  We originally sought n=75 for our experiment, which would be sufficient to detect the expected (large) effect between one of the drug (hydrocortisone; propranolol) groups and placebo. However, recent studies suggest an important role for certain individual differences in the effects of stress hormones on memory (Stockhorst & Antov, 2016), an exploration of which would require a somewhat larger sample size. By increasing the sample size to n=90 (i.e. 15 more participants than originally proposed), we will be able to examine the effect of two potentially important moderating variables (trait dissociation and baseline heart rate variability) on the frequency of intrusive memories without loss of power.	
<b>6</b>	<b>Ethical Considerations</b> (insert details of any ethical issues raised by the proposed amendment/s) We have tested ~65 participants. None have reported side effects of the medications or found the stressful film overly distressing. No other changes to the protocol are required.	
<b>7</b>	<b>Other Information</b> (provide any other information which you believe should be taken into account during ethical review of the proposed changes)	

**Declaration** (to be signed by the Principal Researcher)

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendments to be implemented.
- For student projects, I confirm that my supervisor has approved my proposed modifications.



Signature:

Date: 08/10/2017

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**FOR OFFICE USE ONLY:**

Amendments to the proposed protocol have been *approved* by the Research Ethics Committee.

Signature of the REC Chair:



Date: *10/10/2017*

## Appendix 4: Project documentation

#### 4.1. Information sheet for participants involved in memory consolidation research study using cortisol and propranolol

**You will be given a copy of this information sheet.**

Title of Project: **Examining the effects of stress hormones on emotional memory using cortisol and propranolol**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 5583/002

Names of Researchers An Tong Gong; Zhihui Sim; Adrihani Abd Rashid; Ami Baba

Work Address Research Department of Clinical, Educational and Health Psychology, UCL, 1-19 Torrington Place, London WC1E 7HB

Institute of Cognitive Neuroscience, UCL, Alexandra House, 17 Queen Square, London WC1N 3AZ

Contact Details Email: [an.gong.10@ucl.ac.uk](mailto:an.gong.10@ucl.ac.uk); [zhihui.sim.15@ucl.ac.uk](mailto:zhihui.sim.15@ucl.ac.uk); [adrihani.rashid.16@ucl.ac.uk](mailto:adrihani.rashid.16@ucl.ac.uk); [ami.baba.16@ucl.ac.uk](mailto:ami.baba.16@ucl.ac.uk)  
Tel: 075 1088 7575; 075 1089 1591

We would like to invite women aged between 18 and 35 to take part in this study. You will need to be in good physical and mental health, have average weight (i.e. body mass index or 'BMI' - between 18.5-30.0), with normal or corrected to normal colour vision, **taking oral contraception**, and fluent in English. Because the study involves taking a medication, you cannot take part if you have any of the following: a historical or current diagnosis of a mental health issue that required/requires treatment, if you have been the victim of interpersonal violence or trauma, have known memory problems, serious sleep difficulties, diabetes, asthma, breathing problems like Chronic Obstructive Pulmonary Disease (COPD), a cardiac pacemaker implant or other cardiovascular conditions, a history of epilepsy or neurosurgery, impaired liver or kidney function, or a history of anaphylactic reaction.

This study involves receiving one of two active medications or placebo. Thus, you will not be able to take part if you are sensitive to propranolol or cortisol and are intolerant of lactose or unable to swallow capsules. In addition, you will not be able to take part if you are currently taking cardiovascular or psychiatric medication, are pregnant or breastfeeding, or using psychoactive drugs (other than alcohol, nicotine and caffeine) regularly (i.e. more than twice a month). To take part, you should not be consuming excessive alcohol (i.e. > 14 units per week).

**Details of Study:** You should only participate in this study if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. This study is being conducted by researchers from the Department of Clinical, Educational and Health Psychology at UCL.

**Why are we doing this study?**

Emotional events have a privileged status in our daily lives. However, intensely emotional events or chronic exposure to stressful experiences can create unwanted memories which are distressing. Therefore, it is important to learn about the brain mechanisms involved in the formation of unpleasant emotional memories. Some medications might be helpful in helping us understand emotional memories, particularly medications that affect the ‘stress response’ – such as the steroid drug **hydrocortisone** and the beta-blocker **propranolol** – which can affect processing of emotional information. Participants in this study will therefore receive cortisol or propranolol or a placebo to see how this affects their subsequent memories of unpleasant events. By taking part in this study you will contribute to the scientific knowledge of the effect of these two drugs on ‘memory consolidation,’ which may inform future treatments for psychological disorders such as post-traumatic stress disorder (PTSD).

**Do I have to take part?**

Your participation in the study is entirely voluntary and you are free to withdraw from the study at any time without giving a reason, even if you have previously given your written consent. If you do agree to take part, you will be asked to sign a consent form and will be given this information sheet to keep.

**What are these drugs and are they safe?**

Depending on which group you are randomly allocated to, you will receive a capsule containing hydrocortisone, propranolol or placebo. Hydrocortisone (or cortisol) is an important stress hormone in humans. Propranolol, a ‘beta blocker,’ is a drug typically used to treat conditions such as high blood pressure and anxiety. You will stay in the department for about 1 hr after you take the capsule.

Note that, like all medications, cortisol and propranolol can have side effects (e.g. fatigue, sleep difficulties, nausea, drowsiness/weakness, exacerbation of existing breathing problems). Therefore, there are strict criteria for inclusion in the study.

**What will I have to do?**

If you agree to participate in this study, you should contact the experimenter by email with contact information and a convenient time to call. You will then receive a call from us, and we will ask you a series of questions to check your

eligibility for the study. Please note that based on your answers to these questions you may not be eligible to take part in the study.

If you fulfill our study criteria, we will arrange for you to attend 2 appointments at UCL which will take place 1 week apart. During Session 1, you will be asked to complete some questionnaires about your current mood and usual emotional state. You will be asked to provide a saliva sample so we can measure stress hormones in your body. You will also be asked to place some sticky probes on your body to allow us to measure your heart rate and blood pressure. This is completely safe. You will then watch a short film (~15 minutes). You should be aware that **the film contains highly graphic scenes of interpersonal and sexual violence, injury and death** which are designed to be distressing. **Please do not take part if you are likely to become very distressed by such scenes.** This will be followed by some more questionnaires. After this, you will be given a capsule (hydrocortisone, propranolol or placebo) to swallow with water. You will then be required to remain in the Department for one hour and provide another saliva sample before you leave.

Between Sessions 1 and 2, you will fill in a simple app-based online diary of spontaneous thoughts/memories about the film every evening. You will be reminded to do this daily by email. **The daily information provided between sessions is absolutely crucial for our experiment.** If you are unable or unwilling to complete the brief daily diaries on the first three days and on at least five out of the seven days between sessions, we will not be able to invite you back for the second session and cannot compensate you for your time.

**Please bear in mind that the aim of our research is to develop new ideas for treating psychological problems, and we can only do this effectively if you help us by following the requirements of the study as carefully as possible. If we get bad data from participants, we could end up with the wrong conclusions, and that could ultimately be harmful for the people we hope to help with this research.** You can contact the researchers at any time during or after the study if you experience any difficulties with this requirement.

Seven days after Session 1, you will be asked to return to the Department for Session 2, in which you will complete some final tasks. This will last approximately 30 minutes, at the end of which, we will provide you with some more information about the study and you will receive reimbursement for participation in the study. We will ask if you would like to participate in future research.

#### **What are the possible risks of taking part?**

You should be aware that the film contains graphic scenes of sexual assault, interpersonal violence, injury and death which are designed to be distressing. After the film, people often have spontaneous thoughts and images from the film. These are usually short-lasting. In previous research which used this procedure with hundreds of participants, no one experienced longstanding

intrusive thoughts or emotional problems in response to the film. Any clips you see are in the public domain. However, it is not possible to guarantee zero risk to you. You should therefore not take part if you have personally experienced interpersonal violence/trauma, have concerns about your mental health, or think that you may be strongly psychologically affected by the film.

The medications involved in the study are routinely used in medical practice. They are generally very safe. However, like all medicines hydrocortisone and propranolol can cause side effects. For hydrocortisone, these include increased risk of infection. In particular, if you have never had them, you should keep away from people who have chicken pox or shingles. You should not take part if you have an infection of any kind. Other side effects of cortisol can be nausea, heartburn, headache, dizziness, menstrual period changes, trouble sleeping, increased sweating, changes in eyesight and muscle weakness. If affected, you should not drive or operate machinery. Propranolol can cause tiredness, cold extremities, difficulties sleeping or disturbed sleep, and slow or irregular heartbeat. Other side effects of these drugs are uncommon. If you are concerned, you should talk to your doctor.

**How will I be paid?**

You will receive payment for participation upon *completion of the whole study*. In total, the basic testing and study follow-up in your own time should take ~2.5 hours. You will be compensated £25 for your time.

**How will my data be stored?**

All information which is collected about you during the course of the research will be kept strictly confidential and will be securely stored electronically, using a numbered code so that you cannot be identified. Only researchers directly involved in the study will have access to the data. All data will be stored in accordance with the Data Protection Act 1998. The data will be used only for informing the research question in this study and the results of the research will be disseminated in peer-reviewed scientific journals, but you will in no way be identifiable from such publications. You will receive feedback when the study is completed. Any biological samples we collect from you will also be anonymised. These samples will be destroyed once they are analysed.

**Note – if you have any further questions regarding this study please do not hesitate to contact any of the researchers above.**

**This study has been approved by the UCL ethics committee**

It is up to you to decide whether or not to take part. If you choose not to participate, it will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason.

Please discuss the information above with others if you wish or ask us if there is anything that is not clear or if you would like more information.

**Study Registration Details:**

All data will be collected and stored in accordance with the Data Protection Act 1998. This study has been registered with UCL Data Protection; Number: Z6364106/2016/10/28

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 5583/002

If you have any questions regarding the study, please contact the researchers:  
Research Department of Clinical, Educational and Health Psychology, UCL, 1-19  
Torrington Place, London WC1E 7HB  
Email: an.gong.10@ucl.ac.uk  
Tel: 075 1089 1591

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Please discuss the information above with others if you wish or ask us if there is anything that is not clear or if you would like more information.

It is up to you to decide whether to take part or not; choosing not to take part will not disadvantage you in any way. If you do decide to take part you are still free to withdraw at any time and without giving a reason.

**All data will be collected and stored in accordance with the Data Protection Act 1998.**

**Thank you for reading this information sheet and for considering taking part in this research.**

#### **4.2. Informed consent for participants involved in memory consolidation research study using cortisol and propranolol**

**Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.**

Title of Project:

**Examining the consolidation of emotional memory using cortisol and propranolol**

This study has been approved by the UCL Research Ethics Committee (Project ID Number): 5583/002

Thank you for your interest in taking part in this research. Before you agree to take part, the person organising the research must explain the project to you.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you to decide whether to join. You will be given a copy of this consent form to keep and refer to at any time.

#### **Participant's Statement**

I, \_\_\_\_\_ (print name clearly)

- have read the notes written above and the Information Sheet, and understand what the study involves.
- understand that if I decide at any time that I no longer wish to take part in this project, I can notify the researchers involved and withdraw immediately.
- consent to the processing of my personal information for the purposes of this research study.
- understand that such information will be treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.
- agree that the research project named above has been explained to me to my satisfaction and I agree to take part in this study.
- agree to be contacted after my participation to be asked some quick follow-up questions by the researchers.

- understand that I am being paid for my assistance in this research and that some of my personal details will be passed to UCL Finance for administration purposes.
- understand that I must not take part if I am pregnant or breast feeding.
- understand that my anonymity will be maintained and it will not be possible to identify me from any publications.

Signed:

Date:

Email:

Tel. No.:

### 4.3. Study Advertisement



## Seeking Female Participants

For a study looking at the effects of cortisol and propranolol on the storage of emotional memories

**£25 compensation**

The study will involve 2 visits at UCL which will take place 1 week apart. On Visit 1 (approximately 1.5 hrs), **you will be asked to watch a 15-minute film containing extremely graphic scenes with interpersonal violence**, which are designed to be distressing. **Please do not take part if you are likely to become very distressed by such scenes.** After the film, you will receive cortisol, propranolol (medications affecting the body's response to stress) or a placebo orally. On Visit 2, one week later, you will complete some questionnaires and computer tasks (approximately 30 mins). Between visits, you will need to fill out a short online diary related to the experiment, so it is **essential that you have reliable daily access to the Internet through a computer or smart device.**

**You are invited to participate if you are a healthy woman and:**

- Are aged 18-35 years
- Are taking oral contraception
- Are fluent in English
- Do not have any current mental health problems
- Do not use any psychoactive drugs (other than caffeine, alcohol and tobacco) more than twice a month
- Have average weight (i.e. Body Mass Index between 18.5 and 30.0)

Please note these are not the only study criteria and you will need to undergo a telephone screening to confirm that you are fully eligible to take part.

**Your participation in the study is entirely voluntary.**

For more information or to volunteer for this study, please contact the researcher team

zhihui.sim.15@ucl.ac.uk / Tel: 075 1088 7575

Zhithui Sim zhithui.sim.15@ucl.ac.uk 075 1088 7575										
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#### 4.4. Telephone Screening Questions and Protocol

NB, if in doubt about an inclusion/exclusion criterion, call/email participant back after clarifying with Sunjeev or Georges.

*Hi \_\_\_\_\_, my name is..... I am calling because you expressed your interest in our research study (to do with emotional memory of distressing events). Are you still interested in taking part?*

*Is it ok to speak for five minutes now?*

*Thank you, I just need to ask you a few screening questions to see if you are eligible to participate in the experiment. We ask these questions to everyone who expresses interest. I will let you know whether or not you are eligible and if you are not eligible I will explain why. Okay?*

<p><i>So firstly can I check the spelling of your name?</i></p> <p><i>...Thank you.</i></p>	<p>_____</p>	
<p><i>How old are you?</i></p>	<p>_____</p>	<p><i>(If under 18yrs or over 35yrs SAY: I'm sorry but we are only testing people who are aged 18-35 so I am afraid you are not eligible. Sorry about that.....)</i></p>
<p><i>May I know your height and weight?</i></p>	<p>_____cm _____kg</p>	<p><i>(if BMI not within 18.5-30, SAY: I'm sorry but we are only testing people who have a Body Mass Index within 18.5-30)</i></p>
<p><i>Just to explain a little bit about the study... we will need you to complete a brief online diary each evening between Session 1 and Session 2.</i></p> <p><i>Do you have reliable access to the internet every day, even if it's from your mobile phone?</i></p>	<p>YES / NO</p>	<p><i>(If No, exclude)</i></p>
<p><i>Do you read, write and speak English fluently?</i></p> <p><i>Please can you tell me</i></p>	<p>YES / NO</p> <p>_____</p>	<p><i>(If No, exclude)</i></p>

<i>your profession?</i>		
<i>Are you on an oral-based contraceptive pill?</i>	YES / NO	(If No, exclude)
<i>Can you please tell me the name of oral contraceptive pill you use?</i>		Write down the brand name of the pill
<i>How long have you been using the oral contraceptive pill continuously?</i>		Write down the duration
<i>When was your last period?</i>		Write down the time
<i>What is the reason for you to take the oral contraceptive pill, or would you prefer not to say?</i>		(They can choose not to answer)

<i>Have you ever been a victim of interpersonal violence or trauma, such as being assaulted or witnessing violent injury or death?</i>	YES / NO	<i>(If yes SAY: I'm sorry, as the study contains graphic content in a film, we cannot ethically include people who have a personal history of such events. We're sorry that you cannot take part in this study at this time.)</i>
<i>Have you ever experienced any mental health problems that required or requires treatment?</i>	YES / NO	<i>(If yes SAY: I'm sorry, but due to the nature of the experiment, we can only include people who have no history of mental health problems.)</i>
<i>An important part of this experiment is to look at emotional</i>	YES / NO	<b>(CAN'T TELL YOU TOO MUCH BUT IT IS VERY GRAPHIC AND DISTURBING)</b>

<p><i>memory. The way in which we do this in this experiment is to show participants an extremely graphic and unpleasant video during Session 1. The video depicts scenes of extreme interpersonal violence, injury, death and sexual assault. Although the scenes are freely accessible to the public, I must iterate that they are very graphic. Would you agree to watch this video?</i></p>		<p><i>(If no SAY: I'm sorry then you cannot take part, as this is a crucial part of the study.)</i></p>
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*As far as you know:*

<p><i>Are you sensitive to cortisol?</i></p>	<p>YES / NO</p>	<p><i>(If Yes, exclude)</i></p>
<p><i>Are you intolerant to lactose?</i></p>	<p>YES / NO</p>	<p><i>(if Yes, exclude)</i></p>
<p><i>Are you able to swallow capsule?</i></p>	<p>YES / NO</p>	<p><i>(if No, exclude)</i></p>
<p><i>Are you taking any cardiovascular or psychiatric medication?</i></p>	<p>YES / NO</p>	<p><i>(If Yes, exclude)</i></p>
<p><i>Are you currently using a beta-blocker?</i></p>	<p>YES / NO</p>	<p><i>(If Yes, exclude)</i></p>
<p><i>Do you have any of the following:</i>  <ul style="list-style-type: none"> <li>- <i>Asthma or other breathing problems?</i></li> <li>- <i>Cardiovascular conditions or a cardiac pacemaker?</i></li> </ul> </p>	<p>YES / NO</p>	<p><i>(If Yes, exclude)</i></p>

<ul style="list-style-type: none"> <li>- Diabetes?</li> <li>- Liver or kidney problems?</li> <li>- Problems sleeping?</li> <li>- Any diagnosed memory problems?</li> <li>- Colour blindness?</li> </ul>		
<p>Have you ever had:</p> <ul style="list-style-type: none"> <li>- A severe anaphylactic reaction?</li> <li>- Epilepsy?</li> <li>- Neurosurgery?</li> </ul>	<p>YES / NO</p>	<p>(If Yes, exclude)</p>
<p>Do you have a history of fainting?</p>	<p>YES / NO</p>	<p>(If Yes, exclude)</p>
<p>Do you have low blood pressure? (Systolic blood pressure of &lt;100 mmHg)</p>	<p>YES / NO</p>	<p>(If Yes, exclude)</p>
<p>Are you pregnant or likely to become pregnant in the coming weeks?</p>	<p>YES / NO</p>	<p>(If Yes, exclude)</p>
<p>Are you breastfeeding or likely to breastfeed in the coming weeks?</p>	<p>YES / NO</p>	<p>(If Yes, exclude)</p>
<p>Aside from caffeine, nicotine or alcohol, do you currently use any recreational drugs more than twice per month?</p>	<p>YES / NO</p>	<p>(If yes SAY: I'm sorry we are only testing people who do not use any recreational drugs, as this will interfere with the drugs we are using in the study.)</p>
<p>How much alcohol do you take in a week?</p>	<p>_____</p> <p>—</p>	<p>(If over 14 units or 'standard drinks' SAY: I'm sorry but we are only testing people who consume alcohol at a moderate level, as this will interfere with the drugs we are using in the study.)</p>
<p>The study may involve taking cortisol or propranolol on Day 1 of the study. Would you be</p>	<p>YES / NO</p>	<p>(If no SAY: I'm sorry then you cannot take part, as this is a crucial part of the study.)</p>

<p><i>happy to do this?</i></p> <p><i>Cortisol is an important stress hormone in humans. Propranolol is a drug typically used to treat conditions such as high blood pressure and anxiety. These drugs can have side effects (e.g. fatigue, nausea, drowsiness/weakness). Therefore, you will be asked to remain in the Dept till the effects wear off.</i></p>		
<p><i>Do you wear any visual aids such as glasses or contact lenses?</i></p> <p><i>Do you wear any hearing aids?</i></p>	<p>YES / NO</p> <p>YES / NO</p>	<p><i>(If yes to either SAY: please remember to bring any visual or hearing aids with you on both of your testing sessions, otherwise you will not be able to participate.)</i></p>

That's the end of the screening questions and it seems you are eligible for participating in our study. Before I ask you whether you would like to take part or not, I'd like to remind you what will be expected of you if you do take part.

If you agree to take part in the study you will be asked to:

- Attend UCL on TWO different occasions spaced one week apart. That means that if you attend the first session on a Wednesday you will be asked to return the following Wednesday for the second session. The first session will take about an hour and a half and the second one will take about thirty minutes.
- As part of the experiment we'll be measuring your heart rate – 2 sticky probes, one below the right collar bone, one below the left rib cage. This is a completely harmless procedure which we'll show you how to do.
- We will ask you to complete some questionnaires and tasks.
- We will ask you to watch a short film which contains some graphic scenes including interpersonal violence, injury and death which you may involuntarily remember afterwards.
- We will monitor your eye movements while you watch the film, which is completely non-invasive.
- We will ask you to take a pill which might be cortisol or propranolol.
- We will also ask you to fill in a brief online diary every day during the week between the two sessions. This is essential for our study and we can only invite

you back for the second part of the study if you complete the diary on the 7 days between sessions. Are you sure you can do this?

- At the end of the second session you will be paid £25.

So would you like to take part?  
YES / NO

*(If YES SAY: Great, thank you! Let's book your sessions. (Book sessions))*

*Phone number?*

*It would be helpful if you could read the information sheet carefully before the first session, but we'll ask you to read this at the beginning of the session before you sign the consent form.*

*For the experiment on Day 1, we also require you not to have any food or any drinks containing caffeine two hours prior to the experiment. Because we're looking at your eye movements we also ask that you wear glasses rather than contacts on the first session.*

*For your own comfort, we want to inform you that it may be of your best interest to refrain from wearing a dress or a jumpsuit on Day 1 of the experiment, as it may be difficult to attach the heart rate monitor on with these articles of clothing.*

*Do you have any other questions about the study?*

#### 4.5. Debrief

This study was an investigation into people's intrusive memories of unpleasant events. Intensely emotional events can cause maladaptive consequences in the memory process. For example, you may have heard about Post-Traumatic Stress Disorder (PTSD), which visually involves 're-experiencing' the stressful event through nightmares, repetitive flashbacks and other distressing involuntary memory phenomena (known as intrusive memories). The pharmacological effects on memory of two different drugs, cortisol and propranolol, can be used to investigate intrusive memories. This in turn can often provide important insight into the nature of emotional memories and memory processes, and aid the development of methods to reduce such memories.

Therefore, we measured the effects of cortisol and propranolol (alongside a placebo control) on the frequency of intrusive memories resulting from watching disturbing video clips, over the course of a week. We assessed two types of memory: the intrusive memories and voluntary memory (the memory tasks you completed today). The sleep survey was used to assess sleep quality, which is known to have an impact on memory consolidation. Questionnaires were used to measure participants' general and event-specific moods/emotions.

We anticipate that participants who received the active drugs would have less frequent intrusive memories and possibly worse declarative memory compared to participants who received a placebo. We won't know who received what until the end of the study, which is common in these kind of experiments.

Please contact the experimenters, An Tong Gong, Zhihui Sim, Adrihani Rashid, or Ami Baba, at the following e-mail addresses: [an.gong.10@ucl.ac.uk](mailto:an.gong.10@ucl.ac.uk); [zhihui.sim.15@ucl.ac.uk](mailto:zhihui.sim.15@ucl.ac.uk); [adrihani.rashid.16@ucl.ac.uk](mailto:adrihani.rashid.16@ucl.ac.uk); [ami.baba.16@ucl.ac.uk](mailto:ami.baba.16@ucl.ac.uk), if you have any questions regarding this study.

Thank you again for your participation and cooperation.

## Appendix 5: Questionnaires and measures

### 5.1. Adapted Pittsburgh Sleep Quality Index

- 1) What time did you go to bed last night? \_\_\_\_pm
- 2) How long did it take you to fall asleep? \_\_\_\_\_ minutes
- 3) How many hours of sleep did you get last night? \_\_\_\_\_ hours
- 4) How would you rate your sleep quality overall?
  - a. Very good
  - b. Fairly good
  - c. Fairly bad
  - d. Very bad

### Retrospective Dream Questionnaire

- 1) Do you remember having had any dreams last night?
- 2) Yes \_\_\_\_
- 3) No \_\_\_\_
  
- 4) Could any of these dreams have been described as nightmares? (*Nightmares are defined as 'a vivid dream that is frightening or disturbing, the events of which you can remember clearly and in detail on awakening'.*)  
Yes \_\_\_\_  
No \_\_\_\_
  
- 5) Did you have any night terrors? *A night terror is a 'sudden awakening in fear, possibly accompanied by a scream, but where you do not remember a dream'.*  
Yes \_\_\_\_  
No \_\_\_\_
  
- 6) Please rate the affectivity of your dreams last night on a scale of 1 – 10, with 1 being more negative, and 10 more positive
  
- 7) Would you say the dream you had last night was more positive or negative than usual?
  - i. More positive
  - ii. More negative
  - iii. About the same
  
- 8) Did you dream about anything you saw in the video yesterday?
  
- 9) If yes, please describe

---

**SCORING INSTRUCTIONS FOR THE PITTSBURGH SLEEP QUALITY INDEX:**

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven component scores are then added to yield one "global" score, with a range of 0-21 points, "0" indicating no difficulty and "21" indicating severe difficulties in all areas.

Scoring proceeds as follows:

---

**Component 1: Subjective sleep quality**

Examine question #6, and assign scores as follows:

Response	Component 1 score
"Very good"	0
"Fairly good"	1
"Fairly bad"	2
"Very bad"	3

*Component 1 score:* \_\_\_\_\_

---

**Component 2: Sleep latency**

1. Examine question #2, and assign scores as follows:

Response	Score
≤15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

*Question #2 score:* \_\_\_\_\_

2. Examine question #5a, and assign scores as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

*Question #5a score:* \_\_\_\_\_

3. Add #2 score and #5a score

*Sum of #2 and #5a:* \_\_\_\_\_

4. Assign component 2 score as follows:

Sum of #2 and #5a	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

*Component 2 score:* \_\_\_\_\_

### Component 3: Sleep duration

Examine question #4, and assign scores as follows:

Response	Component 3 score
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

*Component 3 score:* \_\_\_\_\_

---

### Component 4: Habitual sleep efficiency

1. Write the number of hours slept (question #4) here: \_\_\_\_\_

2. Calculate the number of hours spent in bed:

Getting up time (question #3): \_\_\_\_\_

Bedtime (question #1): \_\_\_\_\_

\_\_\_\_\_

*Number of hours spent in bed:* \_\_\_\_\_

3. Calculate habitual sleep efficiency as follows:

(Number of hours slept/Number of hours spent in bed) X 100 = Habitual sleep efficiency (%)

( \_\_\_\_\_ / \_\_\_\_\_ ) X 100 = %

4. Assign component 4 score as follows:

Habitual sleep efficiency %	Component 4 score
> 85%	0
75-84%	1
65-74%	2
< 65%	3

*Component 4 score:* \_\_\_\_\_

## 5.2. Filter Task

### DEMOGRAPHIC INFORMATION

**Participant No.:** \_\_\_\_\_

**Group No:** \_\_\_\_\_

**D.O.B (incl. year):** \_\_\_\_\_

**Email address:** \_\_\_\_\_

*Please circle the most appropriate answer for each question.*

**Handedness:** RIGHT LEFT

**Ethnicity:**

- White:
  - British
  - Irish
  - Any other White background
- Mixed:
  - White and Black Caribbean
  - White and Black African
  - White and Asian
  - Any other mixed background
- Asian or Asian British
  - Indian
  - Pakistani
  - Bangladeshi
  - Any other Asian Background
- Black or Black British
  - Caribbean
  - African
  - Any other Black background
- Other ethnic groups
  - Chinese
  - Other
- Not stated

**Highest academic qualification:**

- 11 years schooling (GSCE)
- 13 years schooling (A levels)
- 14 years schooling (Bachelors degree 1st year completed)
- 15 years schooling (Bachelors degree 2nd year completed)
- 16 years schooling (Bachelors degree 3rd year completed)
- 17 years schooling (Masters/Bachelors degree 4th year completed)
- 18 years schooling (depending on number of post grad years)
- 19 years schooling (depending on number of post grad years)
- 20 years schooling (depending on number of post grad years)

**Height (cm):** \_\_\_\_\_

**Weight (kg):** \_\_\_\_\_

Participant Number: \_\_\_\_\_

Group Number: \_\_\_\_\_

**Music Task**

For each section of music, please rate how pleasant you find it on a scale of 1 to 9, where

1 2 3 4 5 6 7 8 9

(1 = extremely unpleasant)

(5 = midway)

(9 = extremely pleasant)

It should be easy to tell where one section ends and the next begins.

**Set 1:**

**Set 2:**

section 1 =

section 1 =

section 2 =

section 2 =

section 3 =

section 3 =

section 4 =

section 4 =

section 5 =

section 5 =

section 6 =

section 6 =

section 7 =

section 7 =

section 8 =

section 8 =

section 9 =

section 9 =

section 10 =

section 10 =

section 11 =

section 11 =

section 12 =

section 12 =

section 13 =

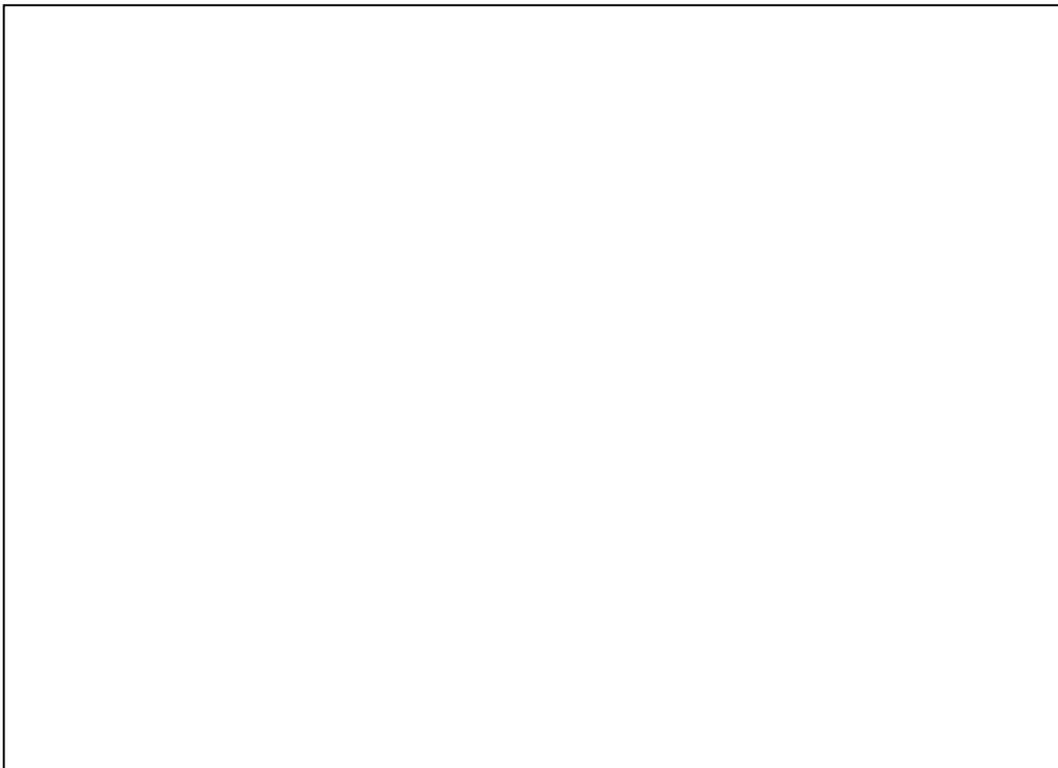
### 5.3. Free recall task

Think back to the video clips from last week.

Please write down everything you can remember about the video clips.

Be as detailed as possible, including information about WHERE things happen, WHEN they happen, WHO they happen to, WHAT the people and scenes look like, etc.

Take your time. The main thing is to recall as much information and detail as you possibly can. Please write about both scenes.

A large, empty rectangular box with a thin black border, intended for the student to write their free recall notes. The box is centered on the page and occupies a significant portion of the lower half of the document.

#### 5.4. Cued recall task

**The next set of questions relate to the first scene in the video. Even if you are not sure about the answer, just make your best guess.**

Q1: What is colour of the walls in the passageway that the woman walks through?

Q2: What two things was the woman carrying?

Q3: What does the woman see when she walks down the passageway?

Q4: What is the woman who is first being attacked wearing?

Q5: What does the man do with his knife while he's threatening the second woman?

Q6: What is the attacker wearing?

Q7: What happens in the background in the passageway while the man is raping the woman?

Q8: What is lying on the floor next to the woman?

Q9: What does the man do while he's lying next to the woman after he rapes her?

Q10: What happens after the man has kicked the woman, at the very end of the video?

**The next set of questions relate to the second scene in the video. Even if you are not sure about the answer, just make your best guess.**

Q11: Where does the fight take place in the second scene?

Q12: How many men are fighting in the beginning of the scene?

Q13: While the two men are fighting, one man falls or is thrown to the ground. What happens next?

Q14: Which arm (left or right) of the man on the floor does the other man break?

Q15: After he breaks the man's arm, what does the attacker do next?

Q16: As he attempts to rape the man on the floor, what is going on in the background?

Q17: What is the man with the fire extinguisher wearing?

Q18: What is the colour of the lighting in the room?

Q19: The camera turns to one of the onlookers at the end of the scene - describe his facial expression.

**On a scale of 0-10, how accurately did you complete the diary?**

**0 - Not at all accurately**

**10 - Extremely accurately**

## 5.5. Verbal instructions for recoding intrusive memories Day 1-7

I will now give you the instructions on what you need to do over the next seven days before you come to the study center again. You'll need to fill in an online diary over the next seven days, including tonight, to record some of your experiences after you leave today. You can do it on your phone but we recommend you do in on your laptop.

It's really important that you understand what we need you to do in terms of recording your experiences in the online diary, and also that you understand what spontaneous, involuntary memories are, which is what we'll be asking you to record. So, let me explain about spontaneous, involuntary memories, which is what we'll be asking you to record.

Over the next week, you will likely experience some spontaneously occurring memories about the film you watched. By 'spontaneous', what we mean is memories of the film that suddenly pop into your mind automatically. We do not mean times when you deliberately think about it or mull it over. The spontaneous memories may pop into your mind when you are doing or thinking about something completely unrelated. Or you may be reminded of the film by things that happen in your environment. The main thing is that you didn't mean to think about the film, but recall something about it, 'out of the blue.'

Spontaneous memories may take the form of 'mental pictures' of the film you saw. They can be visual, but they can also be in any other sensory modality, so you might have memories of the sounds you heard. They can also take a verbal form – that is, words or sentences, statements or questions. Or they could be a mixture of sensory and verbal forms. The key thing is that they should be related to the film and they should occur out of the blue, without you trying to think about them.

In addition, for tomorrow morning only, you will need to complete some additional questions on sleep quality of the night before, which is tonight. This will also be on the app that you are recording intrusive memories on.

You will receive text reminders from us everyday evening, around 8pm, for the next seven days, including today, to remind you to complete the online diary and the questionnaires on sleep quality.

Here is a detailed set of instructions (*write down participant number on the paper instructions, give them to the participant and ask them to use this number to fill in the diary and survey in the next seven days*), please read it carefully. Do you have any questions at this point?

Thank you so much for your time! Would it be okay if we scheduled your appointment next week after seven days, for the same time?

Once again, thank you so much for your time and see you in seven days.

---

## 5.6. Written instructions for recording intrusive memories Day 1-7

**You'll need to fill in an online diary over the next seven days (including in the evening today) to record some of your experiences after you leave today.**

It's really important that you understand what we need you to do in terms of recording your experiences in the online diary. So, let me explain about spontaneous, involuntary memories, which is what we'll be asking you to record.

Over the next week, you will likely experience some spontaneously occurring memories about the film you watched. By 'spontaneous', what we mean is memories of the film that suddenly pop into your mind automatically. We do not mean times when you deliberately think about it or mull it over. The spontaneous memories may pop into your mind when you are doing or thinking about something completely unrelated. Or you may be reminded of the film by things that happen in your environment. The main thing is that you didn't mean to think about the film, but recall something about it, 'out of the blue.'

Spontaneous memories may take the form of 'mental pictures' of the film you saw. They can be visual, but they can also be in any other sensory modality, so you might have memories of the sounds you heard. They can also take a verbal form – that is, words or sentences, statements or questions. Or they could be a mixture of sensory and verbal forms. The key thing is that they should be related to the film and they should occur out of the blue, without you trying to think about them.

**You will be sent a reminder text message at 8pm everyday for the next seven days (including today) to complete the online diary about any memories you might have had on that day related to the video. Try to complete the diary as close as possible to bedtime. To complete the diary, do the following:**

1. Follow the link on the reminder text or email:

[https://uclpsych.eu.qualtrics.com/jfe/form/SV\\_6xuXgWEpplB6VGR](https://uclpsych.eu.qualtrics.com/jfe/form/SV_6xuXgWEpplB6VGR)

2. Once you're on the diary site, you will see this screen:

Mobile/Smart device screen:



Please enter your date of birth  
(DD/MM/YYYY):

---

Participant number:

---

Entry Day (eg. Day 1, Day 2, etc.)

>>

Computer Screen:



Please enter your date of birth (DD/MM/YYYY):

---

Participant number:

---

Entry Day (eg. Day 1, Day 2, etc.)

>>

You will need to provide your DoB and participant number – this is your participant number (give them their card) - so that we can link your responses to the ones you provided today. Then click the “>>” button.

3. You will be taken to the main diary page, which looks like this:

Intrusions diary

	Memory content (briefly describe the content of each spontaneous memory)  Please enter memory content below	Frequency of spontaneous memory  Please enter the number of times the memory occurred below	Type of memory (please tick for each spontaneous memory)			How distressing was the memory? (1 = not at all, 5 = extremely) (if the same memory was experienced more than once, indicate maximum level of distress)					How vivid was the memory? (1 = not at all, 5 = extremely) (if the same memory was experienced more than once, indicate maximum level of vividness)				
			Verbal	Sensory	Both	1	2	3	4	5	1	2	3	4	5
Memory 1	<input type="text"/>	<input type="text"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Memory 2	<input type="text"/>	<input type="text"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Memory 3	<input type="text"/>	<input type="text"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Memory 4	<input type="text"/>	<input type="text"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Memory 5	<input type="text"/>	<input type="text"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

The purpose of this page is to record the unwanted involuntary memories I just mentioned. Before explaining how to fill this out, I'd just want to remind you that the aim of our research is to look at involuntary memories because they seem to be important in many psychological disorders, especially PTSD. So it's also really important that I explain instructions on how to complete the diary as clearly as possible, because if we get bad data it's potentially harmful to the people who we're hoping to help with this research. So please ask me to repeat anything that isn't clear.

OK, so you'll notice that there are several columns.

In the first column, I'd like you to record anything you recall involuntarily about the film you just saw every day for the next 7 days (including today). Record different involuntary memories on different rows. For example, if at the end of the day you recall having a memory in the morning about the men fighting and the same memory again a few minutes later, record that as two separate memories, for example as Memory 1 and memory 2 in these boxes. Just write a brief description of what came to your mind, but be specific (for example, "men fighting" is fine). It might be that in one memory you remember one particular aspect of the men fighting, like the look on one of their faces, whereas the next time you recall what one of the men did to one of the others. It's very helpful for us to know that you had two separate memories in that case. Alternatively, you might have exactly the same memory about the same thing several times in the day, in which case, please record the number of times you had the memory in this second row, with an appropriate brief description. It is common to have multiple occurrences of the same intrusion. We are interested in the number of intrusions you have. If you recall a particular thing several times in the same day, please indicate the number of times you recalled it in the second column on the same row. If you recalled it only once, also indicate this.

The main thing is that you try to be as accurate as possible when you're recording

the memories, both in terms of the number of memories you had, what they were about and how you felt while remembering.

In the third column, please indicate whether the memory was generally verbal (e.g., words, sentences), sensory (e.g., visual, auditory), or both, by selecting the appropriate option.

In the fourth and fifth columns, indicate respectively how distressing and how vivid the memory was for you by selecting the most appropriate number on a scale of 1-5 (1=not at all, 5=extremely). If the same memory was experienced more than once, indicate the maximum level of distress the memory caused.

When you have completed the diary, click the “>>” button.

You may find it useful to set aside a certain time/time(s) near the end of each day to fill in the diary. The end of the day would be good.

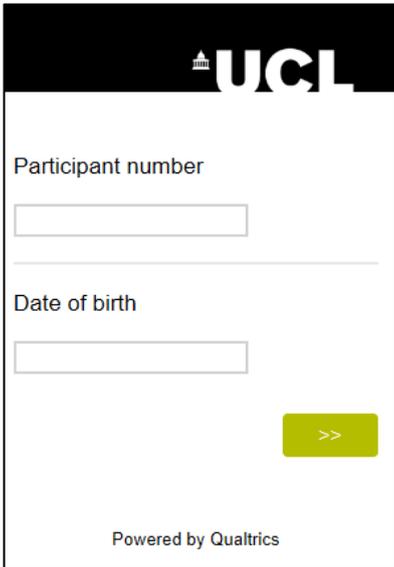
### **Sleep Survey – Instructions**

In addition, for tomorrow only, you will need to complete some additional questions on sleep quality of the night before (i.e. tonight). This will also be on the app that you are recording intrusive memories on.

The link to the survey is as follows:

[https://uclpsych.eu.qualtrics.com/jfe/form/SV\\_1N5z2ikRVNXIWrz](https://uclpsych.eu.qualtrics.com/jfe/form/SV_1N5z2ikRVNXIWrz)

Mobile/Smart Device Screen:



UCL

Participant number

---

Date of birth

>>

Powered by Qualtrics

Computer Screen:

Please enter your date of birth (DD/MM/YYYY):

Participant number:



Powered by Qualtrics

*Should you experience any problems filling in the diary or sleep survey, please contact the researchers at [an.gong.10@ucl.ac.uk](mailto:an.gong.10@ucl.ac.uk).*