The effects of propranolol on intrusive and voluntary memory in an experimental model of psychological trauma

Zhihui Sim

D.Clin.Psy. thesis (Volume 1), 2018

University College London

UCL Doctorate in Clinical Psychology

Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: <u>Zhihui SIM</u>

Date: <u>20 June 2018</u>

OVERVIEW

This thesis examines the effects of propranolol on intrusive and voluntary memory in an experimental model of psychological trauma.

Part 1 systematically reviews research, published between 2007-2017, on post-traumatic disturbed dreaming ('PTDD') and its relationship with post-traumatic stress disorder (PTSD). It shows that recent studies have characterised PTDDs more fully. Findings support and extend existing claims about the relationship between PTDDs and PTSD. However, it also highlights important gaps in the literature, raising questions for future study. The field requires more research which sidesteps the range of methodological pitfalls.

Part 2 reports on a study conducted jointly with another Doctorate in Clinical Psychology trainee. It explored the effects of the beta-blocker propranolol on participants' intrusive memories and voluntary recall of a 'trauma film'. Compared to placebo, propranolol reduced intrusive memories but did not affect voluntary recall. The implications of these results for the Dual Representation Theory (DRT) of episodic memory and for propranolol's use in the secondary prevention of PTSD symptoms are discussed.

Part 3 explores additional conceptual and practical questions encountered in this research. It addresses issues associated with the use of an analogue trauma paradigm, the intrusion diary, and free/cued recall tasks. It then examines further implications of the current findings for research and clinical settings, before concluding with some personal reflections on the research process.

IMPACT STATEMENT

This study takes a step forward in exploring potentially important variables underlying the effects of propranolol on intrusive memories. This paves the way for future research. For instance, the experimental effects of propranolol on intrusive memories in alternative experimental groups and clinical populations can be examined. The factors which affect propranolol's ability to downregulate the expression of intrusive memories (e.g. the timeframe in which propranolol reduces intrusions most effectively and its optimum dosage) can receive further characterisation (e.g. by varying the time point of propranolol administration and its dosage). The effects of propranolol on different types of intrusions and their characteristics can also be elucidated. Moreover, this study underscores the value of doing so in spite of debates surrounding propranolol's effects on post-traumatic stress disorder (PTSD) symptoms as a whole; in fact, it demonstrates the need to consider the impact that any posited intervention for PTSD has on *individual* PTSD symptoms/symptom clusters.

Not only does this study increase the impetus for further clinical research on the specific relationship between propranolol and intrusive memories, it also does so for research on other pharmacological interventions which might likewise ameliorate intrusive memories via similar or related mechanisms (e.g. noradrenaline and amygdala activation). It further catalyses research on the Dual Representation Theory (DRT) and opposing theories, and on psychological treatments based on these – for example, studies aiming to develop components of such treatments and/or assess their therapeutic benefits. Simultaneously, it highlights an exciting new experimental paradigm that can be extended in various ways to probe the structure of/influences on episodic trauma memory and assess the validity of theories in this field. Even more broadly, in combining neuropharmacological and psychological ideas, the study showcases the potential for interdisciplinary

exchange to launch new avenues for enquiry by which evidence in each discipline might be obtained. To maximise the benefits of this study for future research, findings could be disseminated via the online publication of this thesis and articles in relevant academic journals.

Moreover, this study indicates that propranolol can inhibit intrusions with a single dose and with minimal adverse effects, while preserving voluntary memory. This suggests that propranolol can reduce trauma survivors' psychological and emotional distress, while avoiding impairing their ability to voluntarily remember events when needed (e.g. in situations where they may be required to provide legal testimony). In turn, these effects point to propranolol's viability as a treatment for intrusive trauma memories. Pending further research, this paper and related literature can be used to engage with key practitioners and policy-makers on trust- and nation-wide levels, to inform protocols for responding to traumatic events and clinical recommendations for PTSD treatment.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I thank God for his sustenance and provision throughout this entire process.

I would also like to extend my sincerest gratitude to the following people:

- My research supervisors Sunjeev and Val, without whose guidance this thesis would not have been possible;

- An, Adrihani, and Ami, for all the times we toiled together in planning and conducting the empirical study, and for all their help and responses to emergency emails/text messages;

- Wilbur, who proofread my drafts, gave me frank feedback, and remained an immense source of practical and emotional support throughout (particularly when I was at my most stressed); and

- My family and friends, who offered much-appreciated encouragement, company, and food.

PART 1: Literature Review

Post-traumatic disturbed dreaming and its relationship with PTSD: A systematic

review of research from 2007-2017

(9608 words)

Abstract

Aims: There remain major gaps in our understanding of post-traumatic disturbed dreams (PTDDs), yet reviews have not examined the literature systematically. This paper sought to systematically review relevant research studies published from 2007-2017, to determine current knowledge about the characteristics of PTDDs and their relationships with post-traumatic stress disorder (PTSD) and other relevant variables.

Method: PsycInfo, Medline, and EMBASE databases were searched for entries containing terms related to 'dreams', 'nightmares', 'sleep' and 'PTSD'. Searches of reference lists of review papers and using Google Scholar were also conducted. Peer-reviewed papers which were based on primary data, investigated trauma-exposed adults, and gathered information regarding PTSD status/symptoms and at least one characteristic of PTDDs were identified and submitted to a formal quality assessment. 14 studies qualified for inclusion in the review.

Results: Studies characterised PTDDs more fully, both independently and in relation to other types of disturbed dreaming and PTSD re-experiencing symptoms. Findings supported and extended existing claims about the relationship between PTDD and PTSD. They also highlighted PTDD's relationships with comorbid depression, sleep disturbance, and responses to them, as well as other potential influences on PTDD.

Conclusions: This review reinforces challenges to current PTDD theories, which await updating. It also highlights important gaps in the literature, raising important questions for future research. The field requires more investigations which sidestep the range of methodological pitfalls.

<center>**Introduction**</center>

1   Dreaming

A dream can be loosely defined as reportable mental activity that occurs across all sleep stages (Schreuder, Kleijn, & Rooijmans, 2000). Even in *normal* dreams, negative emotions (e.g. anger, fear) and content (e.g. danger/threat, pursuit, harm) occur more frequently than positive ones (e.g. happiness, good fortune; Delaney, 1991; Hall & Van de Castle, 1966). Additionally, Zadra (1996) estimates that 60-75% of adults experience recurrent dreams at some point in their lives, typically during periods of stress or unresolved conflict (Cartwright, 1979).

Within dreams, *dysphoric dreaming* and *nightmares* are sporadically experienced by most adults (Ohayon, Morselli, & Guilleminault, 1997) and are typically non-pathological. However, an estimated 2-8% of the general population are affected by distressing dreams that occur at least weekly. These figures skew higher in childhood to young adulthood, amongst females, and with the presence of psychopathology (e.g. anxiety, psychosis; Levin & Nielsen, 2007). Frequent distressing dreams cause waking distress (Phelps, Forbes, & Creamer, 2008), affect psychological functioning (Lee & Suh, 2016) and physical health (Bixler, Kales, Soldatos, Kales, & Healey, 1979), and are associated with sleep disturbances (Germain & Nielsen, 2003; Ohayon et al., 1997) that negatively impact waking alertness, energy levels, mood and cognition (Curcio, Ferrara, & De Gennaro, 2006; Kirmil-Gray, Eagleston, Gibson, & Thoresen, 1984). However, such dreams have been inconsistently defined across clinical and research settings. Definitions incorporate the following to varying extents: resultant levels of subjective distress (e.g. American Psychiatric Association, 2013; American Academy of Sleep Medicine, 2014), whether the dreamer is awakened (e.g. Zadra & Donderi, 2000), dominant emotions associated with the dream (e.g. Belicki & Cuddy, 1991), and/or

the presence of particular patterns of physiological arousal (Fisher, Byrne, Edwards, & Kahn, 1970).

Levin and Nielsen (2007) suggest a typology of dreaming that considers recent developments and distinctions in research (e.g. more widespread assessment of dream distress, distinctions made between dreams that are associated with awakening and dreams that are not) more comprehensively:

- *Normal* and *dysphoric/bad dreams* are only remembered after awakening at the end of the sleep period, though the latter are associated with greater distress; whereas
- *Nightmares* are frightening dreams from which the dreamer immediately awakens; and
- *Post-traumatic nightmares* comprise content which the dreamer associates with previous traumatic experiences.

However, this classification has not been extensively implemented. Moreover, its underlying assumptions – for instance, that all post-traumatic dreams lead to immediate awakening, and that differences between dream types can be attributed to constructs such as situational stress/conflict and a dispositional tendency towards heightened distress – require further empirical validation. Thus, this review will adopt the following broader terminology: *disturbed dreams* will refer to all dreams which result in distress, and *post-traumatic disturbed dreams* ('PTDDs') to all disturbed dreams whose content the dreamer associates with previous traumatic experiences (where "traumatic events" are those defined as such in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5, p.271; American Psychiatric Association, 2013). This is regardless of dreams' associated phenomenological characteristics (see Introduction, Section 2.2), whether the dreamer awakens immediately, and the dreamer's post-traumatic

stress disorder (PTSD) status. *Nightmares* will refer to disturbed dreams which lead to immediate awakening.

2 PTDDs

2.1 Relationship with PTSD.

The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) and the DSM-5 (American Psychiatric Association, 2013) list PTDDs as a core symptom of PTSD under the intrusion symptom cluster (Criterion B2). The DSM-IV-TR refers to "recurrent distressing dreams *of the [traumatic] event"* (p.463), and the DSM-5 to "recurrent distressing dreams *in which the content and/or affect of the dream are related to the traumatic event(s)*" (p.271). PTDDs are estimated to be the second most common intrusion symptom after waking intrusive memories (Ohayon & Shapiro, 2000). Kilpatrick et al. (1997) reported that 61% of PTSD sufferers across treatment-seeking and community samples had experienced PTDDs in the past 6 months. Leskin, Woodward, Young, and Sheikh (2002) similarly found a 71% point-incidence rate in a U.S.-wide, nationally-representative epidemiological study of PTSD sufferers without comorbid psychopathology. These high prevalence rates hold across a range of traumatic events, such as rape/attempted rape (73%; Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992) and situations encountered in combat (52%; Neylan et al., 1998).

Preliminary evidence suggests that the presence of PTDDs may be associated with more severe concurrent PTSD symptoms (Mellman, David, Bustamante, Torres, & Fins, 2001), and that the trajectory of PTDDs over time parallels that of trauma reactions/PTSD symptoms (Guerrero & Crocq, 1994). The presence of PTDDs may also predict later PTSD symptomatology. For example,

Mellman et al. (2001) found that participants who reported PTDDs following a life-threatening incident were more likely to be diagnosed with PTSD – and have more severe PTSD symptoms – after 6 weeks, compared to those who did not initially report PTDDs. Similarly, Creamer, O'Donnell, and Pattison (2004) found that nightmares of a traumatic event reported several days after the event predicted PTSD status 12 months later.

2.2   Phenomenological characteristics of PTDDs.

Phelps et al. (2008) propose that prototypical PTDDs replicate the traumatic event, recur persistently, and involve cognitive, affective, physiological, and/or behavioural responses which mimic responses to the event that would occur if the individual was awake. However, this description does not adequately capture the complexity of PTDDs.

Firstly, approximately 50% of people who have PTDDs experience *non-replicative* PTDDs, which are related to the traumatic event but do not replay it accurately (Wittmann, Schredl, & Kramer, 2007). Specifically, such PTDDs might distort reality, alter temporal contexts, contain variable degrees of threat, consist of plausible traumatic events that did not occur, or be understood by the dreamer as making symbolic reference to the event (Esposito, Benitez, Barza, & Mellman, 1999; Wilmer, 1996). The DSM-5 PTDD diagnostic criterion (see Introduction, Section 2.1) and dream classifications used by some researchers (e.g. Davis, Pruiksma, Rhudy, & Byrd, 2011; Wilmer, 1996) reflect growing inclusion of such PTDDs in the study and assessment of PTDD phenomena. However, the validity of grouping non-replicative PTDDs with replicative PTDDs remains unclear. Some evidence suggests that replicative PTDDs are more strongly associated with a PTSD diagnosis or more severe PTSD (Mellman, David, Kulick-Bell, Hebding, & Nolan,

1995; van der Kolk, Blitz, Burr, Sherry, & Hartmann, 1984). However, non-replicative PTDDs are also reported by individuals with PTSD (Phelps et al., 2008), while replicative PTDDs are sometimes experienced by individuals who do not have PTSD or do not subsequently develop PTSD (Mellman et al., 2001; Schreuder et al., 2000). The characteristics of replicative and non-replicative PTDDs, and their relationship with PTSD, need to be understood more clearly.

Secondly, while some PTDDs recur persistently, others resolve over time (Hartmann, 1998). While persistence may characterise replicative PTDDs (Schreuder et al., 1998), this has not been prospectively examined in a systematic fashion (Wittmann et al., 2007). Furthermore, there may be phenomenological differences that distinguish persistent and resolving PTDDs from the outset (Phelps et al., 2008), but PTDDs with different trajectories have yet to be fully characterised and compared.

2.3   Potential interactions with other variables.

Variables such as individuals' responses to PTDDs (e.g. fear/avoidance of sleep; Phelps et al., 2008) and psychopathology comorbid with PTSD (e.g. depression; Dow, Kelsoe, & Gillin, 1996) may influence the characteristics of PTDDs, their trajectories over time, and/or their relationship with PTSD. However, these have received little attention in research. Further, chronic PTSD sufferers often experience comorbid sleep disturbances (e.g. REM sleep abnormalities, poor sleep maintenance; Mellman, Nolan, Hebding, Kulick-Bell, & Dominguez, 1997) which can interfere with recovery from PTSD (Babson & Feldner, 2010). PTDDs may reflect or contribute to these sleep disturbances (e.g. via nightmare distress) and feed into the development and/or maintenance of PTSD (Kobayashi, Sledjeski, Spoonster, Fallon, & Delahanty, 2008; Levin & Nielsen, 2007). However,

discrepancies between self-reports and physiological measures of sleep quality in PTSD (Germain, 2013) have not been resolved, and mechanisms which underlie relationships between PTSD and sleep disturbances require further explication (Miller et al., 2017).

2.4   Theoretical accounts of PTDD.

2.4.1   *PTSD models.*

PTSD models propose that traumatic events trigger biological changes that alter the ways in which such events are encoded and stored in memory. For example, trauma memories may comprise unprocessed sensory details and immediate attributions about/responses to the event (Foa & Rothbaum, 1989), or strongly-encoded sensory/affective autonomic information alongside weakly-encoded abstract descriptions (Brewin & Burgess, 2014). When situational cues activate 'fear networks' or trigger involuntary retrieval of sensory representations without accompanying context, intrusive re-experiencing symptoms occur (Brewin, Gregory, Lipton, & Burgess, 2010). Such activation/retrieval processes aid the processing and integration of traumatic material, but inadequate processing (e.g. due to avoidance resulting from a heightened sense of threat) causes recurrent re-experiencing (Ehlers & Clark; 2000; Horowitz, 1976).

PTSD models generally do not differentiate PTDDs from other re-experiencing symptoms and directly apply the above propositions to them (Phelps et al., 2008). Steil and Ehlers (2000) acknowledged potential differences between the mechanisms of waking re-experiencing and PTDDs, but the nature of these differences and the precise featural distinctions between the two have yet to be been elucidated. On one hand, the view of PTDDs as re-experiencing symptoms is supported by the presence of surface similarities between them (e.g. the presence

of sensory content) and correlations between the occurrence of PTDDs and flashbacks (Burstein, 1985). On the other hand, re-experiencing symptoms purportedly involve unprocessed sensory information or weak connections between contextual and sensory representations, but this does not fit easily with the content of non-replicative PTDDs, in which sensory inputs from the original traumatic event are modified by other knowledge (e.g. amalgamation with elements of other events). Alternatively, Esposito et al. (1999) and Schreuder et al. (1998) propose that *replicative* PTDDs specifically be included amongst re-experiencing symptoms. However, even the extent to which replicative PTDDs resemble re-experiencing symptoms remains unclear (e.g. whether they are brief sensory images; whether they consist of sensory/response/meaning information consistent with that experienced during trauma; Ehlers et al., 2002; Foa & Rothbaum, 1989). More research on the characteristics of replicative and non-replicative PTDDs is clearly needed in order to situate them in relation to waking re-experiencing symptoms.

2.4.2   Theories of dreaming.

In contrast to PTSD models, theories of dreaming focus on the hypothesised mechanisms and/or functions of normal dreaming. These are then extended to PTDDs. Distinctions between normal dreaming and PTDDs may be suggested (Phelps et al., 2008).

Payne and Nadel (2004) suggest that dreams reflect the reactivation of memory traces in the hippocampus and neocortex. Reactivation strengthens these traces and integrates them with prior knowledge, facilitating consolidation and learning. This is consistent with PTDDs which resolve over time. Further, the dreamer's waking emotional state or current concerns may drive the activation of salient pieces of information that make up dream content, influencing dream

characteristics/meanings (Newell & Cartwright, 2000). Dreams may thus allow emotionally-salient elements to be integrated with other material, aiding emotional processing and dampening strong affect (Ellman and Weinstein, 1991; Kramer, 1993, 2014). This process is likewise reflected in the resolution of PTDDs over time: from event replay, to images representing dominant emotions about the event, then to images in which dominant emotions are not easily identified (Hartmann, 1998).

Other dreaming theories focus on how failures in typical processes may account for PTDDs which recur persistently. There is little empirical support for these theories, and limited reference to PTSD. Jung (1974) proposed that recurrent replicative PTDDs are failures to translate the 'shock' of traumatic events into symbols that can be integrated into the psyche. Similarly, van der Kolk et al. (1984) posited that recurrent PTDDs may reflect failures to process/integrate emotions about the traumatic event. Crick and Mitchison (1983) further theorised that the brainstem triggers random neurophysiological excitation during REM sleep so that undesirable patterns of neuronal excitation become less likely to occur (i.e. through processes of reverse-learning). Dreams are thought to be by-products of this; recurrent dreams are dreams which cause anxiety and awaken the dreamer, disrupting underlying processes and instead increasing the likelihood of undesirable patterns of excitation being repeated later on.

Early psychoanalytic theorists espoused the notion that normal dreams and recurrent PTDDs are underpinned by different adaptive processes (e.g. Freud, 1900). Normal dreams were thought to enable the gratification of repressed wishes, allowing psychic tension to be discharged and preventing disruptions to sleep and consciousness. Conversely, recurrent PTDDs are primarily influenced by the compulsion to repeat difficult/distressing patterns of behaviour from earlier life, in order to overcome danger and regain control (Freud, 1920/1953; Adams-Silvan & Silvan, 1990). Revonsuo's (2000) threat simulation theory holds that humans'

evolutionary ancestors had a 'threat simulation response' activated by exposure to threat. As part of this, threatening dreams allowed individuals to rehearse threat detection and avoidance, aiding survival. By this view, recurrent PTDDs are an adaptive evolutionary artefact.

Theoretical accounts of PTDD based on theories of dreaming face their own limitations. The evidence for the memory function of dreams is mixed (Frank & Benington, 2006; Siegel, 2001; Vertes, 2004). Additionally, while associations between the presence of dreams and shifts in emotion across sleep and over longer time periods (Cartwright, 1986; Cartwright, Kravitz, Eastman, & Wood, 1991; Kramer, 2014) are broadly compatible with an emotional processing function, they do not prove it directly. Random neuronal excitation in REM sleep cannot explain dreams occurring in other sleep stages (Foulkes, 1990), and contradict observations pointing to the psychological meaning of dreams (e.g. their close relationship with past and present waking concerns; Cartwright, 1990; Domhoff, 2000). Psychoanalytic theories draw on constructs such as 'symbols' and 'compulsions', which are difficult to validate empirically, while empirical support for the predictions of the threat simulation theory is lacking (Esposito et al., 1999; Valli et al., 2005; Valli, Revonsuo, Palkas, & Punamaki, 2006). van der Kolk et al.'s (1984) proposal is consistent with the stress-triggered changes in neurophysiology purported to underlie re-experiencing symptoms, but – as aforementioned – this mechanism does not account for non-replicative PTDDs. Thus, current accounts of PTDD have limited explanatory power overall.

3   Conceptual and Methodological Issues in Existing Research

Conclusions regarding PTDDs and their relationships with other variables are limited by methodological issues – for example, small sample sizes (Wittmann

et al., 2007), and a reliance on delayed retrospective self-report (which is vulnerable to inaccurate recall; Phelps et al., 2008). Laboratory environments also exert ameliorative effects on sleep, perhaps due a sense of safety resulting from the presence of experimenters who are awake. This in turn affects the frequency, content, and affect of PTDDs, challenging the external validity of conclusions derived under laboratory conditions (Foulkes, 1979; Woodward, Arsenault, Murray, & Bliwise, 2000). However, attempts to circumvent this by comparing PTDD sufferers with non-sufferers in the awake state (e.g. via sleep questionnaires) preclude the identification of PTDDs' specific neurophysiological correlates (Phelps et al., 2008). Further, studies have narrowly focused on PTDD frequency, and often neither assess important covariates (e.g. psychological disorders comorbid with PTSD) nor distinguish between different categories of dreams (e.g. replicative, non-replicative; Levin & Nielsen, 2007).

The extent to which findings can be meaningfully compared and consolidated across studies is also constrained by discrepant definitions, ambiguous usage of terminology (e.g. 'distressing', 'related to event'; Phelps, Forbes, Hopwood, & Creamer, 2011), the drawing of samples from a wide range of populations and trauma types, and methodological variation (e.g. in the ways in which retrospective reports are obtained; Wittmann et al., 2007). Additionally, differences between PTSD models and theories of dreaming have led to broader disparities in the foci of research studies (e.g. accuracy of trauma replication in the former, versus latent dream content and affect in the latter; Phelps et al., 2008).

4   Aims of Review

Major gaps in our understanding of PTDDs remain. The phenomenological characteristics (e.g. frequency, intensity, content, affect) and temporal trajectories of

different types of PTDDs (e.g. replicative, non-replicative; persistent, resolving), and their relationships with PTSD and other variables, require further study. This will help to situate different PTDDs in relation to each other and waking re-experiencing symptoms. In turn, this will inform theories of PTDD, dreaming and PTSD, as well as the assessment and treatment of PTDDs and PTSD. Yet, the most recent reviews (e.g. Levin & Nielsen, 2007; Phelps et al., 2008; Wittmann et al., 2007) were conducted 10 years ago and have not systematically examined the literature – for example, they do not completely specify their search strategies and the criteria used to determine study inclusion/exclusion, and do not adequately describe individual studies' characteristics.

This review will seek to address the limitations of previous syntheses by systematically reviewing the literature to address the following questions:

1. What are the phenomenological characteristics of PTDDs?

2. What are the relationships between PTDDs and PTSD (status, severity), as well as other related variables (comorbid psychopathology, sleep disturbance, responses to PTDDs)?

   Theoretical and clinical implications will then be discussed.

   To constrain results to the most recent developments in the field, only studies published in the past 10 years (2007-2017) will be examined.

Method

1   Inclusion and Exclusion Criteria

This review included research studies that:

1. Were published in a peer-reviewed journal between January 2007 and September 2017;

2. Were reported in English;

3. Were based on primary data;

4. Investigated a group which had experienced some specified traumatic event(s) consistent with DSM-5 PTSD Criterion A, and gathered information regarding their PTSD status or symptoms; and

5. Gathered information regarding at least one PTDD characteristic (e.g. frequency, severity, content).

It excluded studies that:

1. Investigated general sleep-related experiences/disturbances without specific measures of dreaming;

2. Were conducted in a psychoanalytic orientation. This was for the sake of parsimony, given its disconnect from other parts of the empirical literature (e.g. broader definitions of what constitutes 'trauma'; Levine, 2014);

3. Investigated PTDDs in children (i.e. <18 years old); or

4. Investigated psychological or pharmacological interventions for PTDD (e.g. Imagery Rehearsal Therapy). Interest in this area has burgeoned in recent years, and the relevant literature has been reviewed elsewhere (e.g. Casement & Swanson, 2012; Nappi, Drummond, & Hall, 2012).

2   Search Strategy

To identify relevant studies, PsycInfo, Medline, and EMBASE databases were searched for entries containing the following terms in their titles or keywords (Table 1). Sleep was used as a search term to ensure that studies that investigated multiple aspects of sleep (including, but not restricted to, dreaming) were identified.

Table 1:

Search terms used in the systematic review

	Terms	Results (summed across databases, including duplicates)
1	dream content/ or dream recall/ or dreaming/	8418
2	dream*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	55840
3	exp NIGHTMARES/	7454
4	nightmar*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	12311
5	sleep/ or nrem sleep/ or rem sleep/	180476
6	1 or 2 or 3 or 4 or 5	237677
7	exp Post-traumatic Stress Disorder/	105280
8	post*traumatic stress disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	100234
9	PTSD.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	76076
10	trauma/ or emotional trauma/ or post-traumatic stress/	436861
11	7 or 8 or 9 or 10	504270
12	6 and 11	6143
13	limit 12 to (full text and peer reviewed journal and human and english language and ("300 adulthood <age 18 yrs and older>" or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs> or 360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 yrs and older>") and yr="2007 -Current")	496

For more comprehensive coverage of the literature, a further search was conducted using Google Scholar using the search terms 'dreams', 'sleep', 'nightmares', and 'PTSD'. Reference lists of relevant review papers were also hand-searched.

Results

Figure 1 outlines the overall search strategy used in this review.

```
┌─────────────────────────────┐      ┌─────────────────────────────────┐
│ Potentially-relevant        │      │ Additional potentially-relevant │
│ references identified via    │      │ references identified via other │
│ database search (N=496)      │      │ sources (i.e. Google Scholar,   │
│                              │      │ hand-search) (N=44)             │
└──────────────┬──────────────┘      └────────────────┬────────────────┘
               │                                      │
               └──────────────┬───────────────────────┘
                              ▼
              ┌──────────────────────────────────────┐
              │ Unique references identified (N=415)  │
              └──────────────┬───────────────────────┘
                             │                    ┌──────────────────────────────────┐
                             ├───────────────────▶│ Irrelevant references excluded    │
                             │                    │ (N=271)                           │
                             ▼                    └──────────────────────────────────┘
       ┌──────────────────────────────────────────────┐
       │ Abstracts/full texts of remaining references   │
       │ retrieved and screened for inclusion and       │
       │ exclusion criteria (N=144)                     │
       └──────────────┬───────────────────────────────┘
                      │                    ┌──────────────────────────────────┐
                      ├───────────────────▶│ References excluded based on       │
                      │                    │ inclusion and exclusion criteria   │
                      │                    │ (N=129; see Appendix 01 for        │
                      │                    │ details)                           │
                      ▼                    └──────────────────────────────────┘
       ┌──────────────────────────────────────┐
       │ References included in a formal quality│
       │ assessment (N=15)                      │
       └──────────────┬───────────────────────┘
                      │                    ┌──────────────────────────────────┐
                      ├───────────────────▶│ References that did not meet the   │
                      │                    │ minimum threshold for inclusion in │
                      │                    │ this review (N=1)                  │
                      ▼                    └──────────────────────────────────┘
       ┌──────────────────────────────────────┐
       │ References included in review (N=14)  │
       └──────────────────────────────────────┘
```

Figure 1. Flow chart outlining the search strategy and number of references identified at each stage (*N*).

The database search identified 496 potential references. An additional 44 were identified via Google Scholar and hand-search. 415 unique references were identified from the resulting pool. 271 references were irrelevant to the topic and excluded. The abstracts/full texts of the 144 remaining references underwent screening to determine if they fulfilled inclusion and exclusion criteria. 15 studies fulfilled these criteria and were included in a formal quality assessment.

1   Quality Assessment

The 15 studies were assessed using the 'QualSyst', a standard assessment tool which allows quantitative and qualitative primary research to be simultaneously appraised (Kmet, Lee, & Cook, 2004). This was determined to be the most appropriate approach given the variety of methodologies employed in included studies. Scores on the QualSyst tool range from 0-1, with higher scores indicating higher research quality. For mixed methods studies, several additional criteria were used to evaluate the overarching design (Pluye, Gagnon, Griffiths, & Johnson-Lafleur, 2009). Further details regarding this scoring system can be found in Appendix 02.

Kmet et al. (2004) stated that minimum thresholds for study inclusion can vary depending on the distribution of scores. A 'liberal' score of 0.55 was adopted as a minimum threshold to provide a comprehensive overview of the literature and allow for practical constraints faced in assessing PTDDs. Of the 15 studies considered for inclusion in this review, 14 studies obtained scores ranging from 0.64-0.95, but the quantitative and qualitative components of Shore, Orton, and Manson's (2009) study obtained scores of 0.50 and 0.10 respectively (Table 2).

Table 2:

Quality ratings of studies appraised using the QualSyst tool

Study	Year	Quality rating		
		Quantitative component	*Qualitative component*	*Mixed methods component*
Davis et al.	2007	0.64	--	--
Davis et al. *based on subset of data from Davis et al., 2007*	2011	0.64	--	--
Habukawa et al.	2007	0.88	--	--
Hinton et al.	2009	0.79	0.70	1.00
King et al.	2013	0.82	--	--
Kobayashi et al.	2008	0.77	--	--
Lazaratou et al.	2008	0.64	--	--
Mellman et al.	2007	0.68	--	--
Phelps et al. *based on subset of data from Phelps et al., 2014*	2011	0.77	--	--
Phelps et al.	2014	0.83	--	--
Picchioni et al.	2010	0.68	--	--
Pigeon et al.	2013	0.95	--	--
Shore et al.	2009	0.50	0.10	0.67
Short et al.	2017	0.64	--	--
Tanev et al.	2017	0.80	--	--

Thus, Shore et al. (2009) was excluded from further analysis. The synthesis presented below is based on the 14 remaining studies.

2 Overview of Studies

2.1 Study designs.

The study designs and sample characteristics of studies reviewed are presented in Table 3.

Table 3:

Study designs and sample characteristics of reviewed studies

Study	Year	Study design	Sample	N	Male (%)	Age (yrs) (Mean, SD / range)	Current PTSD diagnosis (%)	Trauma type	Time since trauma at first assessment
Davis et al.	2007	Cross-sectional	Treatment-seeking civilians with nightmares at least once per week for 3 months	94	21.3	39.9 ± 12.0	55.3	Various (non-veteran)	n.r.
Davis et al. *based on subset of participants from Davis et al., 2007*	2011	Cross-sectional	Treatment-seeking civilians with nightmares at least once per week for 3 months	54 (n=41 with post-traumatic nightmares, post-TNs; n=13 with pre-traumatic nightmares, pre-TNs)	22.2	38.3 ± 12.2	Post-TNs: 58.5; Pre-TNs: 38.5	Various (non-veteran)	n.r.
Habukawa et al.	2007	Cross-sectional with comparison group	Civilians attending a hospital neuropsychiatry department *Comparison group: age- and sex-matched healthy subjects*	20 (n=10 patients; n=10 controls)	50.0	23.9 ± 8.1	Test group: 100.0 Comparison group: 0.0	Various (non-veteran)	15.4 ± 14.1 months
Hinton et al.	2009	Cross-sectional	Cambodian refugees attending a psychiatric outpatient clinic	100	40.0	47.2 ± 6.2	44.0	Combat (non-veteran)	Approx. 30 years
King et al.	2013	Cross-sectional	Military veterans	2341	49.0	35.7 ± 10.0	22.2	Combat	n.r.
Kobayashi et al.	2008	Longitudinal (1 year)	Civilians admitted to Level I trauma centre (i.e. which provides highest level of	314	58.9	37.6 ± 15.0	n.r.	Motor accident	2 weeks

			surgical care to trauma victims)						
Lazaratou et al.	2008	Cross-sectional, retrospective	Civilians	121	58.0	72.2 ± 6.1	n.r.	Natural disaster	50 years
Mellman et al.	2007	Longitudinal (6 weeks)	Civilians with injuries from 'life-threatening incidents' admitted to Level I trauma centres	35	62.9	35.8 ± 11.3	28.6	'Life-threatening incidents'	7 days
Phelps et al. *based on subset of participants from Phelps et al., 2014*	2011	Cross-sectional	Military veterans receiving psychological treatment – all with PTSD and self-reported trauma-related dreams	40	100.0	56.0 ± 9.0	100.0	Primarily combat	31.8 ± 12.8 years
Phelps et al.	2014	Cross-sectional	Military veterans and civilians receiving psychological/psychiatric treatment – all with PTSD and self-reported trauma-related dreams	60	91.7	Veterans: 56.0 ± 9.0 Civilians: 45.8 ± 6.6	100.0	Combat and various (non-veteran)	Veterans: 31.8 ± 12.8 years Civilians: 7.8 ± 8.5 years
Picchioni et al.	2010	Cross-sectional	Military veterans	576	83.0	18-19: 6%, 20-24: 39%, 25-29: 24%, 30-39: 25%, ≥40: 6%	11.1	Combat	3 months
Pigeon et al.	2013	Longitudinal (6 months)	Military veterans in veteran primary care settings with subthreshold/full PTSD and hazardous alcohol use	80	80.0	30.0 ± 7.7	86.3	Combat	33.5 ± 14.8 months
Short et al.	2017	Ecological Momentary Assessment (8 days)	Civilians in community with PTSD	30	38.7	38.0 ± 5.1	100.0	Various (non-veteran)	n.r.
Tanev et al.	2017	Cross-sectional	Treatment-seeking women with PTSD	73	0.0	35.0 ± 11.5	100.0	Rape/physical assault	166 ± 171 months

Thirteen out of 14 studies conducted quantitative analyses, within which Phelps et al. (2011) collated qualitative dream reports in addition to quantitative data though these were not a particular focus of their study. Hinton, Hinton, Pich, Loeum and Pollack (2009)'s study was the only one to adopt a qualitative approach, utilising semi-structured interviews to obtain rich descriptions of participants' beliefs about – and responses to – PTDDs. Ten of the 14 studies were cross-sectional. A further three studies assessed participants over 6 weeks (Mellman, Pigeon, Nowell, & Nolan, 2007), 6 months (Pigeon, Campbell, Possemato, & Ouimette, 2013) and 1 year (Kobayashi et al., 2008) post-trauma. The last study (Short, Allan, Stentz, Portero, & Schmidt, 2017) adopted an Ecological Momentary Assessment (EMA) design, assessing variables multiple times each day over several days.

Only one study prospectively recruited a comparison group (i.e. healthy volunteers; Habukawa, Uchimura, Maeda, Kotorii, & Maeda, 2007). Six other studies grouped participants on a post-hoc basis according to particular characteristics and compared these groups: participants with nightmares that began pre-trauma versus those with PTDDs (Davis et al., 2011), PTSD-positive versus PTSD-negative participants (Davis, Byrd, & Rhudy, 2007; Hinton et al., 2009; Kobayashi et al., 2008), and male versus female participants (King, Street, Gradus, Vogt, & Resick, 2013; Lazaratou et al., 2008). The remaining 7 studies were purely correlative.

2.2   Sample characteristics.

Sample sizes ranged from small (10 patients and 10 controls; Habukawa et al., 2007) to large (2341; King et al., 2013). Davis et al.'s (2011) sample was completely drawn from Davis et al.'s (2007) sample, while Phelps et al.'s (2011) sample formed part of Phelps, Creamer, Hopwood and Forbes' (2014) sample.

Excluding overlaps in participants and Picchioni et al. (2010) – who did not report the mean age of their sample – the mean (±SD) age of participants across studies was 37.8±12.8 years. Participants tended to be in middle age, apart from Habukawa et al.'s (2007) sample of young adults and Lazaratou et al.'s (2008) sample of older adults. Sample characteristics varied widely in other respects. Researchers recruited participants from the community, or from groups seeking or receiving mental health treatment. Eight studies investigated civilian trauma, five studies military combat/wartime experiences, and one study both. Time since trauma exposure varied from days to decades. Five studies required a PTSD diagnosis for inclusion in the sample/test group; PTSD rates in the other studies which recorded PTSD status varied from 11% (Picchioni et al., 2010) to 86% (Pigeon et al., 2013). Ten studies had exclusion criteria related to specified mental health comorbidities (typically psychosis, substance misuse, and suicidality). Only three studies reported comorbidity in samples – these reported moderate depression and anxiety (Phelps et al., 2011; Phelps et al., 2014; Short et al., 2017) and "problematic" alcohol use (Phelps et al., 2011; p.856; Phelps et al., 2014; p.3).

3   Main Findings

This section will consider the definitions and classifications of PTDDs adopted by studies. It will then examine findings related to the phenomenological characteristics of PTDDs, and relationships between PTDDs and PTSD/other variables.

3.1   Definitions and classifications of PTDDs.

Table 4 shows how PTDDs were defined, assessed, and classified in studies reviewed.

Table 4:

Definitions and assessment of PTDDs

Study	Year	Definition of PTDDs	PTDD assessment	PTDD prevalence (% of sample)	PTDD-related variables reported				
					Frequency	Intensity (i.e. distress related to dream)	Severity	Content, affect	Physiological arousal
Davis et al.	2007	'Dreams with negative emotions that wake you up' (referred to as 'nightmares')	Trauma Related Nightmare Survey (TRNS)	100% ([1]see footnote for breakdown by category)	Y	Y	--	Y	Y
Davis et al. *based on subset of participants from Davis et al., 2007*	2011	'Dreams with negative emotions that wake you up' (referred to as 'nightmares')	Trauma Related Nightmare Survey (TRNS)	100% ([2]see footnote for breakdown by category)	Y	Y	--	Y	Y
Habukawa et al.	2007	'Recurrent distressing dreams of the [traumatic] event' (referred to as 'nightmares')	Clinician Administered PTSD Scale (CAPS) – dreams item	80%	--	--	Y	--	--
Hinton et al.	2009	'Recurrent distressing dreams about the trauma'	Structured Clinical Interview for DSM-IV (SCID) – dreams item Semi-structured interview	100% ([3]see footnote for breakdown by category)	Y	--	--	Y	Y
King et al.	2013	'Repeated, disturbing dreams of a stressful military experience'	PTSD Checklist: Military Version (PCL-M) – dreams item	n.r.	--	--	Y	--	--
Kobayashi et al.	2008	Primary definition: 'Recurrent nightmares about… traumatic		15.9% at 2 weeks 18.7% at 3 months	--	--	Y (continuous scores on	--	--

Author	Year	Definition	Measure	Prevalence					
		event(s)'						IES-R, or dichotomized to assess presence of PTDDs on the other measures)	
		'Dreams about [the traumatic event]'	Baseline: Impact of Events Scale-Revised (IES-R) – dreams item						
		'Bad dreams/nightmares about the trauma'	2 weeks: Acute Stress Disorder Interview (ASDI) – dreams item						
		'Memories or nightmares of a traumatic experience'	3 months, 1 year: Pittsburgh Sleep Quality Index-Addendum (PSQI-A) – post-traumatic dreams item						
Lazaratou et al.	2008	'Recurring dreams pertaining to the catastrophic event'	Self-developed questionnaire – dreams item	60%	--	--	Y (presence of PTDDs only)	--	--
Mellman et al.	2007	'Recurrent distressing dreams of the [traumatic] event'	CAPS – dreams item	n.r.	--	--	Y	--	--
Phelps et al. *based on subset of participants from Phelps et al., 2014*	2011	'Recurrent distressing dreams of the [traumatic] event'	Structured interview (including self-developed questionnaire) Nightmare Distress Questionnaire (NDQ)	≥45% meeting DSM-IV post-traumatic dream criterion ([5]see footnote for breakdown by category)	Y	Y	--	Y	Y
Phelps et al.	2014	'Recurrent distressing dreams of the [traumatic] event'	Structured interview (including self-developed questionnaire) Nightmare Distress Questionnaire (NDQ)	n.r.	--	--	--	--	--
Picchioni et al.	2010	'Repeated, disturbing dreams of a stressful military experience'	PCL-M – dreams item	n.r.	--	--	Y	--	--
Pigeon et al.	2013	'Repeated, disturbing dreams of a stressful military experience'	PCL-M – dreams item	n.r.	--	--	Y	--	--

Short et al.	2017	No primary definition		n.r.	--	--	Y	--	--
		'Nightmares and disturbing dreams'	Disturbing Dream and Nightmare Severity Index (DDNSI)						
		'Memories or nightmares of a traumatic experience'	PSQI-A – post-traumatic dreams item						
Tanev et al.	2017	'Recurrent distressing dreams of the [traumatic] event'	CAPS – dreams item	n.r.	--	--	Y	--	--

[1] Davis et al. (2007): Participants' most frequent nightmares were 20.5% replicative, 50% trauma-similar, 29.5% trauma-dissimilar

[2] Davis et al. (2011): Participants' most frequent nightmares were: (Post-TN group) 33% replicative, 39% trauma-similar, 28% trauma-dissimilar; (Pre-TN group) 0% replicative, 33% trauma-similar, 67% trauma-dissimilar

[3] Hinton et al. (2009): Participants' most recent nightmares were: 30% total-reliving, 35% theme-reliving, 35% abstract-theme-reliving

[4] Kobayashi et al. (2008): continuous scores (IES-R), or dichotomized to assess presence of PTDDs (ASDI, PSQI-A)

[5] Phelps et al. (2011): Participants' most distressing/typical dreams – 45% replay, 30% mixed replay/non-replay, 25% non-replay

Definitions of PTDDs were consistent in the majority of studies. Seven studies defined and assessed PTDDs using relevant items from structured interviews (Clinician Administered PTSD Scale; CAPS; Structured Clinical Interview for DSM-IV; SCID) or the PTSD Checklist (PCL) self-report scale. These and two further studies referred to "recurrent"/"repeated", "distressing"/"disturbing" dreams of the traumatic event, in line with the DSM-IV PTDD criterion. Of the five remaining studies, one did not specify a primary definition of PTDDs, two added the requirement that PTDDs awaken the dreamer, two excluded the requirement that PTDDs were "recurrent", and one excluded the requirement that PTDDs caused "distress".

Four studies classified PTDDs further (Davis et al., 2007; Davis et al., 2011; Hinton et al., 2009; Phelps et al., 2011). Classifications generally converged on 3 categories: replicative PTDDs (which accurately replayed scenes from the initial traumatic event), trauma-similar PTDDs (which combined elements of the initial traumatic event with others that did not occur), and trauma-dissimilar PTDDs (which did not explicitly include any elements of the initial traumatic event). While Hinton et al. (2009) used the theory-laden labels "theme-reliving" and "abstract-theme-reliving" for the latter two categories, the allocation of PTDDs to categories was likely equivalent in practice.

3.2 Phenomenological characteristics.

3.2.1 Frequency.

Five studies examined the frequency of PTDDs (Table 4). Estimates ranged from a mean (±SD) of 1.4±1.7 (i.e. PTDDs among PTSD-positive Cambodian refugees receiving psychiatric treatment; Hinton et al., 2009) to 2.9±1.7 PTDDs per week (i.e. post-traumatic nightmares among PTSD-positive and PTSD-negative

trauma-exposed individuals seeking nightmare-specific treatment; Davis et al., 2011). When post-traumatic nightmares and nightmares which began pre-trauma were considered all together, frequency estimates were even higher (4.0±3.8 per week; Davis et al., 2007), and Davis et al. (2011) noted that the difference between the frequencies of the two nightmare types was not significant. Davis et al. (2007) also found that replicative and trauma-similar nightmares occurred more frequently than trauma-dissimilar nightmares, but it is not known if this would still hold true if post-traumatic nightmares had been examined separately from nightmares that began pre-trauma.

Still, the finding that mixed PTSD-positive/PTSD-negative samples can experience more frequent PTDDs than a PTSD-positive sample, and that non-post-traumatic nightmares can occur as frequently as post-traumatic ones, indicates that frequent disturbed dreams are not specific to PTSD. This corroborates prior research on the occurrence of pathological disturbed dreaming in mixed and clinical populations (e.g. Levin & Nielsen, 2007), and underlines the point that frequency estimates obtained in studies might reflect the more general frequency of disturbed dreaming in clinical populations rather than PTDDs specifically.

Phelps et al. (2011) found that changes in PTDD frequency over time varied across individuals. 32.5% of the sample reported retrospectively that PTDD frequency had remained constant, 30% that it had increased, and 32.5% that it had decreased (the remaining participants were unable to say how PTDD frequency had changed over time). Participants attributed changes in frequency to the fluctuating course of PTSD and changes in alcohol use or medication. This requires more rigorous investigation (e.g. longitudinal behavioural monitoring) given potential biases in retrospective report, but is consistent with other research showing that alcohol and benzodiazepines suppress REM sleep and thus decrease the frequency

of dreams (e.g. Feige et al., 2006; Pagel & Parnes, 2001). This highlights the importance of considering alcohol and medication use in PTDD research.

3.2.2 Intensity.

Three studies (Davis et al., 2007; Davis et al., 2011; Phelps et al., 2011) examined PTDD intensity (i.e. how "disturbing" or "distressing" individuals found the experience of a PTDD to be; Blake et al., 1995). On 5-point Likert scales ranging from 0 ("not at all disturbing") to 4 ("extremely disturbing"), scores in Davis et al. (2011) averaged (±SD) 3.1±0.8 ("very disturbing"), while 90% of Phelps et al.'s (2011) sample rated PTDDs from 3-4 ("quite a bit" to "extremely disturbing"). This relatively high level of subjective disturbance builds on earlier literature showing that disturbed dreaming is a source of distress independent of co-occurring psychopathology (Phelps et al., 2008).

Post-traumatic nightmares did not differ significantly in intensity from nightmares that began pre-trauma (Davis et al., 2011; average score of 3.0±0.8 across entire sample; Davis et al., 2007). The intensities of replicative, trauma-similar, and trauma-dissimilar PTDDs were likewise equivalent (Davis et al., 2007; Phelps et al., 2011). This suggests that PTDD intensity is not related to the presence of traumatic content and the extent to which traumatic content is replayed – in turn raising questions about the factors that do contribute to PTDD intensity. Phelps et al. (2011) also examined changes in intensity over time: 57.5% of participants reported no change, while 27.5% reported decreases and 15% increases. Changes were again attributed to alcohol use or medication.

3.2.3 *Severity.*

Ten studies investigated PTDD severity (i.e. the overall disturbance experienced by an individual due to PTDDs experienced). Three studies did so by summing frequency and intensity scores on the CAPS PTDD item (range: 0-8). Habukawa et al. (2007) did not report descriptive statistics for this measure, but Mellman et al. (2007) and Tanev et al. (2017) found mean (±SD) scores of 3.1±2.7 and 5.4 (SD not reported) respectively amongst PTSD-positive participants. In comparison, PTSD-negative participants in Mellman et al. (2007) reported a mean score of 1.2±2.4; Tanev et al. (2017) did not recruit any PTSD-negative participants. Three other studies (King et al., 2013; Picchioni et al., 2010; Pigeon et al., 2013) used single-item scores on the PCL to measure PTDD severity (range: 1-5; "not at all bothered" to "extremely bothered [by PTDDs]" in the past month). Mean scores ranged from 1.7±1.0 ("moderately bothered"; Picchioni et al., 2010) to 3.0±1.3 ("quite a bit bothered"; Pigeon et al., 2013). On the Disturbing Dream and Nightmare Severity Index (DDNSI) self-report questionnaire, Short et al. (2017) found a mean score of 18.6±8.1 (range: 0-37), above the clinical cut-off for a chronic nightmare disorder (Krakow et al., 2002). Differences between studies are difficult to interpret given variation in sample characteristics and measures used (e.g. questionnaires with multiple items investigating different aspects of PTDDs might be more sensitive to small differences in severity, compared to single items investigating PTDDs more generally).

Kobayashi et al. (2008) assessed the presence of PTDDs via dichotomised responses to single items on the Acute Stress Disorder Interview (ASDI; a structured interview) and the Pittsburgh Sleep Quality Index-Addendum (PSQI-A; a self-report questionnaire) at 2 weeks (ASDI), 3 months (PSQI-A) and 1 year (PSQI-A) post-trauma. The presence of PTDDs at earlier time points significantly predicted their presence at later time points, though associations weakened as time passed.

This suggests some continuity in the experience of PTDDs over time. However, differences between measures used raise questions about the validity of comparisons. For example, the ASDI measures only PTDDs, while the PSQI-A measures PTDDs together with "memories" of traumatic events, which could potentially occur before sleep. Further, the persistence of PTDDs over time does not preclude changes in more specific characteristics (e.g. frequency, content).

Two studies investigated sex differences in PTDD severity. King et al. (2013) found that male veterans experienced significantly more severe PTDD than female veterans who reported equivalent overall PTSD severity. However, this difference was small, and analyses did not control for other systematic differences between genders (e.g. age, amount of combat exposure, specific trauma type). The generalisability of findings to civilians is also questionable given that individuals who pursue military professions may constitute a biased sample of the population. In contrast, Lazaratou et al. (2008) found that, compared to men, a significantly larger proportion of women in their sample of earthquake victims reported recurring dreams about the earthquake in the 6 months immediately after trauma exposure. However, PTDDs were assessed using an unvalidated self-developed questionnaire, which inquired about the presence of PTDDs over the 6-month period with a single item. Additionally, as assessment took place 50 years after trauma exposure, self-reports may have been coloured by secondary appraisals and inaccurate recall. These factors may have affected the accuracy and sensitivity of PTDD assessment, reducing conclusions' validity.

3.2.4   Content and affect.

3.2.4.1   Distribution across categories (replicative, trauma-similar, trauma-dissimilar).

Four studies analysed the distribution of index PTDDs (i.e. one representative PTDD per participant, selected on the basis of some study-specific criterion) across replicative, trauma-similar, and trauma-dissimilar PTDD categories. Inconsistent results were found. In Davis et al. (2007), 50% of participants' "most frequent" nightmares were trauma-similar; 29.5% were trauma-dissimilar and 20.5% replicative. However, when Davis et al. (2011) examined participants' most frequent *post-traumatic* nightmares only, these were distributed more evenly across categories (33% replicative, 39% trauma-similar, 28% trauma-dissimilar). This pattern was echoed in Hinton et al. (2009; 30% total-reliving, 35% theme-reliving, 35% abstract-theme-reliving), though the criterion for selection of index PTDDs was not described. In contrast, in Phelps et al. (2011), participants' "most distressing/typical" PTDD was most commonly replicative (45%), followed by trauma-similar (30%) and trauma-dissimilar (25%). The selection of index PTDDs based on different criteria potentially contributed to differences in results; nonetheless, PTSD incidence in Davis et al. (2011; 58.5%) and Hinton et al. (2009; 44%) differed considerably from that in Phelps et al. (2011; 100%), which suggests that replicative PTDDs might be more strongly associated with PTSD status (consistent with past research, e.g. Mellman et al., 2001).

3.2.4.2   Changes in content over time.

Participants' index PTDDs recurred with the same content since trauma exposure, regardless of whether they were replicative, trauma-similar, or trauma-dissimilar (Phelps et al., 2011) – contradicting Hartmann's (1998) description of changes in PTDD content over time. This could be due to discrepancies in PTSD rates between samples (especially as Hartmann did not report this), and/or a specific link between recurring PTDDs and more severe PTSD profiles as per those seen in Phelps et al. (2011; e.g. chronicity of PTSD and treatment-seeking status).

Nevertheless, this at minimum suggests that persistent PTDDs are likely to recur repeatedly with unchanged content, and that more severe PTSD is associated with persistent unchanged PTDDs. It also challenges Schreuder et al.'s (1998) proposal that replicative PTDDs are more likely than non-replicative PTDDs to persist unchanged.

Notably, however, when Phelps et al. (2011) considered the entire sample of PTDDs (i.e. including non-index PTDDs), while 67.5% of participants still reported that the extent to which PTDDs replicated the traumatic event had not changed over time, 25% and 7.5% reported that they had become less or more replicative respectively. Participants attributed these changes to changes in PTSD, alcohol use, and medication. This suggests greater variation in the trajectories of PTDDs than the study of index PTDDs alone would suggest. In addition, the finding that index PTDDs did not change over time despite the influences identified suggests that index and non-index PTDDs may be differentially susceptible to such factors.

3.2.4.3 Other features of content/affect, comparisons with re-experiencing symptoms.

Qualitative dream reports gathered by Phelps et al. (2011) showed that, like re-experiencing symptoms, index PTDDs across replicative, trauma-similar, and trauma-dissimilar categories were "rich in sensory detail" (p.858), were associated with physiological reactivity and behavioural responses, and involved a sense of lack of control. Unlike re-experiencing symptoms, however, they typically comprised "lengthy and elaborate" (p.857) narratives of the actual event or the individual's worst fears about what could have happened. Similar to re-experiencing symptoms, more than 75% of PTDDs were associated with the same emotions participants had felt during the actual traumatic events. The remaining participants experienced

emotions that might have been suppressed during the event (e.g. feeling numb during the event, then despairing or guilty in the PTDD) or generated by subsequent appraisals (e.g. feeling fear during the event, then anger in the PTDD), though a few PTDDs did not fit these interpretations. Fear was the emotion most commonly experienced in index PTDDs, across and within categories. Other emotions (i.e. helplessness, despair, horror, guilt, anger) were also experienced, though less commonly.

Overall, replicative, trauma-similar, and trauma-dissimilar PTDDs were highly comparable in content, phenomenological features, and affect. While they were similar to re-experiencing symptoms, the narratives of PTDDs were more complex, and in the minority of cases involved affective states that were less consistent with those experienced at the point of the event.

3.2.5   *Physiological arousal.*

Four studies examined physiological arousal associated with PTDDs. In Phelps et al. (2011), participants reported experiencing "strong physical sensations" (e.g. increased heartrate, sweating) "moderately" to "quite a bit" during PTDDs. Greater physiological arousal was associated with PTDDs leading to immediate awakening (which occurred in 87.5% of the sample "some" to "all" of the time). Hinton et al. (2009) further found that all participants experienced panic symptoms upon awakening from their most recent PTDD. This suggests that (i) most PTDDs are associated with physiological arousal that is sufficient to cause awakening and that might continue immediately post-awakening, and that (ii) higher physiological arousal distinguishes PTDDs that cause immediate awakening from those that do not. The severity of panic symptoms experienced post-awakening did not differ across post-traumatic nightmares and nightmares that began pre-trauma (Davis et

al., 2011), but were more severe in PTSD-positive individuals (Davis et al., 2007). This suggests that high arousal is not specific to PTDDs, but also that PTSD symptoms contribute to arousal associated with PTDDs.

Tanev et al. (2017) recorded participants' psychophysiological responses to loud tones during waking hours and found that only heart rate responses (HRR) and CAPS PTDD severity scores were significantly positively correlated (r = 0.40). This relationship remained significant even when individual PTSD symptoms, intrusion symptoms, and PTSD symptoms as a whole were each controlled for (all partial r ≥ 0.33). HRR reflects the opposite influences of sympathetic and parasympathetic nervous system activity (Orr, Lasko, Shalev, & Pitman, 1995), while the other psychophysiological responses measured in this study (e.g. skin conductance) primarily reflect sympathetic nervous system activity. Thus, these findings suggest that reduced parasympathetic tone may contribute to PTDDs.

3.3   Associations between PTDDs and other variables.

The variables that each study investigated, the ways in which these were assessed and studies' main findings are presented in Table 5.

Table 5:

Assessment of PTSD and other relevant variables

Study	Year	Main findings	Assessment				
			PTSD status	PTSD severity	Comorbidities	Sleep	Responses
Davis et al.	2007	-Significant differences between PTSD+ and PTSD- groups in various PTDD variables and PTDD categories, depression symptoms, sleep, physiological arousal -Significant differences between PTDD categories on PTSD symptoms, depression symptoms, sleep -PTDD variables predict sleep variables	Y Structured Clinical Interview for DSM-IV (SCID), CAPS	Y Modified PTSD Symptom Scale: Self-Report (MPSS-SR)	Y Beck Depression Inventory-II (BDI-II)	Y Pittsburgh Sleep Quality Index (PSQI)	Y TRNS
Davis et al. *based on subset of participants from Davis et al., 2007*	2011	-Significant differences between post-TN and pre-TN groups in PTSD symptoms, depression symptoms	Y* CAPS	Y MPSS-SR	Y BDI-II	Y PSQI	--
Habukawa et al.	2007	-Presence of PTDDs significantly correlated with % of REM interruptions, wake time after sleep onset, sleep latency	Y* SCID, CAPS	Y* CAPS	--	Y Polysomnography	--
Hinton et al.	2009	-Presence of PTDDs associated with PTSD diagnosis -Presence of PTDDs associated with psychological distress, physiological arousal, sleep difficulties -Beliefs about PTDDs intensify distress	Y SCID	Y* CAPS flashback severity scale	--	--	Y Semi-structured interview
King et al.	2013	-Significant differences between men and women in frequency of PTDDs reported, but small difference overall	Y* PCL-M	Y* PCL-M	--	--	--
Kobayashi et al.	2008	-Significant mediation effects of PTSD symptoms and concurrent	--	Y	Y	Y	--

		PTDDs in the relationship between earlier PTDDs and sleep disturbance at earlier, but not later, timepoints		CAPS	SCID (depression diagnosis)	PSQI	
Lazaratou et al.	2008	--	--	Y* Self-developed questionnaire	--	--	--
Mellman et al.	2007	-PTDD severity at baseline predicts subsequent PTSD status -PTDD severity at baseline associated with relative REM beta electroencephalogram (EEG) power	Y CAPS	Y* CAPS	Y* SCID (diagnosis)	Y Polysomnography	--
Phelps et al. *based on subset of participants from Phelps et al., 2014*	2011	-No significant differences in PTSD severity between PTDD categories -Significant differences between levels of physiological arousal of those whose PTDDs led to immediate awakening and those whose PTDDs did not	Y* CAPS	Y CAPS	Y* BDI-II, Beck Anxiety Inventory (BAI), Alcohol Use Disorders Identification Test (AUDIT)	Y* PSQI, PSQI-A	--
Phelps et al.	2014	-Significant positive correlations between the following and PTSD severity: PTDD intensity, whether PTDDs were 'acted out', strong physical sensations in PTDDs, inability to relax after waking, various responses to PTDDs -Variance in PTSD severity contributed significantly to by: 'acting out' the dream, difficulty putting dreams out of mind on waking, fear of falling asleep, avoiding/disliking someone because they were in the dream (alongside sleep-related variables). -Reponses to PTDDs and inability to relax accounted for >50% of variance in PTSD severity	Y* CAPS	Y CAPS	Y* BDI-II, BAI, AUDIT	Y* PSQI, PSQI-A	Y NDQ
Picchioni et al.	2010	-PTDD severity fully mediates the relationship between combat stressors and PTSD status, and partially mediates the relationship between combat stressors and PTSD symptoms -Insomnia and PTDD severity combined fully mediates the relationship between combat stressors and depression symptoms	Y PCL-M	Y PCL-M	Y Patient Health Questionnaire (PHQ) – depression subscale	Y* Insomnia Severity Index (ISI)	--
Pigeon et al.	2013	-Significant differences between those who had PTDDs and those who did not, on: baseline PTSD symptom severity, baseline depression severity, 6-month PTSD status and PTSD symptom severity -No significant differences between PTDD categories in baseline	Y CAPS	Y PCL-M	Y Center for Epidemiological Studies-Depression (CES-D), AUDIT	Y* ISI	--

		alcohol use					
Short et al.	2017	-Daily PTDDs significantly predicted by baseline fear of sleep, daily PTSD symptoms -Daily PTDDs significantly associated with poorer daily sleep efficiency	Y* SCID	Y PCL-5	Y BDI-II, BAI, SCID, 1-2 items from State-Trait Anxiety Inventory (STAI)	Y ISI, PSQI	Y Fear of Sleep Inventory (FOSI)
Tanev et al.	2017	--	Y* CAPS	Y* CAPS	Y* BDI-II	--	--

Note. * Variable was measured but was not included in analyses related to PTDDs.

3.3.1 *PTSD status.*

Five studies examined the relationship between PTSD status and aspects of PTDDs. Cross-sectionally, PTSD status was significantly related to the presence and frequency of PTDDs (Davis et al., 2007; Hinton et al., 2009), consistent with past research demonstrating an association between PTSD status and PTDD prevalence (Ohayon & Shapiro, 2000). Further, Picchioni et al. (2010) showed that the relationship between combat stressors and PTSD status in a veteran sample was fully mediated by PTDD severity. However, PTSD status was not associated with PTDD intensity (Davis et al., 2007). In Davis et al. (2007), PTSD-positive individuals' index nightmares were mostly replicative (32.7%) or trauma-similar (51.9%), whereas PTSD-negative individuals' index nightmares were mostly trauma-similar (47.2%) or trauma-dissimilar (50.0%). This difference may simply reflect the higher proportion of trauma-similar/replicative nightmares amongst post-traumatic nightmares compared to nightmares that began pre-trauma, yet other tentative findings also point to the conclusion that PTSD-positive individuals are more likely than PTSD-negative individuals to experience PTDDs which replicate the traumatic event to a greater extent (see Results, Section 3.2.4.1). The relationship between PTDD categories and PTSD status requires further investigation.

Longitudinal studies also found that PTDD severity significantly predicted subsequent PTSD status. Participants who were diagnosed with PTSD 6 weeks post-trauma were retrospectively found to have had more severe PTDDs at baseline (Mellman et al., 2007). Likewise, a larger proportion of participants whom Pigeon et al. (2013) classified as experiencing more severe PTDDs at baseline were diagnosed with PTSD 6 months later (41%), compared to those classified as experiencing less severe PTDDs (9.7%).

Some analyses did not consider potential confounding factors. For instance, Picchioni et al.'s (2010) mediation model did not take sleep disturbances and reciprocal effects into account, while Mellman et al. (2007) did not adjust for baseline PTSD symptom severity and depression status (which was also significantly associated with PTSD status). Nevertheless, the relationship between PTSD status and PTDD presence, frequency, and severity generally held across different samples and methodologies.

3.3.2 *PTSD severity.*

Excluding PTDD symptoms, three studies showed that PTSD severity was significantly positively associated with the presence (Kobayashi et al., 2008), intensity (Phelps et al., 2011), and severity (Pigeon et al., 2013) of concurrent PTDDs. Three other studies added to these conclusions. Davis et al. (2011) found that individuals with post-traumatic nightmares and those with nightmares that began pre-trauma differed significantly in PTSD severity. Picchioni et al. (2010) showed that PTDD severity partially mediated the association between concurrent combat stress and PTSD severity, and had the second-largest effect on this relationship amongst all PTSD symptoms. Short et al. (2017) further demonstrated the relationship between PTDD severity and PTSD severity on a narrower timescale – nightly PTDD severity was predicted by waking PTSD symptoms in the previous day when baseline PTSD severity was controlled for.

Two studies investigated PTDDs and PTSD severity over time. PTDD severity and PTSD severity followed downward trajectories of similar magnitude (26% and 18% respectively) over 6 months (Pigeon et al., 2013). Comparatively, the change in insomnia severity over the same period was much smaller, suggesting a stronger association between PTSD severity and PTDDs relative to the relationship

between PTSD severity and general sleep disturbance. Moreover, the presence/severity of PTDDs significantly predicted PTSD severity at later time points – the presence of PTDDs 2 weeks and 3 months post-trauma respectively predicted PTSD severity 6 weeks and 1 year post-trauma (Kobayashi et al., 2008), and more severe PTDD at baseline also predicted more severe PTSD 6 months later (Pigeon et al., 2013). Associations between earlier PTSD severity and the later presence of PTDDs were also noted (Kobayashi et al., 2008).

Overall, convergent evidence from a range of samples and methodologies supports the presence of a close association, and potential bidirectional influences, between PTSD severity and the presence and severity of PTDD. Further, both Kobayashi et al. (2008) and Pigeon et al. (2013) controlled for potential confounds in analyses (e.g. medication use, severity of depression and alcohol use), reducing the likelihood that observed associations were spurious.

Three other studies examined cross-sectional relationships between PTSD severity and other aspects of PTDDs. Two studies (Davis et al., 2007; Phelps et al., 2011) compared participants with replicative, trauma-similar and trauma-dissimilar index PTDDs on PTSD severity. Findings were inconsistent. Davis et al. (2007) found that participants with replicative nightmares had the most severe PTSD, which decreased stepwise across categories. In contrast, Phelps et al. (2011) found no significant differences between categories. However, Davis et al.'s (2007) results may merely have reflected differences between post-traumatic nightmares and nightmares that began pre-trauma. Thus, on balance, Phelps et al.'s (2011) finding is likely more valid.

Additionally, Phelps et al. (2014) found that PTSD severity was significantly positively correlated with particular phenomenological features of PTDDs (i.e. behavioural enactment of the PTDD, strong physical sensations), arousal (i.e. difficulties relaxing after awakening), and responses to PTDDs (i.e. fear of sleep,

difficulties shifting attention away from PTDDs on awakening, avoiding/disliking others because they had appeared in the PTDD, or thinking that the PTDD seemed real). Among these, PTDD enactment, difficulties relaxing after awakening, fear of sleep, difficulties shifting attention away from PTDDs on awakening, and avoiding/disliking others because they had appeared in the PTDD also contributed significantly to variance in PTSD severity.

3.3.3   Comorbid psychopathology.

The main comorbidity examined in reviewed studies was depression. Five studies consistently demonstrated a cross-sectional relationship between depression and PTDDs. Depression status and the concurrent presence of PTDDs were significantly positively associated (Kobayashi et al., 2008). Likewise, depression severity and PTDD severity were positively correlated (Pigeon et al., 2013); PTDD severity mediated the relationship between combat stress and depression severity (Picchioni et al., 2010). Relative to nightmares that began pre-trauma, post-traumatic nightmares were associated with more severe depression (Davis et al., 2011). These findings suggest a specific relationship between depression and PTDDs. In terms of PTDD categories, replicative nightmares were associated with more severe depression compared to trauma-similar and trauma-dissimilar nightmares (Davis et al., 2007), but this might again reflect the aforementioned relationship between depression and PTDDs.

Evidence regarding the longitudinal relationship between depression and PTDDs was less clear. Kobayashi et al. (2008) found that depression status 6 weeks post-trauma predicted the later presence of PTDDs at 3 months and 1 year post-trauma, but Short et al. (2017) noted that baseline depression severity was not associated with nightly PTDD severity. It is difficult to compare findings due to

differences in quantities and time scales of measurement – nevertheless, it might be that depression predicts the general presence of PTDDs, while day-to-day fluctuations in PTDD severity are more strongly associated with other factors closer in time. Conversely, baseline PTDD severity did not predict depression severity 6 months later (Pigeon et al., 2013), suggesting that PTDDs did not contribute significantly to later depression symptoms. However, post-traumatic nightmares were associated with more severe depression symptoms upon awakening compared to nightmares that began pre-trauma (Davis et al., 2011), pointing to PTDDs' immediate effects on mood.

Only two studies assessed other comorbidities using validated measures. No significant associations were found between PTDDs and baseline/daily anxiety levels (Short et al., 2017), and between PTDDs and alcohol use (Pigeon et al., 2013). Nonetheless, further research is warranted given the small number of studies.

3.3.4   Sleep disturbance.

Five studies assessed the relationship between self-reported sleep quality and PTDDs. Post-traumatic, replicative, and more frequent nightmares were all associated with poorer concurrent overall sleep quality (Davis et al., 2007; 2011). Similarly, studies assessing specific aspects of sleep quality found that the presence of PTDDs was associated with concurrent sleep maintenance and onset problems (Hinton et al., 2009; Kobayashi et al., 2008), and more severe PTDD was associated with poorer sleep efficiency on the same night (Short et al., 2017). These findings were corroborated by two polysomnographic studies: self-reported PTDD severity was significantly positively correlated with the percentage of REM interruptions experienced during sleep and wake time after sleep onset (Habukawa

et al., 2007), and significantly negatively correlated with sleep latency (Habukawa et al., 2007) and relative REM beta electroencephalogram (EEG) power (Mellman et al., 2007).

Kobayashi et al. (2008) found that the cross-sectional and longitudinal relationships between PTDDs and sleep disturbance changed over time. At 3 months, the presence of PTDDs was associated with concurrent sleep onset and sleep maintenance problems; however, at 1 year, the presence of PTDDs was only associated with concurrent sleep onset problems. Additionally, closer in time to trauma exposure, PTDDs' presence and severity were associated with subsequent sleep onset and maintenance problems via intermediate PTSD severity and PTDDs concurrent to the sleep problems. In contrast, later in the year, the presence of PTDDs was directly associated with subsequent sleep maintenance problems. These findings suggest that mechanisms underpinning the relationship between PTDDs and sleep disturbance may shift over time. For example, the influence of PTSD and PTDDs themselves on sleep may decline over time, even as individuals' responses to PTDDs (e.g. fear of sleep) contribute increasingly to/maintain sleep disturbance. Further investigation is needed to determine PTDDs' trajectories more precisely and pursue explanations for changes observed.

3.3.5 Responses to PTDDs.

Three studies investigated the cross-sectional relationship between PTDDs and fear of sleep. Fear of sleep was positively-correlated with nightmare frequency (Davis et al., 2007) and nightly PTDD severity (Short et al., 2017). These findings were corroborated by several qualitative reports that individuals did not go back to bed after awakening from PTDDs because they were afraid of experiencing another PTDD (Hinton et al., 2009).

Hinton et al. (2009) found that, in the context of Cambodian cultural beliefs, some participants believed that PTDDs were real experiences of their souls, during which they might meet the souls of perpetrators/vengeful ghosts and be attacked by supernatural beings. Events occurring within PTDDs could thus imply real danger, increasing dreamers' sense of threat. This suggests that waking cognitive appraisals of PTDDs, informed by wider cultural contexts, may heighten distress associated with PTDDs. Additionally, participants in Hinton et al. (2009) frequently experienced flashbacks to related events upon awakening from PTDDs. Cultural beliefs, cognitive appraisals and waking re-experiencing secondary to PTDDs were not investigated in the other reviewed studies, but demand further research given their potential contributions to dreamers' experience of PTDDs and/or overall distress.

Discussion

1   Summary of Main Findings

PTDDs have been more fully characterised within and across replicative, trauma-similar, and trauma-dissimilar categories. PTDDs which persisted did so with unchanged content, and there was some indication of a general tendency for the presence, frequency, intensity, and content of PTDDs to remain largely constant over time. PTDDs from different categories had similar phenomenological features and affect, resulted in similar high levels of subjective distress, and were associated with physiological arousal and frequent immediate awakening. Thus, overall, despite differences between PTDDs categories in the extent to which they replicate traumatic events (and potentially their frequency; Davis et al., 2007), the relatively limited dissimilarity between PTDD categories suggests that existing category labels

are primarily descriptive (in terms of dream content) and do not necessarily correspond to symptoms with different underlying aetiology or maintenance factors.

At the same time, variations within PTDDs were evident. Estimates of PTDD frequency and severity varied across studies; replicative, trauma-similar, and trauma-dissimilar PTDDs varied in the extents to which they replicated traumatic events. While these findings highlight the complexity of PTDDs, they also underscore differences in sample characteristics and research methodologies. In addition, characteristics such as high frequency, intensity, and physiological arousal were found to apply more generally to disturbed dreaming. The non-specificity of these characteristics is consistent with the proposed existence of broader psychopathological/distress factors that drive aspects of disturbed dreaming in general (e.g. dispositional 'affect distress' and situational 'affect load'; Levin and Nielsen, 2007).

On the whole, PTDDs demonstrated considerable similarity with re-experiencing symptoms. They differed mainly in narrative complexity, the extent to which trauma-similar and trauma-dissimilar PTDDs replicated the traumatic event, and the minority of cases in which PTDDs' associated affect differed from that experienced during the traumatic event. These differences highlight the need to update/extend current PTDD theories (e.g. to account for the more complex narratives of PTDDs within PTSD models).

PTSD status/severity were associated with the presence, frequency, intensity and severity of PTDDs, other phenomenological features of PTDDs, and PTDD-related arousal. Longitudinally, PTDD severity predicted subsequent PTSD status, and bidirectional influences between PTSD severity and the presence/severity of PTDDs were indicated. Overall, these findings support and extend claims regarding the relationship between PTSD and PTDDs, and again

raise questions for current PTDD theories (e.g. to explain how PTDDs contribute to PTSD).

Depression status/severity were associated with the presence and severity of concurrent PTDDs, and depression may influence later PTDDs. Poorer concurrent sleep quality was consistently associated with the presence, frequency, and severity of PTDDs; however, this relationship changed over time, perhaps pointing to varying effects of PTDDs on sleep quality. Studies also pointed to the influences which drug/alcohol use, medication, cultural beliefs, and cognitive appraisals may exert on the experience/characteristics of PTDDs.

2   Strengths and Limitations of Studies

Definitions of PTDDs and classifications used by studies reviewed (i.e. replicative, trauma-similar, trauma-dissimilar) were more consistent than those used in research preceding 2007. Studies that diverged from the majority definition generally specified components that were excluded/included. Most studies used measures with well-established validity and reliability (e.g. PTSD status determined via CAPS, the 'gold standard' of PTSD diagnosis). These factors all aided comparisons between studies.

However, this review also highlighted some important gaps in the literature. For instance, despite increased interest in the relationship between abnormal sleep architecture and PTSD (e.g. Lobo et al., 2015; Moran et al., 2017), there was a dearth of studies investigating the *specific* neurophysiological correlates of PTDDs during sleep (i.e. recording EEG as PTDDs occurred). Studies rarely gathered qualitative data, restricting the depth to which PTDDs could be explored and understood in the context of participants' individual experiences. Longitudinal study designs were not often adopted. When they were, follow-up periods varied but did

not extend beyond a year post-trauma. Inconsistent assessment of variables across time points also prevented PTDDs' temporal trajectories from being clearly delineated. Studies seldom recruited comparison groups (e.g. trauma-exposed participants with PTSD but without PTDDs, or trauma-exposed participants without PTSD but with PTDDs), while comparisons between groups defined post-hoc may have introduced experimenter bias, especially if researchers were not blinded to trends in the data.

Studies varied substantially in sample characteristics (e.g. trauma type, treatment status, PTSD status), which supported the generalisability of results where these were consistent across studies but made reasons for inconsistent findings more difficult to ascertain. Further, researchers did not consistently report certain important sample characteristics (e.g. comorbid psychopathology). Methodologically, a general reliance on self-report measures to uncover relationships (e.g. between PTDD and depression) was not ideal given the tendency for such measures to correlate statistically with one another (e.g. due to participants' response biases across measures). Delays in retrospective reporting and the use of single questionnaire items may also have compromised accurate, sensitive measurement. These issues underline the importance of using independent convergent measures (e.g. polysomnography), as well as more immediate and comprehensive self-report measures (e.g. full questionnaires, dream reports completed immediately after waking).

3 Implications for Research and Clinical Practice

More research (e.g. regarding PTDDs' phenomenological characteristics) is needed to confirm and expand on findings from this review. Specific aspects of PTDDs also bear additional exploration – for example, their neurophysiological

correlates, trajectories over time, and secondary effects on re-experiencing and mood post-awakening. In addition, mechanisms underlying PTDDs' relationships with PTSD status/severity, comorbid depression, and sleep disturbance, as well as factors that potentially influence PTDDs but have not been investigated in depth (e.g. alcohol/medication, anxiety, cultural beliefs, cognitive appraisals), await further exploration. Three-way interactions between PTDDs, PTSD and other variables could be mapped. Deeper inroads into these research areas would facilitate attempts to ameliorate PTSD and PTDDs.

The following methodological recommendations would likely enhance the quality of further research in this field. Prospective, longitudinal studies would aid conclusions about how PTDDs and their relationships with other variables develop over time. The collection and analysis of qualitative data (e.g. dream reports) would not only enable a richer understanding of the content of PTDDs, but also allow researchers to code characteristics such as PTDDs' similarity to the traumatic event (e.g. by comparing dream reports to descriptions of the traumatic event), decreasing reliance on participants' self-report. When investigating PTDDs, individual categories of PTDDs (replicative, trauma-similar, trauma-dissimilar) and index/non-index PTDDs each warrant independent examination given the differences between them highlighted by this review. Factors such as alcohol and medication use should also be considered given their potential influence on PTDDs. In addition, to increase the validity and reliability of measurement, studies should use convergent methods alongside self-report (e.g. clinician ratings, physiological measures). For example, participants could be awakened at specific points during the sleep cycle for questioning about pre-awakening dream mentation. PTDDs should also be assessed as close in time to their occurrence as possible.

To facilitate cross-study comparisons, studies should continue to use consistent definitions and validated measures of PTSD/PTDDs (e.g. structured

interviews such as CAPS). They should gather and report sample characteristics such as comorbid psychopathology. As resources permit, studies should also recruit samples with a wider range of trauma and participant characteristics, then conduct analyses in and across narrower sub-groups. This would increase the extent to which findings can be compared, whilst ensuring that study findings are applicable within and across populations.

Finally, this review informs the assessment and treatment of PTDDs in clinical settings. It has implications for the ways in which the DSM-5 PTDD criterion (i.e. "recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event[s]") is interpreted. Distress caused by trauma-dissimilar PTDDs is equivalent to that caused by replicative PTDDs, suggesting that a dream may be classified as a PTDD even if its contents do not obviously replicate aspects of the traumatic event. Clinicians should be alert to the possibility that such dreams are nonetheless a potential trauma-related symptom. Further, "recurrent" dreams generally involve unchanged repetition of the same content. Findings also suggest that affect "related to" the traumatic event is typically equivalent to that experienced during the traumatic event. Of course, minority exceptions to the rule (e.g. non-index PTDDs whose contents change over time, PTDDs associated with inconsistent affect) also need to be acknowledged.

In addition, strong associations between PTDDs and PTSD over time emphasise the need to assess for the presence, characteristics, and severity of PTDDs in the context of known PTSD (and vice versa) throughout PTSD/PTDD treatment. Evidence that trauma-similar and trauma-dissimilar PTDDs can be as distressing and persistent as replicative PTDDs underscores the value of targeted assessment/treatment of these. This review also highlights other factors that might influence the experience and characteristics of PTDDs (e.g. alcohol/medication, responses to PTDDs), for consideration during assessment.

4   Conclusion

Recent studies characterise PTDDs more fully. They also support and extend existing claims about PTDDs' relationships with PTSD, depression, and sleep disturbance. Findings reinforce challenges to current PTDD theories, which await updating. However, there are also important gaps in the literature, pointing to potential avenues for further research. Overall – as is often the case with systematic reviews – more questions have been raised than answered, and the field requires more investigations which sidestep the range of methodological pitfalls.

References

Adams-Silvan, A., & Silvan, M. (1990). 'A dream is the fulfilment of a wish': Traumatic dream, repetition compulsion, and the pleasure principle. *International Journal of Psycho-Analysis*, *71*, 513-522.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR.* Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

American Academy of Sleep Medicine. (2014). International classification of sleep disorders (3rd ed.). Darien, IL: American Academy of Sleep Medicine.

Babson, K.A., & Feldner, M.T. (2010). Temporal relations between sleep problems and both traumatic event exposure and PTSD: A critical review of the empirical Literature. *Journal of Anxiety Disorders*, *24*(1), 1-15.

Belicki, K., & Cuddy, M.A. (1991). Nightmares: Facts, fictions and future directions. In J. Gackenbach & A.A. Sheikh (Eds.), *Dream images: A call to mental arms* (pp. 99-115). Amityville, NY: Baywood.

Bixler, E.O., Kales, A., Soldatos, C.R., Kales, J.D., & Healey, S. (1979). Prevalence of sleep disorders in the Los Angeles metropolitan area. *The American Journal of Psychiatry*, *136*, 1257-1262.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., & Keane, T.M. (1995). The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress*, *8*, 75-90.

Brewin, C.R., & Burgess, N. (2014). Contextualisation in the revised dual representation theory of PTSD: A response to Pearson and colleagues. *Journal of Behavior Therapy and Experimental Psychiatry*, *45*, 217-219.

Brewin, C.R., Gregory, J.D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. *Psychological Review*, *117*(1), 210-232.

Burstein, A. (1985). Post-traumatic flashbacks, dream disturbances, and mental imagery. *The Journal of Clinical Psychiatry, 46*(9), 374-378.

Cartwright, R. (1979). The nature and function of repetitive dreams: a speculation. *Psychiatry*, *42*, 131-137.

Cartwright, R. (1986). Affect and dream work from an information processing point of view. *The Journal of Mind and Behaviour*, *7*(2,3), 411-428.

Cartwright, R. (1990). A network model of dreams. In R.R. Bootzin, J.F. Kihlstrom, & D.L. Schacter (Eds.), *Sleep and cognition* (pp.179-189). Washington, DC: American Psychological Association.

Cartwright, R.D., Kravitz, H.M., Eastman, C.I., & Wood, E. (1991). REM latency and the recovery from depression: Getting over divorce. *American Journal of Psychiatry*, *148*(11), 1530-1535.

Casement, M.D., & Swanson, L.M. (2012). A meta-analysis of imagery rehearsal for post-trauma nightmares: Effects on nightmare frequency, sleep quality, and post-traumatic stress. *Clinical Psychology Review*, *32*(6), 566-574.

Creamer, M., O'Donnell, M.L., & Pattison, P. (2004). The relationship between acute stress disorder and post-traumatic stress disorder in severely injured trauma survivors. *Behaviour Research and Therapy*, *42*, 315-328.

Crick, F., & Mitchison, G. (1983). The function of dream sleep. *Nature*, *304*(14), 111-114.

Curcio, G., Ferrara, M., & De Gennaro, L. (2006). Sleep loss, learning capacity and academic performance. *Sleep Medicine Reviews*, *10*(5), 323-337.

*Davis, J.L., Byrd, P., & Rhudy, J.L. (2007). Characteristics of chronic nightmares in a trauma-exposed treatment-seeking sample. *Dreaming*, *17*(4), 187-198.

*Davis, J.L., Pruiksma, K.E., Rhudy, J.L., & Byrd, P. (2011). A comparison of lifelong and posttrauma nightmares in a civilian trauma sample: Nightmare characteristics, psychopathology, and treatment outcome. *Dreaming*, *21*(1), 70-80.

Delaney, G. (1991). *Breakthrough dreaming.* New York, NY: Bantam Books.

Domhoff, G. W. (2000). The repetition principle in dreams: is it a possible clue to a function of dreams? In M. K. R. H. A. Moffit (Ed.), *The Functions of Dreaming* (pp. 293-320). Albany: SUNY Press.

Dow, B.M., Kelsoe, J.R., & Gillin, J.C. (1996). Sleep and dreams in Vietnam PTSD and depression. *Biological Psychiatry*, *39*(1), 42-50.

Ehlers, A., & Clark, D. M. (2000). A cognitive model of post-traumatic stress disorder. *Behaviour Research and Therapy*, *38*(4), 319-345.

Ehlers, A., Hackmann, A., Steil, R., Clohessy, S., Wenninger, K., & Winter, H. (2002). The nature of intrusive memories after trauma: The warning signal hypothesis. *Behaviour Research and Therapy*, *40*(9), 995-1002.

Ellman, S.J., & Weinstein, L.N. (1991). REM sleep and dream formation: A theoretical integration. In S. J. Ellman & J. S. Antrobus (Eds.), *Wiley series on personality processes. The mind in sleep: Psychology and psychophysiology* (pp.466-488). Oxford, England: John Wiley.

Esposito, K., Benitez, A., Barza, L., & Mellman, T. (1999). Evaluation of dream content in combat-related PTSD. *Journal of Traumatic Stress*, *12*(4), 681-687.

Feige, B., Gann, H., Brueck, R., Hornyak, M., Litsch, S., Hohagen, F., & Riemann, D. (2006). Effects of alcohol on polysomnographically recorded sleep in healthy subjects. *Alcoholism, Clinical and Experimental Research*, *30*(9), 1527-1537.

Fisher, C., Byrne, J., Edwards, A., & Kahn, E. (1970). A psychophysiological study of nightmares. *Journal of the American Psychoanalytic Association*, *18*, 747-782.

Foa, E.B., & Rothbaum, B.O. (1989). Behavioural psychotherapy for post-traumatic stress disorder. *International Review of Psychiatry*, *1*(3), 219-226.

Foulkes, D. (1979). Home and laboratory dreams: Four empirical studies and a conceptual re-evaluation. *Sleep*, *2*, 233-251.

Foulkes, D. (1990). Dreaming and consciousness. *European Journal of Cognitive Psychology*, *2*(1), 39-55.

Frank, M.G., & Benington, J.H. (2006). The role of sleep in memory consolidation and brain plasticity: Dream or reality? *The Neuroscientist*, *12*, 477-488.

Freud, S. (1900). The interpretation of dreams. In J. Strachey (Ed.), *The Standard Edition of the Complete Psychological Works of Sigmund Freud, Vol. 4 & 5*. London: Hogarth Press.

Freud, S. (1920/1953). Beyond the pleasure principle. In J. Strachey (Ed.), *The standard edition of the complete psychological works of Sigmund Freud*, vol. 18 (pp. 7-66). London, England: Hogarth Press.

Germain, A. (2013). Sleep disturbances as the hallmark of PTSD: Where are we now? *American Journal of Psychiatry*, *170*(4), 372-382.

Germain, A., & Nielsen, T.A. (2003). Sleep pathophysiology in post-traumatic stress disorder and idiopathic nightmare sufferers. *Biological Psychiatry*, *54*(10), 1092-1098.

Guerrero, J., & Crocq, M. A. (1994). Sleep disorders in the elderly: Depression and post-traumatic stress disorder. *Journal of Psychosomatic Research*, *38*(Suppl. 1), 141-150.

*Habukawa, M., Uchimura, N., Maeda, M., Kotorii, N., & Maeda, H. (2007). Sleep findings in young adult patients with post-traumatic stress disorder. *Biological Psychiatry*, *62*, 1179-1182.

Hall, C., & Van de Castle, R. (1966). *The content analysis of dreams.* New York, NY: Appleton-Century-Crofts.

Hartmann, E. (1998). Nightmare after trauma as paradigm for all dreams: A new approach to the nature and function of dreaming. *Psychiatry, Interpersonal and biological processes*, *61*(3), 223-228.

*Hinton, D.E., Hinton, A.L., Pich, V., Loeum, J.R., & Pollack, M.H. (2009). Nightmares among Cambodian refugees: The breaching of concentric ontological security. *Culture, Medicine, and Psychiatry*, *33*, 219-265.

Horowitz, M.J. (1976). *Stress response syndromes.* Oxford, England: Jason

    Aronson.

Jung, C. (1974). *Dreams.* Princeton, NJ: Princeton University Press.

Kilpatrick, D.G., Resnick, H.S., Freedy, J.R., Pelcovitz, D., Resick, P., Roth, S., &

    van der Kolk, B. (1997). Post-traumatic stress disorder field trial: Evaluation

    of the PTSD construct – Criteria A through E. In T.A. Widiger & A.J. Frances

    (Eds.), *DSM-IV Sourcebook* (pp. 803-844). Washington: American

    Psychiatric Press.

*King, M.W., Street, A.E., Gradus, J.L., Vogt, D.S., & Resick, P.A. (2013). Gender

    differences in post-traumatic stress symptoms among OEF/OIF veterans: An

    item response theory analysis. *Journal of Traumatic Stress*, *26*, 175-183.

Kirmil-Gray, K., Eagleston, J.R., Gibson, E., & Thoresen, C.E. (1984). Sleep

    disturbance in adolescents: Sleep quality, sleep habits, beliefs about sleep,

    and daytime functioning. *Journal of Youth and Adolescence*, *13*(5), 375-384.

*Kobayashi, I., Sledjeski, E.M., Spoonster, E., Fallon, W.F., & Delahanty, D.L.

    (2008). Effects of early nightmares on the development of sleep

    disturbances in motor vehicle accident victims. *Journal of Traumatic Stress*,

    21(6), 548-555.

Kmet, L.M., Lee, R.C., & Cook, L.S. (2004). *Standard quality assessment criteria for

    evaluating primary research papers from a variety of fields.* Alberta Heritage

    Foundation for Medical Research.

Krakow, B.J., Melendrez, D.C., Johnston, L.G., Clark, J.O., Santana, E.M., Warner,

    T.D., …Lee, S.A. (2002). Sleep Dynamic Therapy for Cerro Grande Fire

    evacuees with posttraumatic stress symptoms: A preliminary report. *Journal

    of Clinical Psychiatry*, *63*(8), 673-684.

Kramer, M. (1993). The selective mood regulatory function of dreaming: An update and revision. In A. Moffitt, M. Kramer, & R Hoffmann (Eds.), *The functions of dreaming* (pp.419-476). Albany, NY: State University of New York Press.

Kramer, M. (2014). An overview of the dreaming process and the selective affective theory of sleep and dreams. *Psychotherapie Forum*, *19*, 130-137.

*Lazaratou, H., Paparrigopoulos, T., Galanos, G., Psarros, C., Dikeos, D., & Soldatos, C. (2008). The psychological impact of a catastrophic earthquake: A retrospective study 50 years after the event. *The Journal of Nervous and Mental Disease*, *196*(4), 340-344.

Lee, R., & Suh, S. (2016). Nightmare distress as a mediator between nightmare frequency and suicidal ideation. *Dreaming*, *26*(4), 308.

Leskin, G.A., Woodward, S.H., Young, H.E., & Sheikh, J.I. (2002). Effects of comorbid diagnoses on sleep disturbance in PTSD. *Journal of Psychiatric Research*, *36*(6), 449-452.

Levin, R., & Nielsen, T.A. (2007). Disturbed dreaming, post-traumatic stress disorder, and affect distress: A review and neurocognitive model. *Psychological Bulletin*, *133*(3), 482-528.

Levine, H.B. (2014). Psychoanalysis and Trauma. *Psychoanalytic Inquiry*, *34*(3), 214-224.

Lobo, I., Portugal, L.C., Figueira, I., Volchan, E., David, I., Pereira, M.G., & de Oliveira, L. (2015). EEG correlates of the severity of post-traumatic stress symptoms: A systematic review of the dimensional PTSD literature. *Journal of Affective Disorders*, *183*, 210-220.

Mellman, T.A., Nolan, B., Hebding, J., Kulick-Bell, R., & Dominguez, R. (1997). A

    polysomnographic comparison of veterans with combat-related PTSD,

    depressed men, and non-ill controls. *Sleep*, *20*, 46-51.

Mellman, T.A., David, D., Bustamante, V., Torres, J., & Fins, A. (2001). Dreams in

    the acute aftermath of trauma and their relationship to PTSD. *Journal of*

    Traumatic Stress, *14*, 241-247.

Mellman, T.A., David, D., Kulick-Bell, R., Hebding, J., & Nolan, B. (1995). Sleep

    disturbance and its relationship to psychiatric morbidity after hurricane

    Andrew. *American Journal of Psychiatry*, *152*, 1659-1663.

*Mellman, T.A., Pigeon, W.R., Nowell, P.D., & Nolan, B. (2007). Relationships

    between REM sleep findings and PTSD symptoms during the early

    aftermath of trauma. *Journal of Traumatic Stress*, *20*(5), 893-901.

Miller, K.E., Brownlow, J.A., Woodward, S., & Gehrman, P.R. (2017). Sleep and

    dreaming in posttraumatic stress disorder. *Current Psychiatry Reports*,

    19(10), 71. doi:10.1007/s11920-017-0827-1

Moran, J.K., Crombach, A., Elbert, T., Nandi, C., Bambonyé, M., Wienbruch, C., …

    Weierstall, R. (2017). The individual contribution of DSM 5 symptom clusters

    of PTSD, life events, and childhood adversity to frontal oscillatory brain

    asymmetry in a large sample of active combatants. *Biological Psychology*,

    129, 305-313.

Nappi, C.M., Drummond, S.P.A., & Hall, J.M.H. (2012). Treating nightmares and

    insomnia in post-traumatic stress disorder: A review of current evidence.

    Neuropharmacology, *62*(2), 576-585.

Newell, P.T., & Cartwright, R.D. (2000). Affect and cognition in dreams: A critique of the cognitive role in adaptive dream functioning and support for associative models. *Psychiatry*, *63*(1), 34-44.

Neylan, T.C., Marmar, C.R., Metzler, T.J., Weiss, D.S., Zatzick, D.F., Delucchi, K.L., Schoenfeld, F.B. (1998). Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *American Journal of Psychiatry*, *155*, 929-933.

Ohayon, M.M., Morselli, P.L., & Guilleminault, C. (1997). Prevalence of nightmares and their relationship to psychopathology and daytime functioning in insomnia subjects. *Sleep*, *20*(5), 340-348.

Ohayon, M.M., & Shapiro, C.M. (2000). Sleep disturbances and psychiatric disorders associated with post-traumatic stress disorder in the general population. *Comprehensive Psychiatry*, *41*, 469-478.

Orr, S.P., Lasko, N.B., Shalev, A.Y., & Pitman, R.K. (1995). Physiologic responses to loud tones in Vietnam veterans with post-traumatic stress disorder. *Journal of Abnormal Psychology*, *104*, 75-82.

Pagel, J.F., & Parnes, B.L. (2001). Medications for the treatment of sleep disorders: An overview. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(3), 118-125.

Payne, J.D., & Nadel, L. (2004). Sleep, dreams, and memory consolidation: The role of the stress hormone cortisol. *Learning & Memory*, *11*, 671-678.

Phelps, A.J., Forbes, D., & Creamer, M. (2008). Understanding post-traumatic nightmares: An empirical and conceptual review. *Clinical Psychology Review*, *28*, 338-355.

*Phelps, A.J., Forbes, D., Hopwood, M., & Creamer, M. (2011). Trauma-related dreams of Australian veterans with PTSD: Content, affect and phenomenology. *Australian and New Zealand Journal of Psychiatry*, *45*, 853-860.

*Phelps, A.J., Creamer, M., Hopwood, M., & Forbes, D. (2014). Features of post-traumatic dreams related to PTSD severity. *Journal of Traumatic Stress Disorders and Treatment*, *3*(3). doi:10.4172/2324-8947.1000127.

*Picchioni, D., Cabrera, O.A., McGurk, D., Thomas, J.L., Castro, C.A., Balkin, T.J., … Hoge, C.W. (2010). *Military Psychology*, *22*, 340-355.

*Pigeon, W.R., Campbell, C.E., Possemato, K., & Ouimette, P. (2013). Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. *Journal of Psychosomatic Research*, *75*, 546-550.

Pluye, P., Gagnon, M., Griffiths, F., & Johnson-Lafleur, J. (2009). A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in Mixed Studies Reviews. *International Journal of Nursing Studies*, *46*, 529-546.

Revonsuo, A. (2000). The reinterpretation of dreams: An evolutionary hypothesis of the function of dreaming. *Behavioral and Brain Sciences*, *23*, 877-901.

Rothbaum, B.O., Foa, E.B., Riggs, D.S., Murdock, T., & Walsh, W. (1992). A prospective examination of post-traumatic stress disorder in rape victims. *Journal of Traumatic Stress*, *5*, 455-475.

Schreuder, B., Kleijn, W., & Rooijmans, H. (2000). Nocturnal re-experiencing more than forty years after war trauma. *Journal of Traumatic Stress*, *13*(3), 453-463.

Schreuder, B.J., van Egmond, M., Kleijn, W,C., & Visser, A.T. (1998). Daily reports

   of post-traumatic nightmares and anxiety dreams in Dutch war victims.

   Journal of Anxiety Disorders, *12*, 511-524.

Shore, J.H., Orton, H., & Manson, S.M. (2009). Trauma-related nightmares among

   American Indian veterans: Views from the dream catcher. *American Indian*

   and Alaska Native Mental Health Research, *16*(1), 25-38.

*Short, N.A., Allan, N.P., Stentz, L., Portero, A.K., & Schmidt, N.B. (2017).

   Predictors of insomnia symptoms and nightmares among individuals with

   post-traumatic stress disorder: An ecological momentary assessment study.

   Journal of Sleep Research, *27*(1), 64-72.

Siegel, J.M. (2001). The REM sleep-memory consolidation hypothesis. *Science*,

   294(5544), 1058-1063.

Steil, R., & Ehlers, A. (2000). Dysfunctional meaning of post-traumatic intrusions in

   chronic PTSD. *Behaviour Research and Therapy*, *38*(6), 537−558.

*Tanev, K.S., Orr, S.P., Pace-Schott, E.F., Griffin, M., Pitman, R.K., & Resick, P.A.

   (2017). Positive association between nightmares and heart rate response to

   loud tones: Relationship to parasympathetic dysfunction in PTSD

   nightmares. The *Journal of Nervous and Mental Disease*, *205*(4), 308-312.

Valli, K., Revonsuo, A., Palkas, O., Ismail, K., Ali, K., & Punamaki, R. (2005). The

   threat simulation theory of the evolutionary function of dreaming: Evidence

   from dreams of traumatized children. *Consciousness and Cognition*, *14*(1),

   188-218.

Valli, K., Revonsuo, A., Palkas, O., & Punamaki, R. (2006). The effect of trauma and

   dream content: A field study of Palestinian children. *Dreaming*, *16*(2), 63-87.

van der Kolk, B., Blitz, R., Burr, W., Sherry, S., & Hartmann, E. (1984). Nightmares and trauma: A comparison of nightmares after combat with lifelong nightmares in veterans. *American Journal of Psychiatry*, *141*(2), 187-190.

Vertes, R.P. (2004). Memory consolidation in sleep: Dream or reality. *Neuron*, *44*(1), 135-148.

Wilmer, H. A. (1996). The healing nightmare: war dreams of Vietnam veterans. In D. Barrett (Ed.), *Trauma and dreams (pp. 85-99).* Cambridge, MA: Harvard University Press.

Wittmann, L., Schredl, M., & Kramer, M. (2007). Dreaming in post-traumatic stress disorder: A critical review of phenomenology, psychophysiology and treatment. *Psychotherapy and Psychosomatics*, *76*, 25-39.

Woodward, S.H., Arsenault, N.J., Murray, C., & Bliwise, D.L. (2000). Laboratory sleep correlates of nightmare complaint in PTSD inpatients. *Biological Psychiatry*, *48*(11), 1081-1087.

Zadra, A. (1996). Recurrent dreams: their relation to life events. In D. Barrett (Ed.), *Trauma and dreams.* Cambridge, MA: Harvard University Press.

Zadra, A., & Donderi, D.C. (2000). Nightmares and bad dreams: Their prevalence and relationship to well-being. *Journal of Abnormal Psychology*, *109*, 273-281.

PART 2: Empirical Paper

The effects of propranolol on intrusive and voluntary memory in an experimental

model of psychological trauma

(9626 words)

Abstract

Aims: Dual Representation Theory (DRT) proposes that the co-occurrence of intrusive trauma memories and impaired voluntary recall of traumatic events in post-traumatic stress disorder (PTSD) is due to strongly-encoded sensory representations, weakly-encoded contextual representations, and weak connections between the two. Noradrenaline may be specifically involved in the consolidation of sensory representations. Thus, administration of the β-adrenoceptor antagonist propranolol during trauma memory consolidation may decrease intrusive memories while preserving voluntary recall. However, this has not been adequately investigated. This study thus aimed to elucidate the effects of propranolol on intrusive and voluntary trauma memory, to test the veracity of the DRT's predictions and clarify propranolol's therapeutic effects on intrusive memories.

Method: Healthy participants viewed a 'trauma film', then immediately received either an 80mg dose of propranolol or placebo. In the subsequent week, participants recorded film-related intrusive memories daily in an online diary. Voluntary recall of the film was tested a week later via free and cued recall tasks.

Results: Participants who received propranolol had fewer, and less vivid and distressing, intrusive memories compared to controls. Voluntary recall of the film was equivalent across groups. Some memory outcomes were predicted by changes in physiological arousal across the film or treatment.

Conclusions: Results support propranolol's ability to disrupt intrusive memory consolidation, but not voluntary memory consolidation, when administered immediately post-encoding. This dissociation is consistent with the DRT's predictions, and supports the theory. Further research is needed to determine if findings generalise to other experimental groups and clinical populations, so as to confirm the clinical usefulness of propranolol.

Introduction

1   Intrusive Memories in Post-Traumatic Stress Disorder (PTSD)

Post-traumatic stress disorder (PTSD) following exposure to traumatic events (e.g. actual/threatened death, serious injury) is characterised by "recurrent, involuntary, and intrusive distressing memories [of the trauma]" (American Psychiatric Association, 2013, p.271). These memories can be automatically retrieved by cues without "deliberate effort or search" (p.210), and can thus spontaneously intrude on individuals' thoughts (Brewin, 2001).

PTSD sufferers report having between one to four such memories. These are mostly brief, possess prominent sensory qualities (i.e. "images"; Hackmann, 1998, p.301), and elicit physiological reactions and strong emotional responses, invoking the experience of reliving aspects of the traumatic event (Berntsen, 2007; Hackmann, Ehlers, Speckens, & Clark, 2004; Reynolds & Brewin, 1999; van der Kolk & Fisler, 1995). Intrusive memories that invoke reliving (ranging from a transient sense of re-experiencing to a complete loss of connection to the present self and surroundings; Brewin, 2015) are typically referred to as 'flashbacks'. The extents to which intrusive memories lack context, invoke reliving, and result in distress predict subsequent PTSD severity (Michael, Ehlers, Halligan, & Clark, 2005). In particular, intrusive *images* may evoke more intense affect compared to other types of intrusive memories (e.g. verbal intrusions). While visual intrusive images have received the most attention in literature, intrusive images can also occur in other sensory modalities (Brewin, Gregory, Lipton, & Burgess, 2010).

1.1   Dual Representation Theory (DRT).

Theories of PTSD based on the premise that episodic memories are represented in a single system (e.g. Foa & Rothbaum, 1998) suggest that trauma

memories involve atypically-strong connections between stimulus, response, and meaning components of a fear network in the brain. Retrieval cues easily activate the entire network, resulting in the presence and characteristics of intrusive memories. However, such theories encounter difficulties when trying to explain the frequent co-occurrence of intrusive trauma memories and *impaired voluntary recall* of traumatic events in PTSD (Brewin, Dalgleish, & Joseph, 1996; Brewin & Holmes, 2003).

In contrast, Dual Representation Theory (DRT) proposes that all events are encoded in memory as two parallel representations: a sensory representation (S-rep) and a contextual representation (C-rep). S-reps are low-level representations comprising sensory details (supported by cortical and subcortical sensory areas) and internal autonomic representations of affective states experienced during the event (supported by the insula; Brewin & Burgess, 2014). These components are linked via processes in the basolateral complex of the amygdala (LeDoux, 1996; Monfils, Cowansage, Klann, & LeDoux, 2009). By contrast, C-reps are subsets of sensory input recoded into allocentric, abstract structural descriptions, and integrated with the encoding context and other semantic/autobiographical memories (Brewin & Burgess, 2014). Temporal and spatial contextual information in C-reps are supported by the hippocampus and surrounding medial temporal lobe (MTL) structures, while sensory information is supported by parietal sensory association regions (Brewin et al., 2010).

When neutral memories are encoded, S-reps decay quickly and become relatively inaccessible, although temporary egocentric representations can be retrospectively generated from C-reps. The encoding of moderately emotional memories is similar, but involves the formation of more enduring C-reps and S-reps, presumably via upregulation of both amygdala and hippocampal functioning. S-reps and corresponding C-reps are closely associated, such that retrieved events are

usually accompanied by contextual information. This also facilitates top-down

control of retrieval via pre-existing connections between the prefrontal cortex (PFC)

and the MTL (which supports C-reps, as abovementioned).

However, exposure to traumatic events maladaptively upregulates amygdala

functioning and downregulates hippocampal functioning. This results in strongly-

encoded and enduring S-reps alongside weakly-encoded C-reps. The associations

between trauma-related S-reps and their corresponding C-reps are also weak.

Thus, events are retrieved involuntarily in response to situational cues without

appropriate context and re-experienced as if occurring in the present, even as

voluntary retrieval attempts fail. Responses to intrusive memories (e.g.

behavioural/cognitive avoidance) maintain weak C-rep encoding and poor

integration of S-reps and C-reps. Intrusive memories can be reduced by

strengthening associations between S-reps and C-reps, allowing S-reps to

elaborate C-reps, and integrating C-reps with existing autobiographical and

semantic knowledge (e.g. exposure therapy; Brewin et al., 2010).

1.1.1 Support for DRT.

DRT's claims have received some empirical support. For example, Holmes,

Brewin, and Hennessy (2004) and Holmes, James, Kilford, and Deeprose (2010)

instructed participants to complete a visuospatial task, a verbal task, or no task,

either while viewing negatively-valenced film clips ('trauma film') or 30 minutes after

viewing. Compared to no-task controls, those in the visuospatial condition later

experienced fewer intrusive memories of the film, while those in the verbal condition

experienced more intrusive memories. The frequency of intrusive memories was not

related to declarative memory performance. This supports DRT's proposal that

there are two distinct memory systems, and that intrusive memories arise from

strongly-encoded representations in a sensory memory system (which are thus affected by competition for resources from visuospatial tasks; Brewin & Holmes, 2003).

Additionally, DRT's proposed neurological bases for S-reps and C-reps are consistent with existing knowledge about amygdala, hippocampal, and PFC function. The amygdala is crucial in encoding, consolidating, and retrieving memories of emotional events (e.g. enhancement of attentional and elaborative processes; Roozendaal, McEwen, & Chattarji, 2009; van Stegeren et al., 2007; Wolf, 2008). Neuroimaging findings demonstrate its activation during exposure to emotional stimuli across sensory modalities, with activation increasing as arousal increases (Cahill et al., 1996; Phan, Wager, Taylor, & Liberzon, 2002; Zald, 2003). Patients with bilateral amygdala damage show impaired memory for emotional material (Adolphs, Cahill, Schul, & Babinsky, 1997; Cahill, Babinsky, Markowitsch, & McGaugh, 1995). MTL structures, including the hippocampus, are critical for the consolidation of episodic memory (Eichenbaum, 2004; McClelland, McNaughton, & O'Reilly, 1995). The PFC inhibits amygdala function and facilitates control over episodic memory retrieval (Elzinga & Bremner, 2002; Euston, Gruber, & McNaughton, 2012).

DRT's proposed neurological bases are also consistent with knowledge about changes in amygdala and hippocampal function under conditions of extreme stress and in PTSD. In general, amygdala activation increases as stress increases to extreme levels (Elzinga & Bremner, 2002). It is also more responsive to general emotional stimuli and specific trauma reminders in PTSD, with greater activation associated with more severe PTSD symptoms (Shin, Rauch, & Pitman, 2006). In contrast, while hippocampal activity initially increases with stress, this activation subsequently decreases when stress reaches extreme levels (Elzinga & Bremner, 2002; Metcalfe & Jacobs, 1998; Vyas, Mitra, Rao, & Chattarji, 2002). Further, PFC

activation and its responsivity to trauma reminders are blunted at extreme stress levels (Ramos & Arnsten, 2007) and in PTSD (Bremner et al., 1999a; 1999b). Thus, overall, under extreme stress or in PTSD, increased amygdala activation and decreased PFC activation may facilitate the formation of strongly-encoded S-reps, even as decreased hippocampal activation results in weakly-encoded C-reps (Elzinga & Bremner, 2002).

2   A Potential Role for Noradrenaline in Intrusive Trauma Memories

2.1   Noradrenaline.

Noradrenaline (NA) is a catecholamine neuromodulator secreted by the adrenal medulla and released at the ends of sympathetic nerve fibers. It acts as a neurotransmitter in the sympathetic and central nervous systems. The majority of NA neurons in the brain are located in the locus coeruleus in the brainstem and project to a wide network of brain regions, including the amygdala, hippocampus, and neocortex. The NA network modulates sensory, attentional, and memory processes to gather and process information so that meaningful (e.g. threatening) stimuli can be responded to appropriately (Southwick et al., 1999; van Stegeren, 2008).

2.2   The stress response and its effects on moderately emotional memory via NA and the amygdala.

Stress is "a real or anticipated disruption of homeostasis or an anticipated threat to wellbeing" (Ulrich-Lai & Herman, 2009; p.397) of a physical or psychological nature (Joels & Baram, 2009). Upon exposure to stress, neural signals are relayed to the neocortex and limbic system, which modulate

hypothalamic activity. This results in a compensatory stress response in the autonomic nervous system (comprising the sympathetic and parasympathetic nervous systems; SNS and PNS respectively) and hypothalamic-pituitary-adrenal (HPA) axis (a network of descending projections from the paraventricular nucleus of the hypothalamus to the pituitary gland and then to the adrenal cortex; Lovallo, 2016; Wolf, 2008). These influence the actions of various target systems (Joels & Baram, 2009), generating the physiological experience of stress (e.g. increased heart rate, blood pressure) and impacting neurological function (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007).

As part of the stress response, the outputs of sympathetic preganglionic fibers originating in the solitary nucleus activate the adrenal medulla, causing it to secrete NA and adrenaline. These stimulate peripheral β-adrenoceptors on vagal nerve afferents terminating in the solitary nucleus. NA cell groups in turn activate the basolateral amygdala directly or via the locus coeruleus (Roozendaal et al., 2009; van Stegeren et al., 2007; Wolf, 2008). In parallel, the HPA axis mediates the secretion of cortisol from the adrenal cortex, which readily crosses the blood-brain barrier and binds to neuronal glucocorticoid and mineralocorticoid receptors in the basolateral amygdala (Lovallo, 2016). The interaction between NA and cortisol in the basolateral amygdala increases amygdala activity (e.g. Cahill, Prins, Weber, & McGaugh, 1994; Roozendaal, Okuda, van der Zee, & McGaugh, 2006), in turn modulating downstream PFC and hippocampal activity. This concerted activation across brain structures is involved in strengthening the encoding, consolidation and storage of emotional memories (McGaugh, 2004; Roozendaal, Barsegyan, & Lee, 2008), leading moderately stressful/emotionally-arousing experiences to be better-remembered than neutral ones (McIntyre & Roozendaal, 2007; van Stegeren, 2009).

### 2.2.1 Evidence for the involvement of NA in emotional memory via action at the amygdala.

The aforementioned role of NA in emotional memory is supported by converging evidence.

2.2.1.1 Animal models.

In animal models of emotional learning, the infusion of adrenoceptor agonists into the basolateral amygdala during or immediately after training on stress tasks enhances subsequent memory performance (Ferry, Roozendaal, & McGaugh, 1999; Hatfield & McGaugh, 1999; Figure 1A), while amygdala lesions block the consolidation-enhancing effects of NA agonists (Roozendaal et al., 2008). Exposure to stress is also associated with increased NA activity in the PFC in animals (Goldstein, Rasmusson, Bunney, & Roth, 1996).

In contrast, adrenergic antagonists administered in similar timeframes block adrenaline-driven enhancements in memory. For example, Liang, Juler, and McGaugh (1986) found that when propranolol – a β-adrenoceptor antagonist, or 'beta-blocker', typically used to treat anxiety symptoms and cardiac conditions such as hypertension – was applied directly to the amygdalae of rats alongside subcutaneous adrenaline injections, these rats subsequently demonstrated significantly poorer retention compared to control rats that had only received adrenaline (Figure 1B). β-adrenergic blockade is also associated with inhibited long-term potentiation in the animal hippocampus (*in vitro*; Kemp & Manahan-Vaughan, 2008).

(A)   (B)
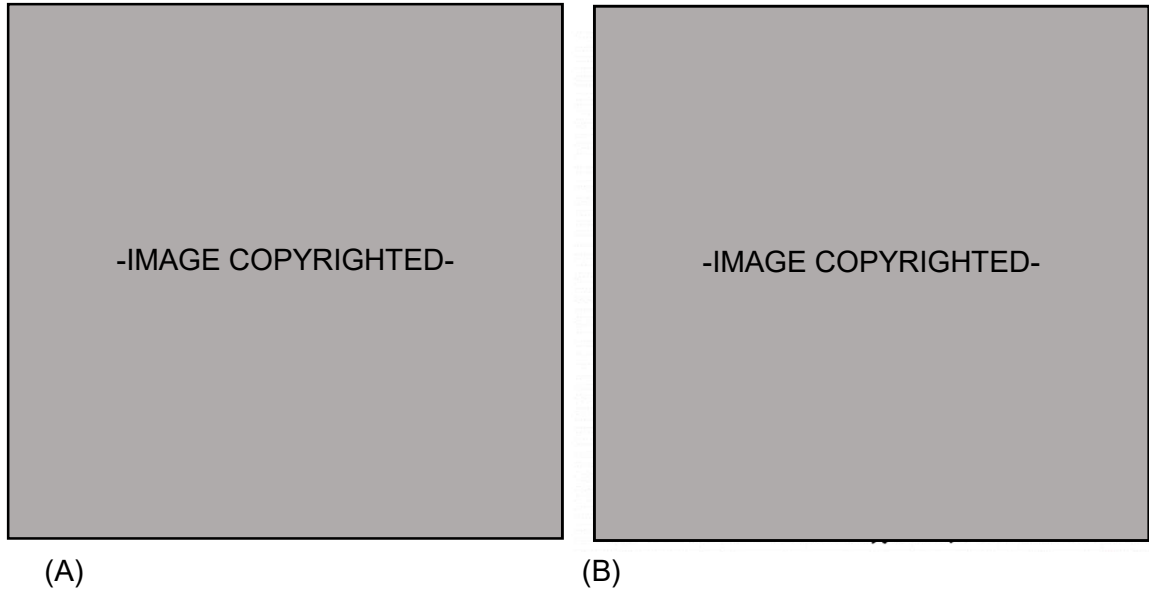
Figure 1. Effects of manipulations of NA activity on emotional memory in animal models.

(A) Rats that received 0.25μg infusions of NA into the basolateral amygdala immediately after training on a hidden platform water maze task showed significantly greater retention 24h later (i.e. required significantly shorter times to locate the platform) compared to controls which received only the vehicle (Hatfield & McGaugh, 1999).

(B) Rats that received 0.2μg infusions of propranolol (Prop.) into the amygdala and subcutaneous injections of adrenaline (epinephrine; Epi.) immediately post-training demonstrated significantly poorer retention 24h later (i.e. avoided a shock compartment for shorter times), compared to controls which received only the vehicle (Veh.) and adrenaline (Liang et al., 1986).

2.2.1.2   Research in humans.

In humans, increased NA activity during memory consolidation (e.g. via stimulation of the vagal nerve; Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006) is associated with superior long-term memory for emotional material (Southwick et al., 2002; Figure 2A). Elevated NA levels also increase hippocampal responsivity to emotional stimuli (Kukolja, Klingmuller, Maier, Fink, & Hurlemann, 2011) and enhance long-term memory consolidation in humans (van Stegeren, 2008). Conversely, the administration of propranolol 60-90 minutes prior to encoding (such that plasma concentrations peak during encoding or immediately after) is associated with blunted amygdala reactivity to emotional stimuli (Hurlemann et al., 2010; Strange & Dolan, 2004; van Stegeren et al., 2005; Figure 2B) and blocks the typically-observed benefits of emotional arousal for memory (Cahill et al., 1994; Figure 2C). These effects likely involve the activation of central β-adrenoceptors (Cahill et al., 1994; Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013; Maheu, Joober, Beaulieu, & Lupien, 2004; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998; see Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006 for review).

(A)

(B)

(C)
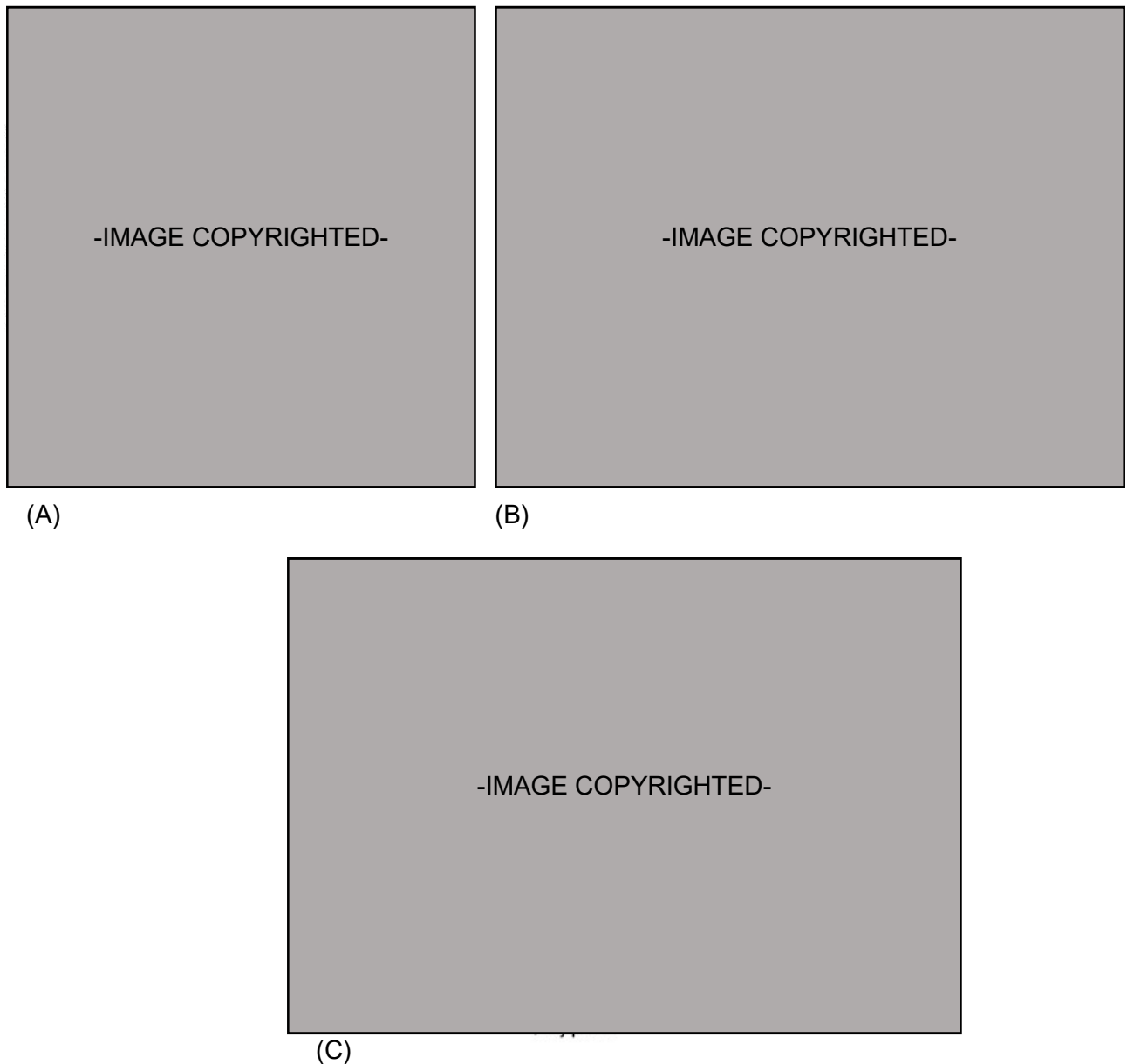
Figure 2. Effects of manipulations of NA activity on emotional memory in humans.

(A) Peak changes in levels of plasma 3-methoxy-4-hydroxyphenylglycol (MHPG; an NA metabolite) within 2h after viewing an emotionally-arousing short story were significantly positively correlated with memory for the story 1 week later across the sample (Southwick et al., 2002).

(B) Participants underwent fMRI scanning as they viewed neutral (CAT1) and emotional (CAT3) pictures.   *(i)* In the placebo condition, amygdala activation was significantly higher when participants viewed CAT3 pictures compared to when they viewed CAT1 pictures.   *(ii)* In the beta-blocker (propranolol) condition, amygdala activation was not significantly different across viewings of CAT1 and CAT3 pictures.   *(iii)* When activation in (ii) was subtracted from activation in (i), the placebo condition demonstrated significantly greater activation in the left amygdala compared to the beta-blocker condition (images are left-right mirrored; van Stegeren et al., 2005).

(C) Participants received a placebo or beta-blocker (propranolol) 1h before viewing a neutral story or a story in which emotional events were introduced midway (i.e. in phase 2). The effect of emotional arousal on memory performance was blocked in the propranolol group (A/BB; arousing story/beta-blocker) compared to the placebo group (A/P; arousing story/placebo; Cahill et al., 1994).

2.3   NA, PTSD, and intrusive trauma memories.

Current evidence supports a broad association between PTSD and NA dysfunction. Relative to non-sufferers, PTSD sufferers show higher levels of central and peripheral NA activity at baseline, and greater NA responsivity to trauma reminders and other affective stimuli (e.g. as measured by increased concentrations of NA or NA metabolites in cerebrospinal fluid/plasma, reduced availability of noradrenaline transporters in the locus coeruleus, and increases in pupil dilation, heart rate and blood pressure; Bailey, Cordell, Sobin, & Neumeister, 2013; Hendrickson & Raskind, 2016; Pervanidou et al., 2007; Southwick et al., 1999). Increases in amygdala activation/responsivity observed in PTSD are also consistent with the known effects of elevated NA on the amygdala (see Introduction, Section 1.1.1).

Other findings suggest that NA activity may have a specific relationship with intrusive trauma memories in PTSD. The severity of intrusive memories experienced by PTSD sufferers is correlated with urinary excretion of NA (Lemieux and Coe, 1995; Yehuda et al., 1992), while intravenous infusion of the adrenoceptor agonist yohimbine increases intrusive memories retrieved in PTSD (Southwick et al., 1993). However, the effects of NA likely extend to intrusive memory formation. As mentioned earlier in Introduction, Section 2.2, activity in the amygdala, hippocampus, and PFC – regions involved in emotional memory formation – increases under conditions of moderate emotional stress, via NA-based mechanisms. As stress rises to extreme levels (e.g. in traumatic events), amygdala activation continues to increase, while hippocampal and PFC activation decreases (see Introduction, Section 1.1.1). These observations are consistent with the impact of further increases in NA activity on the amygdala and PFC: for example, in the case of the PFC, NA binds to high-affinity α-2A receptors and enhances functioning at moderate concentrations, but binds to lower-affinity α-1 receptors and impairs

functioning at high concentrations (Ramos & Arnsten, 2007). The DRT suggests that this potentially NA-mediated dissociation contributes to strongly-encoded S-reps, and thus to the formation of intrusive trauma memories (see Introduction, Section 1.1.1).

Synaptic connections between human neurons continue to undergo structural changes up to approximately 6 hours post-encoding. Newly-encoded memory traces remain vulnerable to disruption in this period (McGaugh, 2000). If NA facilitates the consolidation of trauma memories and the formation of intrusive trauma memories, propranolol administered such that peak concentrations are reached within this 6-hour window can be expected to disrupt intrusive memory formation, reducing intrusive memories.

However, clinical studies have not adequately addressed this issue. A retrospective study (McGhee et al., 2009) found that the severity of intrusive PTSD symptoms experienced by veterans taking propranolol did not differ significantly from that of veterans with similar injuries who were not taking propranolol. However, researchers did not consider variations in injury severity and the characteristics of propranolol administration (e.g. timing, dosage), and did not confirm drug effects (e.g. by ascertaining concentrations of NA in the body). Additionally, the use of single questionnaire items to assess intrusive PTSD symptoms may have missed subtler effects. In contrast, Hoge et al. (2012) and Pitman et al. (2002) discovered that propranolol administered post-trauma decreased participants' physiological responses to scripts of traumatic experiences (which presumably elicited intrusive trauma memories) 5 weeks and 3 months post-trauma. However, propranolol was administered multiple times over several days, which may have resulted in its effects at memory consolidation being confounded with those at memory reactivation/retrieval. Nicholson, Bryant, and Felmingham (2014) showed that PTSD sufferers experienced more intrusive memories of novel negatively-valenced stimuli

relative to non-trauma-exposed controls, and that higher numbers of intrusive memories were correlated with larger increases in NA levels at the point of stimulus exposure. Yet, the study did not account for the finding that PTSD sufferers also experienced more intrusive memories than trauma-exposed PTSD-negative controls, despite equivalent increases in NA across groups.

Otherwise, the majority of clinical studies have focused on the broader relationship between post-trauma administration of propranolol and PTSD incidence and/or overall PTSD symptom severity. These have yielded equivocal findings (e.g. Pitman et al., 2002; versus Stein, Kerridge, Dimsdale, & Hoyt, 2007), with recent systematic reviews (Amos, Stein, & Ipser, 2014; Argolo, Cavalcanti-Ribeiro, Netto, & Quarantini, 2015; Sijbrandij, Kleiboer, Bisson, Barbui, & Cuijpers, 2015) concluding that post-trauma administration of β-adrenergic blockers such as propranolol does not reduce overall PTSD severity, and either does not reduce PTSD incidence (Argolo et al., 2015; Sijbrandij et al., 2015) or has effects supported only by low quality evidence (Amos et al., 2014).

Nonetheless, this does not preclude a relationship between propranolol and intrusive trauma memories specifically. Moreover, the overall body of research is small, and of low to moderate methodological quality (Sijbrandij et al., 2015). Time points at which propranolol was administered relative to the traumatic event varied widely across studies (i.e. <6 hours to <48 hours), limiting the comparability of results and often resulting in drug concentrations peaking more than 6 hours after encoding (by which time the memory trace might have stabilised and become impervious to propranolol's effects). In addition, as outcomes were typically assessed at 1-month follow-up or later, differences between propranolol and control groups may have decayed in line with natural recovery. Variation in patient characteristics (e.g. gender; van Stegeren, 2008) and the type/severity of traumatic events, as well as failures to control for variation in cortisol levels with time of day

(van Stegeren et al., 2007), may also have obscured the effects of propranolol. Finally, the sample sizes of studies on preventative agents for PTSD were generally small (often n<50; Sijbrandij et al., 2015). This meant that when the type/severity of trauma were associated with low rates of PTSD, final cell sizes were small, decreasing the precision of effects (i.e. these were associated with large confidence intervals).

3 Rationale for and Aims of Study

The DRT is an account of episodic memory that proposes that the co-occurrence of intrusive trauma memories and impaired voluntary recall of traumatic events in PTSD is due to strongly-encoded S-reps, weakly-encoded C-reps, and weak connections between the two. It is consistent with current evidence. Concurrently, research has shown that NA secreted as part of the body's response to stress facilitates the encoding and consolidation of moderately emotional memory via amygdala activity. However, NA may also be involved in upregulating amygdala activity and downregulating PFC activity during the encoding and consolidation of *trauma* memories. This causes S-reps to be strongly-encoded – a key mechanism underlying intrusive memories in PTSD.

The above implies that the administration of adrenoceptor antagonists such as propranolol during trauma memory consolidation may decrease intrusive memories, suggesting a host of exciting therapeutic implications. However, relevant studies are limited in number and methodological quality, and have mostly focused on the more general relationship between propranolol and PTSD. The effects of propranolol on intrusive memories await further exploration. Further, in view of the posited role of NA and the amygdala in S-reps (as opposed to C-reps, which are served by MTL structures), studies testing propranolol's effects on intrusive (S-rep-

mediated) memory and voluntary (C-rep-mediated) memory can be used to probe the validity of the DRT. Yet, pharmacological studies of PTSD prevention and DRT research have tended to proceed independently.

Thus, as part of a larger study, this study investigated the effects of a single dose of propranolol – administered immediately after participants viewed a 'trauma film' – on participants' intrusive and voluntary memory of the film, relative to placebo controls. This permitted the potential therapeutic effects of propranolol on intrusive memories to be further clarified, while testing the veracity of predictions arising from the DRT.

4 Hypotheses

1. Given the downregulating effect of propranolol on amygdala functioning (Hurlemann et al., 2010), propranolol administered post-'trauma film' was expected to impair the consolidation of sensory aspects of the film, making involuntary retrieval of these less likely. Hence, it was hypothesised that – compared to the placebo group – participants receiving propranolol would experience fewer intrusive memories of the film, less vivid and distressing intrusive memories, and/or a quicker reduction of intrusive memories over time (as seen for nitrous oxide, another putative consolidation-blocking drug; Das et al., 2016).

2. Impaired voluntary memory for traumatic events is presumed to be the result of weakly-encoded C-reps and weak associations between S-reps and C-reps. These are likely underpinned by decreased hippocampal activation resulting from high cortisol levels (Bremner et al., 1995) and poor PFC control at retrieval, rather than NA-related effects at consolidation. Given that

the functioning of these structures is less susceptible to downregulation by propranolol, it was hypothesised that participants receiving propranolol and participants receiving placebo would demonstrate equivalent levels of performance and physiological arousal on voluntary memory tasks.

3. Participants were expected to experience the 'trauma film' as emotionally aversive and stressful. Thus, it was hypothesised that the sample would display heightened negative emotion and physiological arousal across the film, as indexed by state psychological and physiological measures. Propranolol was expected to exert downregulating effects on the sympathetic nervous system (Southwick et al., 1999), resulting in a greater reduction in physiological arousal post-treatment in the propranolol group compared to the placebo group.

Method

This study was approved by the UCL Research Ethics Committee (Appendices 03 and 04).

1   Design

The research reported in this paper is part of a larger study which adopted a double-blind, randomised, between-subjects design. Participants were allocated to receive propranolol, hydrocortisone, or placebo following viewing of a 'trauma film' (see Method, Section 3.1). Data was jointly collected with another UCL Doctorate in Clinical Psychology trainee and two Master's degree students; each trainee independently analysed data from placebo controls and only one other treatment

arm (i.e. propranolol or hydrocortisone; Gong, 2018; see Appendix 05). This paper will focus on comparisons between the propranolol and placebo groups.

2   Participants

Using a power calculation performed using G*Power version 3.1.9.2 (Faul, Erdfelder, Buchner, & Lang, 2009), and assuming a large effect size (f=0.4) based on previous studies examining the effects of pharmacological and behavioural manipulations on intrusive memories (e.g. Das et al., 2016; Holmes, James, Coode-Bate, & Deeprose, 2009; Soni, Curran, & Kamboj, 2013), α=0.05, and power=0.8, the minimum sample size for the broader study was estimated to be N=66 (i.e. n=22 per group). However, given ongoing uncertainty about the likely effects of drug treatment on memory, a larger sample was recruited. The current sample size was thus N=88.
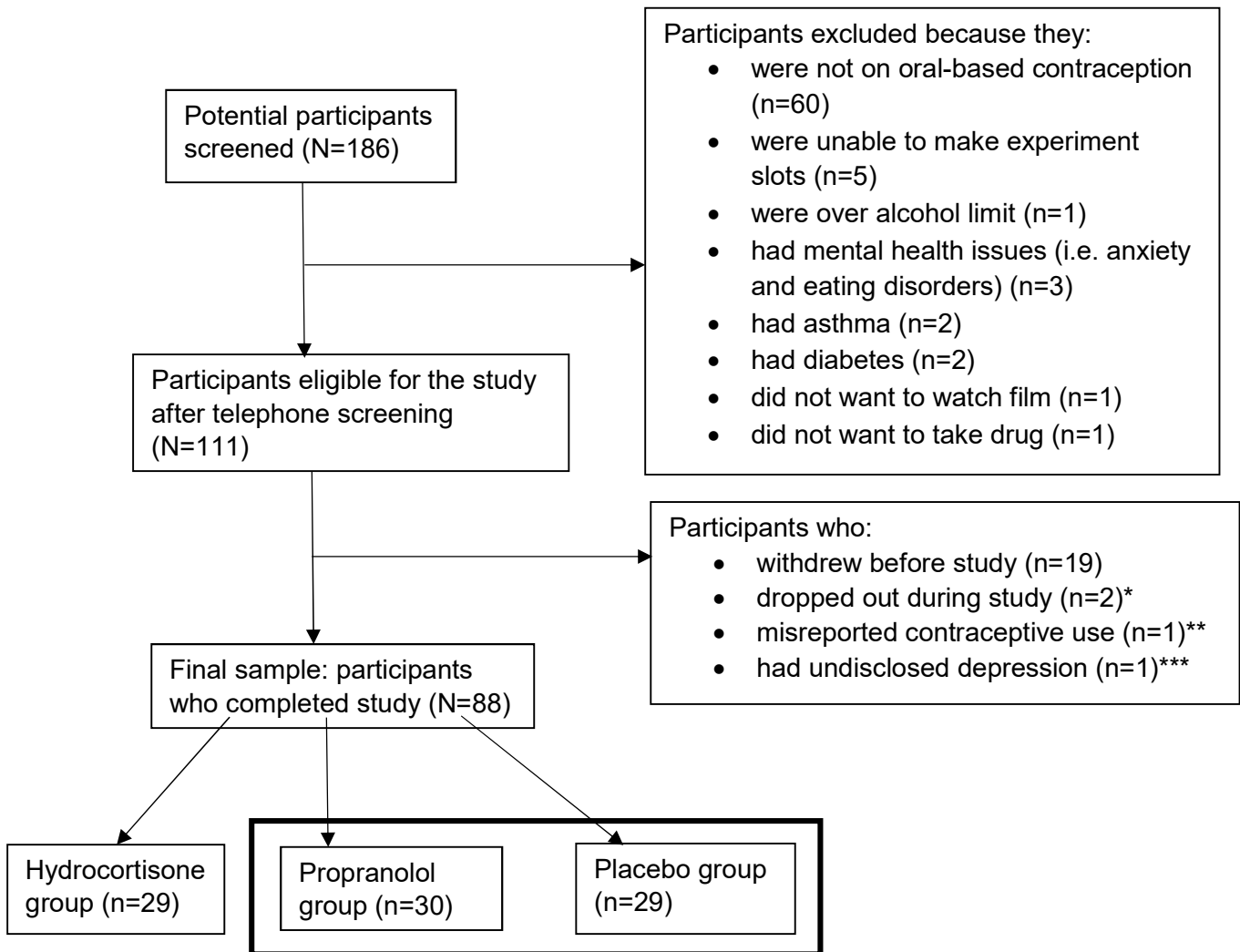
Participants were recruited via online advertisements and flyers placed around the campuses of central London universities. Potential participants underwent a telephone screening to confirm their eligibility for the study.

To control for potential gender differences in responses to stress and emotional memory (van Stegeren, 2008), all participants were women. Participants included were in good physical and psychiatric health, between 18-35 years of age, had a body mass index between 18.5-30 kg/m^2, had normal blood pressure, used recreational drugs ≤2 times per month, consumed ≤14 units of alcohol per week, were fluent in English, had reliable internet access, and were willing and able to complete a memory diary daily for 7 days. Participants were also required to have been taking an oral hormone-based contraceptive for ≥1 month at the point of screening (mean=36.3±38.4 months) to limit the effects of variation in circulating ovarian hormone levels on intrusion frequency (Soni et al., 2013). Exclusion criteria

included: medical contraindication of propranolol/hydrocortisone consumption, a history of mental health difficulties requiring treatment, current use of cardiovascular or psychiatric medication, and experience of significant interpersonal violence.

All participants provided written informed consent (Appendices 06 and 07). They were made aware of the graphic nature of the 'trauma film' and the potential side effects of propranolol/hydrocortisone, and informed of their right to withdraw at any point in the study. Each received a £25 honorarium upon completion of the study.

Of the participants who were screened, 88 participants formed the final sample (Figure 3). The placebo group consisted of 29 participants, and the propranolol group of 30 participants.

```
┌─────────────────────────┐        ┌──────────────────────────────────────────┐
│ Potential participants  │        │ Participants excluded because they:        │
│ screened (N=186)        │        │   • were not on oral-based contraception   │
└─────────────────────────┘        │     (n=60)                                 │
                                   │   • were unable to make experiment         │
                                   │     slots (n=5)                            │
                                   │   • were over alcohol limit (n=1)          │
                                   │   • had mental health issues (i.e. anxiety │
                                   │     and eating disorders) (n=3)            │
                                   │   • had asthma (n=2)                       │
┌─────────────────────────┐        │   • had diabetes (n=2)                     │
│ Participants eligible    │        │   • did not want to watch film (n=1)       │
│ for the study after      │        │   • did not want to take drug (n=1)        │
│ telephone screening      │        └──────────────────────────────────────────┘
│ (N=111)                  │
└─────────────────────────┘        ┌──────────────────────────────────────────┐
                                   │ Participants who:                          │
                                   │   • withdrew before study (n=19)           │
                                   │   • dropped out during study (n=2)*        │
                                   │   • misreported contraceptive use (n=1)**  │
                                   │   • had undisclosed depression (n=1)***    │
┌─────────────────────────┐        └──────────────────────────────────────────┘
│ Final sample:           │
│ participants who        │
│ completed study (N=88)  │
└─────────────────────────┘
```

Hydrocortisone group (n=29)   Propranolol group (n=30)   Placebo group (n=29)

Note.

* Adverse response to 'trauma film' led to premature termination of the experiment.

** On Day 1 testing session, participant reported contraceptive use inconsistent with screening (i.e. 2 weeks' use instead of > ~1 month).

*** On Day 1 testing session, participant disclosed depressive symptoms inconsistent with screening inclusion/exclusion criteria.

Figure 3. The numbers of participants included at each stage of the larger study.

The propranolol and placebo groups are the focus of this paper.

3 Materials

3.1 Analogue trauma paradigm – 'trauma film'.

The 'trauma film' consisted of two consecutively-screened scenes from the film 'Irréversible' (StudioCanal, France, 2002) depicting a violent rape (Scene 1; 12 minutes long) and a man being beaten to death in a club (Scene 2; 2 minutes long). The film included brief, verbally-narrated descriptions of scene context prior to each scene. Distressing intrusive memories are reliably reported after viewing this film (Das et al., 2016), and other recent studies have used this film as a means to induce intrusive memories (Graebener, Michael, Holz, & Lass-Hennemann, 2017; Rombold et al., 2016).

Participants viewed the film on a 15-inch laptop monitor in a darkened lab, with audio presented through headphones. Their eye movements during the film were recorded (GP3 Eye Tracker, Gazepoint, Vancouver, Canada) and later analysed using Gazepoint software to determine if participants across different groups had paid similar amounts of attention to the film (as operationalised by the average gaze duration and average number of fixations on defined areas of interest for each group). A chinrest was used to limit head movements and ensure recording accuracy.

3.2 Treatment arms (propranolol versus placebo).

Based on dosages previously found to have significant effects on emotional memory (e.g. Maheu et al., 2004), an 80mg dose of propranolol was used. Two 40mg propranolol tablets (Accord Healthcare Ltd, Middlesex, UK) were crushed and re-encapsulated in-house in identical opaque gelatine capsules, which were then filled with additional lactose powder. As two capsules were needed to contain the

required amount of propranolol, the placebo group also received two capsules, but these contained only lactose powder.

3.3   Self-report measures.

On Day 1, participants completed questionnaires assessing trait (i.e. stable, dispositional; Allport & Odbert, 1936) depression, anxiety, and dissociation on the Beck Depression Inventory-II (BDI-II; Beck, Steer, Ball, & Ranieri, 1996), Trait Anxiety Scale of the State Trait Anxiety Inventory for Adults (STAI; Spielberger, 1983), and Dissociative Experiences Scale (DES-II; Carlson & Putnam, 1993) respectively. General sleep quality over the past month was assessed using the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Acute emotional states pre- and post-film were assessed using the Positive and Negative Affect Schedule (PANAS; a 20-item questionnaire consisting of 10 positive and 10 negative items; Watson, Clark, & Tellegen, 1988) and 6 emotion-related visual analogue scales (E-VAS's; 'disgust', 'fear', 'anger', 'sadness', 'distress', 'happiness'; Appendix 08). The Bodily Symptoms Scale (BSS; Bond & Lader, 1974), comprising a further 13 scales, was used to assess acute drug-induced effects prior to drug administration and an hour after drug administration (Appendix 09). Items measuring physical sensations and cognitive states (e.g. nausea, memory impairment) were of primary interest.

On Day 2, participants also reported the quality and length of their sleep on the night of Day 1.

3.4 Physiological measures.

In the testing session on Day 1, a digital device with a cuff was placed on participants' left wrists (BM40 XL, Beurer UK Limited) to measure systolic and diastolic blood pressure (BP) pre-film, pre-treatment (post-film), and 1 hour post-treatment. Additionally, electrocardiogram (ECG) data was recorded continuously using a BodyGuard 2 ECG device (FirstBeat Technologies, Finland) at a sampling rate of 1000 Hz, using Ag/AgCl electrodes attached below the right clavicle and left ribcage. Heart rate (HR) data was extracted from three periods: a 5-minute epoch immediately prior to the film (i.e. indexing baseline HR), a second epoch lasting the duration of the film (i.e. indexing HR during the film), and a third 5-minute epoch 1 hour post-treatment (i.e. indexing HR with the influence of treatment). Changes in BP and HR are thought to be mediated by SNS and PNS contributions (Guyenet, 2006; Thayer, Ahs, Fredrickson, Sollers, & Wager, 2012).

ECG data was also recorded in the Day 8 testing session during the voluntary free/cued recall tasks.

3.5 Memory assessments.

In the Day 1 testing session, participants were given a detailed description of the nature of intrusive memories and instructions on how to record these. For 7 days starting on Day 1, participants recorded all 'trauma film'-related intrusive memories experienced in an online diary (Qualtrics, Provo, UT; Bisby, King, Brewin, Burgess, & Curran, 2010) once per day, as close to bedtime as possible. They were required to briefly describe the content of each intrusion (to confirm that it was film-related), and rate its vividness and distress. To increase compliance, the importance of diary completion was stressed to participants on Day 1; participants also received email and phone-text reminders at 8pm daily.

In the Day 8 testing session, participants completed two surprise voluntary recall tasks.

1. *Free recall task:* Participants were instructed to type "everything [they could] remember" about the 'trauma film', recalling "as much information and detail" as possible. Two researchers blind to treatment then independently coded the number of accurately-recalled 'gist units' (i.e. salient main events which could not be altered without altering the fundamental storyline of the film; Adolphs, Denburg, & Tranel, 2001; Cahill & van Stegeren, 2003) and 'detail units' (i.e. peripheral information/features; Adolphs et al., 2001) present in each participant's written excerpt (two-way random intraclass correlations; ICC Scene 1 Gist=0.98; ICC Scene 1 Detail=0.99; ICC Scene 2 Gist=0.94; ICC Scene 2 Detail=0.97). Disagreements in coding were discussed and the relevant responses re-coded upon agreement. The numbers of gist, detail, and overall idea (i.e. the sum of gist and detail) units for each scene that participants had recalled accurately were expressed as proportions of the pool of *all* accurately-recalled gist/detail/idea units across the entire sample for that scene. The separate coding of gist and detail units allowed possible differences between memory for the gist and detail of emotional material (Adolphs, Tranel, & Buchanan, 2005) to be taken into account.

2. *Cued recall task:* Participants answered 19 questions on film events (Das et al., 2016). They were instructed to make their best guess if they did not know an answer. Two independent researchers blind to treatment scored participants' responses; participants were awarded 1 point for each correct answer, 0.5 points for each partially-correct answer, and 0 points for each incorrect answer (two-way random intraclass correlations; ICC Scene

1=0.92; ICC Scene 2=0.98). Disagreements in scoring were again discussed and the relevant responses re-scored upon agreement.

4 Procedure

Participants who passed the telephone screening were invited to attend the first testing session on Day 1, and a second session on Day 8 if they completed the first session and the memory diary. All sessions took place between 2-7pm to minimise the effects of fluctuating bodily cortisol levels over the day (van Cauter & Turek, 1995). As far as possible, the two sessions for each participant were scheduled at similar times. Participants were instructed not to consume food and caffeine for two hours prior to the first testing session (Smith, Brice, Nash, Rich, & Nutt, 2003).

4.1 Day 1.

In the first session, written consent was obtained (Appendices 06 and 07). ECG electrodes were attached to the participants. Participants then completed the BDI-II, STAI Trait Anxiety Scale, DES-II, and PSQI. They further completed the PANAS and E-VAS's, and had their BP measured. They were instructed to put on headphones and position their head on the chinrest, and the eye tracker was calibrated. Participants were given brief instructions regarding the 'trauma film', and reminded of the graphic nature of the film and that they could withdraw at any time without giving a reason. They then viewed the film, had their BP measured again and completed the PANAS, E-VAS's, and BSS.

Subsequently, participants swallowed two capsules containing propranolol or placebo. They were then engaged in filler tasks for 1 hour: specifically, they

provided demographic information, had their heights and weights measured, and listened to a series of 25 classical music clips via headphones while rating each for pleasantness (Holmes et al., 2010). After 1 hour, participants were asked to report any adverse effects experienced. Experimenters and participants guessed the treatment participants had received. Participants had their BP measured again, and completed the PANAS, E-VAS's, and BSS. At the end of the session, participants were given verbal and written instructions regarding the recording of intrusive memories.

4.2   Days 1-7.

Participants logged film-related intrusive memories nightly for 7 days, starting on the day of the 'trauma film'. On Day 2, participants also reported the quality and length of their sleep the night before.

4.3   Day 8.

On Day 8, participants attended their second testing session. ECG electrodes were again attached, and they completed the free and cued recall tasks. Participants were debriefed in full and received payment.

5   Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics (Version 24.0; IBM Corp, 2016). Data were inspected for normality both visually and statistically. Equality of variance was examined using Levene's test, and data generally met this assumption.

Intrusion data were nearly complete (0.7% missing) and were missing completely at random (Little's MCAR test: $\chi^2(76)=56.26$, $p=0.956$), with complete data on Days 1, 4, 5, and 6 for the number of intrusions and on Days 1, 4, 5, 6 and 7 for intrusion vividness and distress. Given declining intrusion frequency, vividness, and distress over time, missing data points were replaced by the next day's values. Similarly, voluntary memory data were complete apart from one participant who did not complete the free recall task for Scene 2.

Values with a Z-score >3 were identified as outliers and winsorised to the next highest non-outlier + 1.

Results

1 Baseline Participant Characteristics

Table 1 shows the means and standard deviations of treatment groups on baseline characteristics. Mean BDI-II scores were in the "minimal" range for both groups (Beck, Steer, & Brown, 1996), and mean scores on the DES-II indicated "low levels" of trait dissociation (Carlson & Putnam, 1993).

Table 1:

Baseline participant characteristics (means ± SD)

	Placebo (n=29)	Propranolol (n=30)	*t*-test
Age	23.76 ± 3.64	23.20 ± 3.46	0.60
BMI (kg/m^2)	22.01 ± 2.60	22.42 ± 2.91	-0.56
Education (years)	16.24 ± 2.20	15.83 ± 1.60	0.82
BDI-II total	6.79 ± 4.09	4.33 ± 5.14	2.03*
STAI Trait Anxiety Scale total	38.62 ± 7.82	33.03 ± 8.73	2.59*
DES-II total	9.37 ± 6.65	6.81 ± 6.43	1.51
Sleep latency (min)	25.52 ± 15.08	19.73 ± 16.06	1.43
Sleep duration (hrs)	7.21 ± 1.07	7.59 ± 0.83	-1.55
Sleep efficiency (%)	90.28 ± 9.74	89.33 ± 8.59	0.40

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

Between-group differences in baseline variables were generally small. However, there were imbalances in self-reported trait depression and anxiety, with the propranolol group reporting lower baseline BDI-II scores ($t(57)=2.03$, $p=.047$) and STAI scores ($t(57)=2.59$, $p=.012$) compared to the placebo group. These differences were likely due to chance variation, especially in view of the large number of comparisons conducted. Nevertheless, depression and anxiety may affect the retrieval of negative/threat-related information (Mitte, 2008; Reynolds & Brewin, 1999), which might have impacted memory for the film. They were thus considered in analyses of intrusion and voluntary recall data (see Results, Section 5).

2 Treatment Acceptability and Blinding

2.1 Adverse drug-induced effects.

Participants did not report any adverse drug-induced effects during the experiment session.

Independent samples t-tests showed that there were no significant between-group differences on drug-induced effects 1 hour post-treatment (as measured by the BSS), apart from the propranolol group reporting significantly less muscle tension than the placebo group ($t(57)=2.75$, $p=.009$; Table 2).

Table 2:

Drug-induced effects 1h post-treatment (means ± SD)

	Placebo (n=29)	Propranolol (n=30)	*t*-test
Memory impairment	6.52 ± 11.76	2.23 ± 6.21	1.74
Palpitations	6.07 ± 10.32	4.83 ± 9.96	0.47
Nausea	3.24 ± 6.01	5.97 ± 17.21	-0.82
Drowsiness	27.83 ± 28.84	18.87 ± 25.41	1.27
Muscle tension	11.00 ± 13.94	3.10 ± 6.76	2.75**
Headache	4.79 ± 12.24	3.23 ± 7.12	0.60
Tremor	4.90 ± 12.37	0.93 ± 2.18	1.70
Confusion	4.24 ± 11.63	1.90 ± 4.36	1.03

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

2.2 Guesses on treatment by participants and experimenters.

When experimenters and participants were asked to guess the treatments participants had received, chi-square tests showed that the distribution of guesses

across treatments did not differ significantly between treatment groups for both experimenters ($\chi^2(2)$=0.54, p=.762) and participants ($\chi^2(2)$=1.87, p=.393). This suggests that the double-blinding procedure was successful.

3 Film Check

3.1 Eye tracking data.

Independent samples t-tests showed that the average gaze duration and average number of fixations on defined areas of interest in the film did not differ significantly across treatment groups ($t(55)$=1.21, p=.230; $t(55)$=1.76, p=.084 respectively; Table 3). This suggests that groups attended to the film equivalently.

Table 3:

Gaze duration and fixations on areas of interest (means ± SD)

	Placebo (n=27)	Propranolol (n=30)	*t*-test
Gaze duration (s)	2.54 ± 1.89	1.88 ± 2.18	1.21
Number of fixations	8.61 ± 5.77	5.79 ± 6.29	1.76

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

3.2 Changes in affect and autonomic arousal.

Paired samples t-tests showed that, across the sample, mean positive affect decreased significantly from pre- to post-film, while mean negative affect increased significantly (as measured by both the PANAS and E-VAS; Table 4). Mean systolic BP also increased significantly. Changes in negative affect measured by the PANAS were significantly positively correlated with changes in systolic BP (r=.30,

p=.020), supporting a link between altered affect due to the film and increased autonomic arousal. There were small, non-significant increases in diastolic BP (pre- to post-film) and mean HR (pre-film to during film). Taken altogether, these findings suggest that the film had effects on affect and arousal in line with expectations.

Table 4:

Changes in measures of affect and arousal associated with 'trauma film' (means ± SD) (n=59)

	Pre-film	Post-film (PANAS, E-VAS, BP) / during film (HR)	*t*-test
PANAS – positive affect	28.59 ± 8.11	19.88 ± 6.44	11.14***
E-VAS – positive affect	5.41 ± 2.50	1.97 ± 1.72	10.63***
PANAS – negative affect	12.42 ± 3.24	23.69 ± 8.29	-10.69***
E-VAS – negative affect	0.34 ± 0.54	5.57 ± 2.46	-16.16***
Systolic BP (mmHg)	112.66 ± 12.39	117.54 ± 13.44	-3.49**
Diastolic BP (mmHg)	71.17 ± 7.61	72.10 ± 8.16	-1.27
Mean HR (beats/min)	78.41 ± 10.00	79.69 ± 13.24	-1.00

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

4 Treatment Check

Mixed ANOVAs were used to compare placebo and propranolol groups on indices of autonomic arousal from pre-treatment (i.e. systolic and diastolic BP measured post-film, mean HR measured during the film) to 1 hour post-treatment.

As seen in Figure 4A, time point had a significant main effect on systolic BP ($F_{(1,56)}$=28.07, *p*<.001), with systolic BP decreasing over time across the sample. The main effect of group on systolic BP was not significant ($F_{(1,56)}$=1.48, *p*=.228).

The time point*group interaction approached significance (F(1,56)=3.76, p=.058),

with the propranolol group showing a steeper decline in systolic BP compared to the

placebo group. As seen in Figure 4B, both groups showed very slight changes in

diastolic BP across time points, but the effects of time point and group were non-

significant (F(1,56)=1.25, p=.269; F(1,56)=1.48, p=.228 respectively), as was the
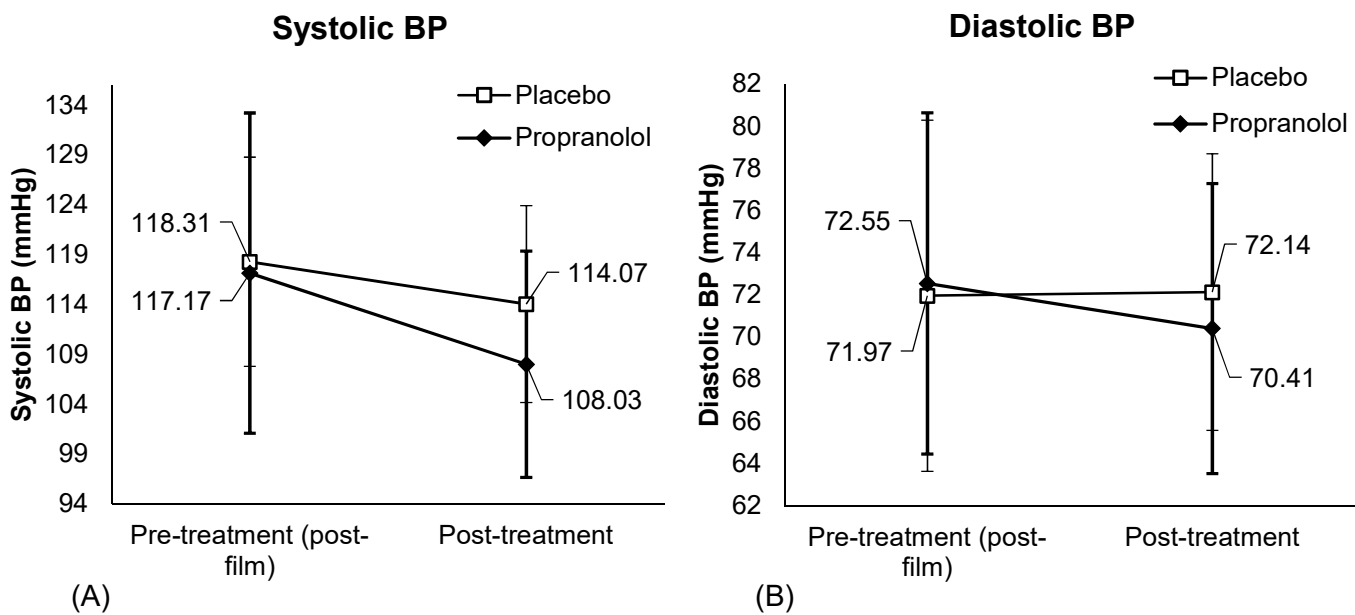
time point*group interaction (F(1,56)=1.72, p=.195).

Figure 4. Changes in systolic and diastolic BP pre- to post-treatment. Symbols are

mean values; error bars are SDs.

Figure 5 shows the significant main effects of time point and group on mean

HR (F(1,56)=29.37, p<.001; F(1,56)=4.18, p=.046 respectively). Mean HR

decreased between time points across the sample, and the propranolol group had a

lower mean HR overall compared to the placebo group. The time point*group

interaction was significant (F(1,56)=9.06, p=.004), with the propranolol group

showing a steeper decline in mean HR compared to the placebo group.
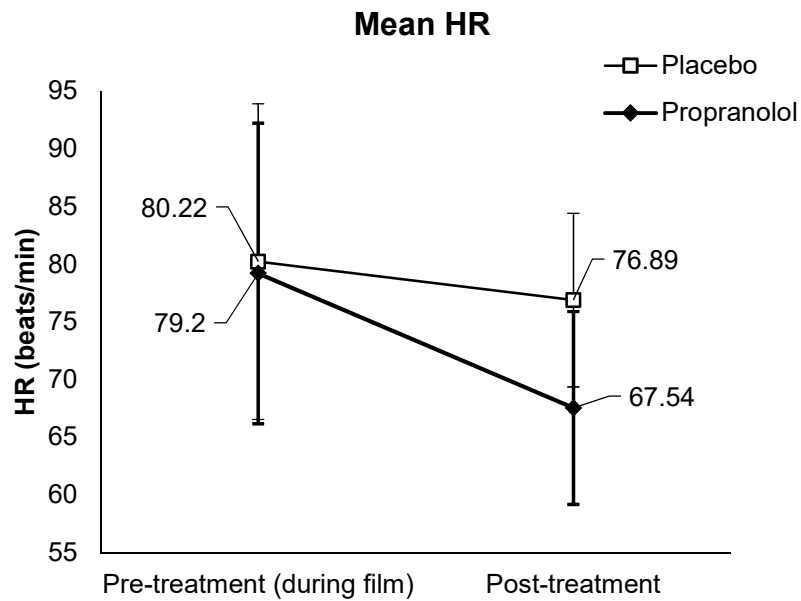
Mean HR

Figure 5. Changes in mean HR pre- to post-treatment. Symbols are mean values; error bars are SDs.

Overall, despite an absence of significant changes in diastolic BP, changes in both systolic BP and mean HR suggested a decline in autonomic arousal across the sample pre- to post-treatment, consistent with termination of the film stimulus and natural reductions in arousal over time. In addition, mean HR and systolic BP decreased more steeply across time points in the propranolol group compared to the placebo group, in line with the known effects of propranolol.

5 Intrusion and Voluntary Recall Data

As intrusion data were positively skewed and included zero-values, a log(x+1) transformation was applied prior to analysis. However, figures are based on raw data to facilitate interpretation.

5.1   Intrusion frequency.

Figure 6 shows the number of film-related intrusive memories experienced by participants in the week following the 'trauma film'. A mixed ANOVA with one between-subjects factor ('group', i.e. placebo versus propranolol) and one within-subjects factor ('day', i.e. Days 1-7) was conducted. There was a significant main effect of group ($F(1,57)=4.77$, $p=.033$), with the propranolol group reporting significantly fewer intrusions overall compared to the placebo group. There was also a significant main effect of day ($F(4.61,262.60)=39.02$, $p<.001$). Planned contrasts showed that, across the sample and from Day 3 onwards, the number of intrusions experienced on any day was significantly different from the number of intrusions experienced the day before. Nevertheless, the day*group interaction effect was not significant ($F(4.61,262.60)=0.73$, $p=.590$), suggesting that the speed at which intrusions decreased over the days did not differ significantly between groups.
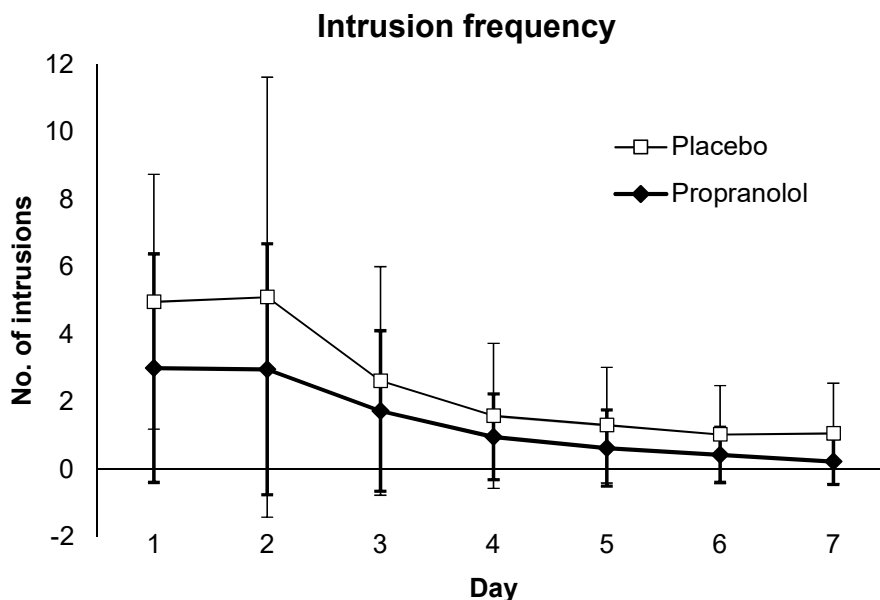

Figure 6. Film-related intrusions experienced in the week following the 'trauma film'. Symbols are mean values, error bars are standard deviations.

5.2 Intrusion vividness and distress.

Mixed ANOVAs revealed significant main effects of group on intrusion vividness ($F(1,56)=7.07$, $p=.010$) and distress ($F(1,56)=5.27$, $p=.025$), with the propranolol group reporting significantly less vivid and distressing intrusions than the placebo group overall (Figures 7A and 7B respectively). There were also significant main effects of day on vividness ($F(5.04,282.25)=40.49$, $p<.001$) and distress ($F(6,336)=40.24$, $p<.001$). Planned contrasts showed that, across the sample and from Day 2 onwards, intrusion vividness and distress on any day were significantly lower than intrusion vividness and distress the day before. The group*day interaction effect was not significant for both intrusion vividness ($F(5.04,282.25)=1.15$, $p=.335$) and distress ($F(6,336)=1.35$, $p=.233$), suggesting that the speeds at which intrusion vividness and distress decreased over the week did not differ significantly between groups.

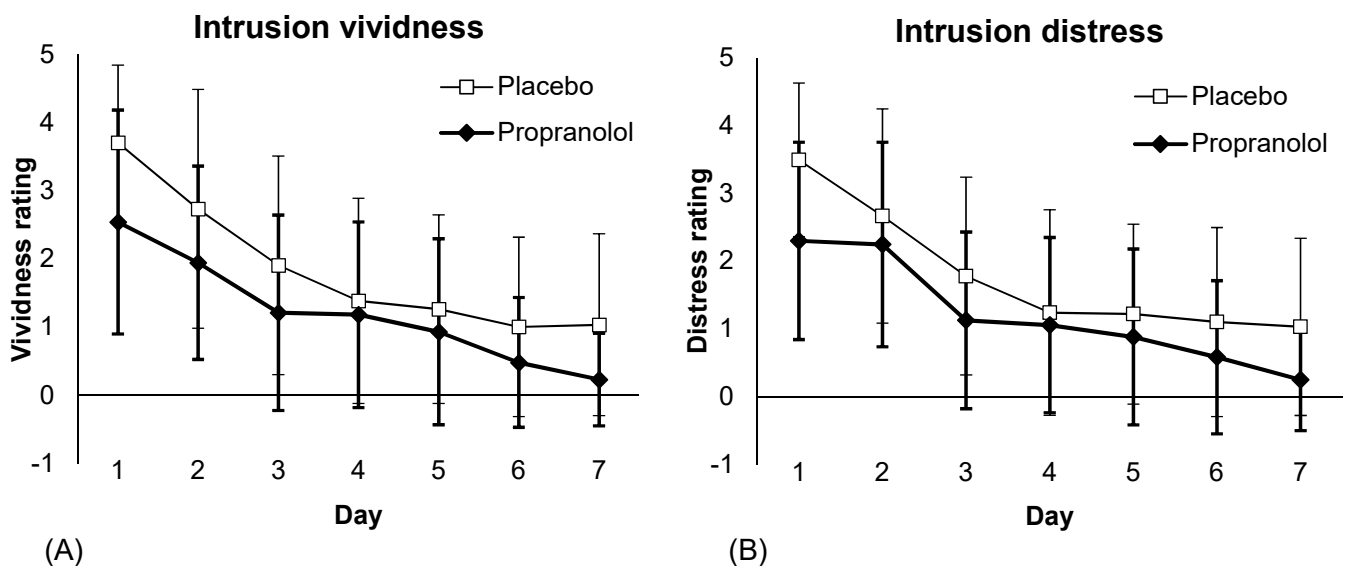(A)   (B)

Figure 7. Ratings of intrusion vividness and distress over the week between testing sessions. Symbols are mean values, error bars are standard deviations.

### 5.3   Voluntary recall performance.

Independent samples *t*-tests showed that there were no significant between-group differences in average free recall performance across scenes (regardless of whether gist, detail, or total idea units were considered; Figure 8).

Free recall performance
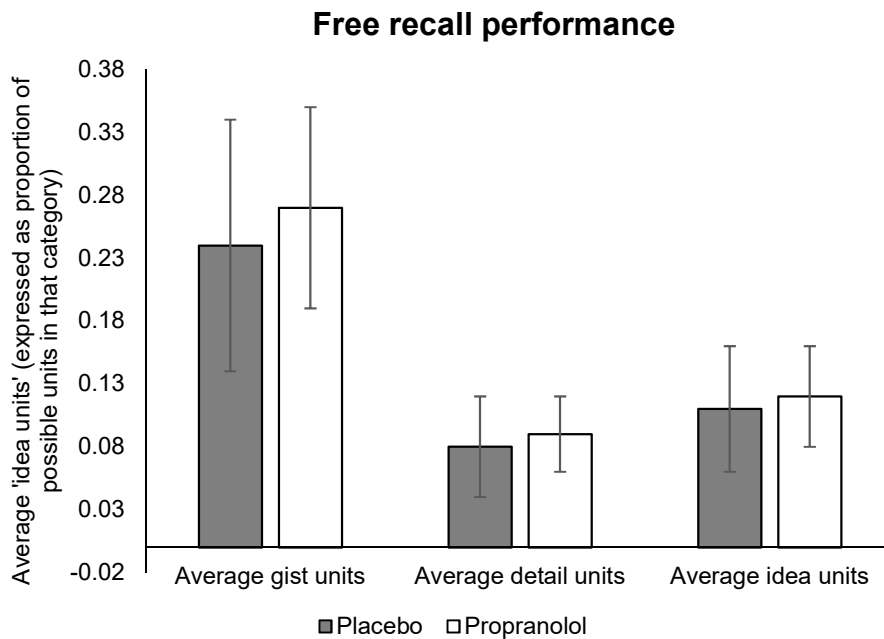
Figure 8. Free recall performance – operationalised as the number of accurately-recalled 'idea units' (i.e. gist, detail, or total idea units), expressed as a proportion of the pool of possible 'idea units' in that category and averaged across the two scenes. Heights of bars are mean values, error bars are SDs.

Free recall performance for Scenes 1 and 2 were also examined separately. Differences between groups were non-significant (Scene 1 gist: $t(57)=-0.62$, $p=.538$; Scene 1 detail: $t(57)=-0.15$, $p=.881$; Scene 1 idea: $t(57)=-0.37$, $p=.714$; Scene 2 gist: $t(56)=-1.39$, $p=.169$; Scene 2 detail: $t(56)=-1.56$, $p=.124$; Scene 2 idea: $t(56)=-1.61$, $p=.114$).

An independent samples *t*-test showed that placebo and propranolol groups did not differ significantly in their cued recall performance (Figure 9).
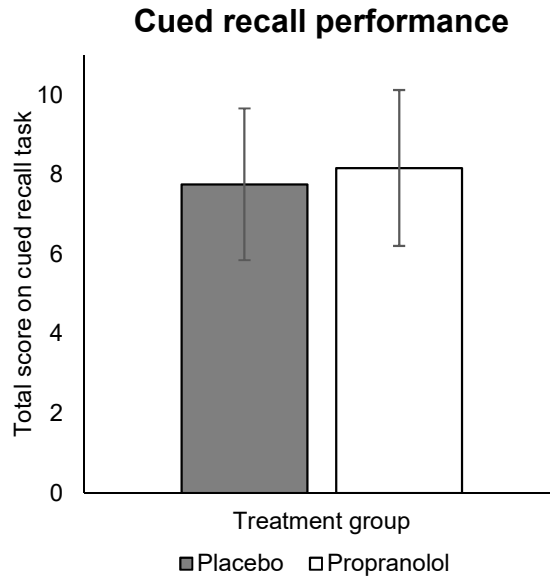
Figure 9. Cued recall performance – operationalised as total scores on cued recall task. Heights of bars are mean values, error bars are SDs.

Cued recall performance for Scenes 1 and 2 were also examined separately. Differences between groups were likewise non-significant (Scene 1: *t*(57)=0.76, *p*=.450; Scene 2: *t*(57)=-1.50, *p*=.140).

5.3.1 *Changes in autonomic arousal during free and cued recall tasks.*

As seen in Figure 10, a mixed ANOVA showed that time point had a significant main effect on mean HR (*F*(1.56,88.62)=21.45, *p*<.001). Planned contrasts showed that this was the result of significant decreases in mean HR between baseline and each of the voluntary recall tasks (free recall, cued recall), as

well as a significant decrease in mean HR between the free recall task and the cued recall task. The main effect of group and the group*time point interaction were both non-significant ($F(1,57)=0.21$, $p=.650$; $F(1.56,88.62)=0.44$, $p=.593$ respectively).
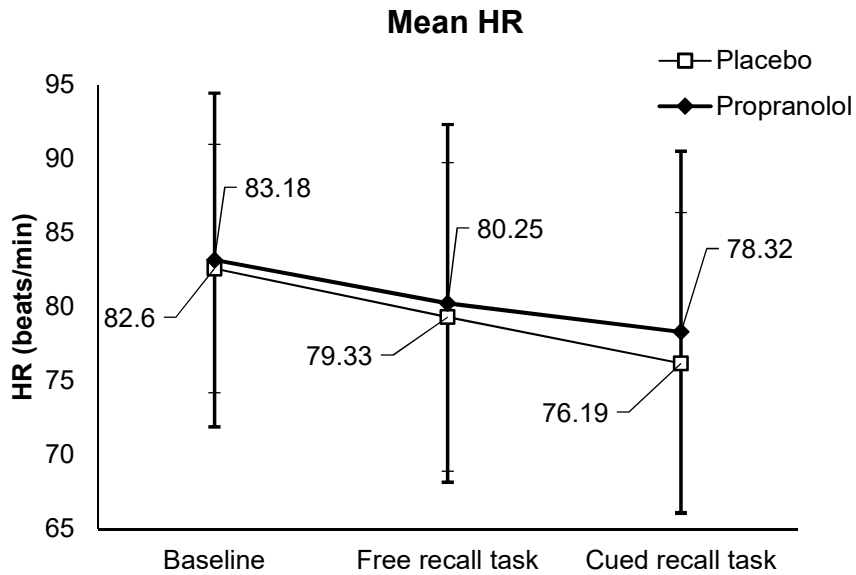

Figure 10. Mean HR measured in Day 8 testing session: at baseline, during free recall task, and during cued recall task. Symbols are mean values, error bars are standard deviations.

5.4   Correlations between intrusion and voluntary recall data.

As shown in Table 5, the total number of intrusions, Day 2 intrusions, and Day 3 intrusions were significantly positively correlated with average free recall performance (Pearson's *r*). No intrusion outcomes were significantly correlated with cued recall performance.

Table 5:

Correlations between intrusion data and voluntary recall outcomes

	Free recall			Cued recall
	Average gist	*Average detail*	*Average idea*	*Total score*
Intrusions				
Day 1	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Day 2	*r*=0.52, *p*<.001	*r*=0.41, *p*=.001	*r*=0.46, *p*<.001	*n.s.*
Day 3	*r*=0.44, *p*=.001	*r*=0.30, *p*=.021	*r*=0.35, *p*=.007	*n.s.*
Day 4	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Day 5	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Day 6	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Day 7	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Total	*r*=0.39, *p*=.003	*r*=0.31, *p*=.019	*r*=0.34, *p*=.009	*n.s.*

Note. n.s. = non-significant

5.5   Exploration of possible mediator variables.

Relationships between treatment and intrusions/voluntary recall may have been affected by differences between groups in: (i) trait depression and anxiety (see Results, Section 1); (ii) lengths of time which had elapsed between the experiment session and bedtime; and (iii) durations of sleep on Day 1. For example, more time between the experiment session and bedtime might have permitted more intrusions to occur, while lengthier sleep might have allowed film-related memory traces to be reactivated and consolidated to a greater extent (Payne & Nadel, 2004). In addition, a clearer grasp of the relationship between intrusive memories/voluntary recall and the magnitude of initial autonomic responses to the film and treatment (i.e. changes in BP/mean HR across these) would aid the interpretation and application of findings.

Thus, Pearson correlations between the above potential mediator variables and memory outcomes (i.e. intrusions, average free recall, total cued recall) were calculated. These are shown in Table 6.

Table 6:

Correlations between possible mediator variables and intrusion data, voluntary recall outcomes

	Intrusions								Free recall			Cued recall
	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Total*	*Average gist*	*Average detail*	*Average idea*	*Total score*
Trait mood (depression, anxiety)												
BDI-II total score	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*r*=0.26, *p*=.044	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
STAI total score	*r*=0.28, *p*=.034	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*r*=0.33, *p*=.011	*r*=0.30, *p*=.020	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Day 1 factors												
Time between session and bedtime on Day 1	*r*=0.35, *p*=.007	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*r*=0.26, *p*=.045	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Autonomic responses												
Changes in systolic BP across film	*r*=0.41, *p*=.001	*n.s.*	*n.s.*	*n.s.*	*r*=0.28, *p*=.035	*n.s.*	*r*=0.30, *p*=.022	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Changes in diastolic BP across treatment	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*r*=-0.27, *p*=.044	*r*=-0.27, *p*=.040	*n.s.*

Note.

- *n.s.* = non-significant
- The following potential mediator variables were not significantly correlated with any memory outcomes, and were thus not included in the table:
    - *Day 1 factors:* duration of sleep on Day 1
    - *Autonomic responses:* changes in HR and diastolic BP across film; changes in HR and systolic BP across treatment

5.5.1 Trait depression and anxiety.

BDI-II scores were significantly positively correlated with Day 6 intrusions; STAI scores were significantly positively correlated with Day 1, Day 6, and Day 7 intrusions. Neither was significantly correlated with total intrusions or voluntary recall outcomes. As correlations were weak (i.e. r= 0.26 to 0.33), BDI-II and STAI scores were not adjusted for in analyses of intrusion data, as per previously-published guidelines (European Medicines Agency, 2015).

5.5.2 Day 1 factors.

Duration of sleep on Day 1 was not significantly correlated with any intrusion outcomes or voluntary recall outcomes. The length of time which had elapsed between the experiment session and bedtime on Day 1 was significantly positively correlated with Day 1 and Day 7 intrusions. However, a further independent samples t-test showed that treatment groups did not differ significantly on this variable (t(56)=1.00, p=.320), suggesting that it did not confound intrusion data.

5.5.3 Autonomic responses.

Across the film, changes in systolic BP were significantly correlated with Day 1 intrusions (r = 0.41) and with later Day 5 (r = 0.28) and Day 7 (r = 0.30) intrusions, but not with voluntary recall outcomes. Changes in diastolic BP and HR across the film were not significantly correlated with any intrusion and voluntary recall measures. Across treatment, changes in diastolic BP were significantly negatively correlated with some free recall measures (i.e. average accurately-recalled detail and idea units); changes in systolic BP and HR were not significantly correlated with any intrusion or voluntary recall measures.

When only the propranolol group was examined, changes in HR across treatment were significantly correlated with Day 7 intrusions (r=0.45, p=.014); there were no other significant correlations between autonomic responses to treatment and intrusion/voluntary recall measures.

Discussion

1 Summary of Main Findings

Findings were consistent with study hypotheses. Compared to placebo controls, participants who received propranolol immediately after watching a 'trauma film' experienced fewer film-related intrusive memories in the following week. The intrusions they experienced were also less vivid and distressing. However, groups did not differ significantly in the speed at which intrusions decreased over time, in voluntary (free, cued) recall performance a week after the film, or in their arousal during voluntary recall tasks.

These effects were observed in the context of:

- General equivalence between groups on baseline characteristics and attention paid to the film;
- The film exerting expected effects on affect and autonomic arousal (i.e. systolic BP), and propranolol exerting expected effects on autonomic arousal (i.e. systolic BP, mean HR);
- Evidence of successful double-blinding; and
- A low likelihood of findings being confounded by between-group differences in: trait mood, lengths of time which had elapsed between the testing session and bedtime on Day 1, and durations of sleep on Day 1.

Changes in systolic BP across the film were significantly correlated with intrusions on specific days (i.e. Days 1, 5, and 7). Changes in diastolic BP across treatment were significantly negatively correlated with some free recall measures across the sample. However, when the propranolol group was examined in isolation, only changes in mean HR across treatment were significantly correlated with any memory outcomes, and only with Day 7 intrusions. Total intrusions and intrusions on specific days (i.e. Days 2 and 3) were significantly correlated with free recall performance, but not cued recall performance.

2 Interpretation of Findings, Links with Previous Literature

2.1 Effects of propranolol on intrusions and voluntary recall.

The effects of propranolol on intrusions are broadly consistent with the proposed involvement of NA in the consolidation of intrusive trauma memories, and its corollary – i.e. that the administration of propranolol, a β-adrenoceptor antagonist, impairs the consolidation of such memories. Specifically, it suggests that a single 80mg dose of propranolol can disrupt the consolidation of intrusive trauma memories when administered immediately following a traumatic event. The effects of this disruption are seen not only in reduced intrusion frequency, but also in the reduced vividness of, and distress associated with, intrusions that do occur. However, the magnitude of participants' autonomic responses to propranolol administration was significantly linearly correlated with Day 7 intrusions only. The reasons for this are unclear. Perhaps the relationship between individuals' initial autonomic responses to propranolol and intrusions is non-linear, and/or affected by other variables (e.g. interactions between NA and other neurotransmitters, feedback loops). More research is needed to clarify this issue.

Moreover, the dissociation between propranolol's effects on intrusive memories and the absence of effects on voluntary recall is consistent with the DRT's proposal of two parallel memory systems/types of representations which are differentially affected by propranolol, and evidence supporting this (e.g. Holmes et al., 2010). Given the close relationship between NA and amygdala activation, propranolol's effects are also consistent with S-reps' and C-reps' proposed reliance on the amygdala and extra-amygdala regions respectively.

Points where findings diverged from prior literature also broadly corroborate the DRT's claims. Hoge et al. (2012) and Pitman et al. (2002) found that propranolol decreased physiological responses associated with involuntary trauma imagery. By comparison, in the present study, propranolol and placebo groups did not differ in their autonomic responses during voluntary recall of film events. Notwithstanding issues with the earlier studies (see Introduction, Section 2.3), this difference can be interpreted within a DRT framework. In the earlier studies, internal autonomic representations of affective states experienced during the traumatic event (part of S-reps) might have been involuntarily retrieved; these were susceptible to disruption by propranolol. However, in the present study, weak associations between S-reps and C-reps may have led to voluntarily-retrieved C-reps not being retrieved alongside internal autonomic representations (and thus showing less susceptibility to propranolol's effects).

However, Adolphs et al. (2005) concluded that pre-existing amygdala damage selectively impaired recall of the gist (and not detail) of emotional stimuli. This is inconsistent with the DRT's predictions, as well as with present findings that propranolol did not affect memory for both the gist and detail of the 'trauma film' (despite its proposed effects on the amygdala). Further research is needed – e.g. on the differential effects of downregulated amygdala activity on the encoding,

consolidation and retrieval of trauma and moderately emotional memory – to determine how these might be reconciled.

2.2 Relationship between intrusion data and voluntary recall.

Total intrusions and intrusions on Days 2 and 3 were significantly correlated with free recall performance. This suggests that the S-rep and C-rep memory systems may be less distinct than previously thought, and points to the need to investigate links between them in order to identify mechanisms that might strengthen associations between S-reps and C-reps (and thereby reduce intrusive memories). In contrast, intrusion data was not significantly correlated with cued recall performance (consistent with Holmes et al., 2004). This difference might be due to divergent task demands. Specifically, free recall tasks, which do not restrict the content/details of what is remembered, may be more sensitive to participants' ability to voluntarily recall details of complex stimuli such as the film scenes used in this study. Comparatively, cued recall tasks require participants to recall particular details of the film pre-determined by the experimenter, some of which might not be central to the gist of the film. Cued recall performance may thus be affected by chance variation in the amounts of attention participants paid to these details.

This underscores the importance of a precise understanding of task demands and the nature of constructs being measured, and the value of using multiple convergent measures to ensure that existing effects are not overlooked. Further studies could continue to administer free recall tasks alongside cued recall tasks, and vary the nature of/questions used in cued recall tasks. This would confirm the replicability of findings, distinguish the role of experimental artefact, and further clarify the relationship between S-rep and C-rep systems.

2.3   Autonomic responses to film and treatment.

This study presents preliminary evidence that the magnitude of individuals'
autonomic response to a traumatic event predicts some intrusion outcomes, while
the extent of subsequent recovery from this predicts some voluntary recall
outcomes. These findings require further replication and exploration, and may yield
fruitful avenues for future research (e.g. about differences between the effects of
encoding-related versus consolidation-related processes on S-reps and C-reps).

Different measures of autonomic arousal did not necessarily show the same
trends across the film and treatment. For example, changes in systolic BP were
significant, whereas changes in diastolic BP were not. In past research, emotional
arousal has been shown to affect both systolic and diastolic BP (e.g. James, Yee,
Harshfield, Blank, & Pickering, 1986), but there have also been instances in which
significant changes in systolic BP co-occurred with non-significant changes in
diastolic BP (e.g. Nagengast, Baun, Megel, & Leibowitz, 1997). It is unclear why this
was the case, though one possible contributing factor may be the differences
between the impacts of different emotions on systolic and diastolic BP (e.g.
happiness may be negatively associated with systolic BP, while anxiety may be
positively associated with diastolic BP; James et al., 1986). Similarly, the non-
significant increase in mean HR across the film may be accounted for by different
emotional reactions exerting opposing influences on HR (e.g. increases in HR
related to fear and anger, decreases in HR related to disgust and sadness; Kreibig,
2010). These potential explanations require further investigation.

3   Strengths and Limitations of Study

This study mimicked real-world treatment of intrusive memories by
administering treatment only after encoding. It also addressed the methodological

limitations of existing studies examining propranolol's effects on PTSD. For example, the utilisation of an experimental analogue trauma paradigm modelling aspects of PTSD in healthy participants reduced potential confounds arising from variations in patient, trauma, and treatment characteristics. Memory assessment in the week immediately following the film increased sensitivity to the short-term effects of propranolol.

However, the study was also limited in several ways. For instance, the paradigm only allowed comparisons to be made between the propranolol group and controls at equivalent time points, but not with reference to some baseline measure of intrusive memories. This obstacle is inherent in the study of intrusive memories, as these can only be assessed *after* a stressful event and drug treatment; baseline measures of a propensity to form, retrieve, or report intrusive memories would necessarily be unrelated to the contents of the 'trauma film'. Further, in comparison to the assessment of intrusive memories starting on the day of the film, voluntary recall was only tested a week later. Perhaps earlier assessment of voluntary recall might have resulted in different findings – this would be the case if, for example, propranolol had in fact affected voluntary recall, but differences between groups had been reduced by natural recovery over the week. More detailed coding/analysis of intrusion content (e.g. intrusive images versus verbal thoughts, whether intrusions were related to Scene 1 or 2) might also have enabled relevant relationships and underlying mechanisms to be further elucidated. Additional analyses could be conducted to determine if there was a differential association between group and intrusive memory versus voluntary recall.

Drawing conclusions regarding SNS and PNS activity based on BP and HR measurements may be overly simplistic, in view that they do not directly index SNS or PNS activity, and that autonomic arousal is controlled by complex interactions between the SNS and PNS. Alternative physiological measures such as HR

variability could be considered – for example, the root mean square of successive RR interval differences purportedly indexes PNS activity, while the ratio of low frequency-to-high frequency power is thought to measure SNS dominance. However, the interpretation of these parameters is complex (Shaffer & Ginsburg, 2017). Plasma levels of MHPG could also be used to estimate NA levels in the body more directly (Southwick et al., 2002).

It should also be acknowledged that this study does not directly prove the neuropharmacological bases for S-reps and C-reps proposed by the DRT. Rather, it merely supports the differential effects of NA on S-reps and C-reps, not the claims about 'weak encoding' of C-reps and the effects of this on S-rep retrieval, given that levels of voluntary recall which constitute 'strong' versus 'weak' encoding have not been established. Similarly, it does not differentiate between the DRT and other theories such as Ehlers and Clark's (2000) emotional processing theory, in view of its focus on consolidation processes as opposed to encoding or the 'fragmentation' of the trauma memory.

Participants might have varied in more subtle ways that affected film recall – for example, fluency in the language used in the film (French) may have made its contents more distinctive/memorable, and/or more emotionally-affecting. Randomisation would likely have reduced the effects of such factors, but these may be worth considering and controlling for in subsequent use of this paradigm. Lastly, a relatively selective, healthy sample was used in this study, while the 'trauma film' is also necessarily a mild analogue of actual life-threatening experiences typical of events associated with acute stress disorder and PTSD. These factors raise concerns about generalisability.

4   Scientific and Clinical Implications

This study advances our understanding of the variables that contribute to the effect of propranolol on intrusive memories, and lends empirical support to the importance of further research despite the ongoing controversy of propranolol's effects across PTSD symptoms in general. In fact, propranolol's ability to inhibit intrusions with a single dose and minimal adverse effects suggests that it is a potentially viable treatment for intrusive memories. Additionally, as propranolol preserves voluntary memory for traumatic events, it might be particularly helpful should legal testimonies from trauma survivors be required (James et al., 2016). This supports its therapeutic use, at least in women using hormone-based contraception. The study results also support the development and use of psychological treatments based on the DRT (e.g. exposure therapy, visuospatial tasks post-trauma; Holmes et al., 2010).

Moving forward, it is critical that future research examines the experimental effects of propranolol for intrusive memories in alternative experimental groups (e.g. women not on contraception, men) and clinical populations. Further, given that propranolol has demonstrated effects within this paradigm, future studies could adapt this protocol to more fully characterise the factors that affect propranolol's ability to downregulate the expression of intrusive memories. For example, by varying the time points of propranolol administration and its dosage, the timeframe in which propranolol reduces intrusions most effectively and its optimum dosage can be confirmed. The effects of propranolol on different types of intrusions (e.g. verbal cognitions, intrusions in different sensory modalities) and their characteristics (e.g. affect, length) can also be elucidated. This research will be important in determining whether propranolol is in fact a clinically useful drug in the secondary prevention of PTSD symptoms.

Concurrently, studies adapting this paradigm may serve to further explore intrusive memory formation and differentiate the DRT from other theories (e.g. administering other drugs that affect MTL structures in order to examine C-reps; using neuroimaging to map the neuroanatomical bases of intrusive memory formation). Such studies may also help to clarify some of the unexplained findings arising from this study: for example, interactions between propranolol and other neurotransmitters (that might have contributed to the lack of significant associations between participants' autonomic responses to propranolol and subsequent intrusions) could be examined by the concurrent administration of other drugs which affect other neurotransmitters.

References

Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory*, *4*(3), 291-300.

Adolphs, R., Denburg, N.L., & Tranel, D. (2001). The amygdala's role in long-term declarative memory for gist and detail. *Behavioral Neuroscience*, *115*(5), 983-992.

Adolphs, R., Tranel, D., & Buchanan, T.W. (2005). Amygdala damage impairs emotional memory for gist but not details of complex stimuli. *Nature Neuroscience*, *8*(4), 512-518.

Allport, G.W., & Odbert, H.S. (1936). Trait names: A psycho-lexical study. *Psychological Monographs*, *47*(1), 211.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Amos, T., Stein, D.J., & Ipser, J.C. (2014). Pharmacological interventions for

preventing post-traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews, 2014*(7), 1-58. doi: 10.1002/14651858.CD006239.pub2

Argolo, F.C., Cavalcanti-Ribeiro, P., Netto, L.R., & Quarantini, L.C. (2015).

Prevention of post-traumatic stress disorder with propranolol: A meta-analytic review. *Journal of Psychosomatic Research*, *79*, 89-93.

Bailey, C.R., Cordell, E., Sobin, S.M., & Neumeister, A. (2013). Recent progress in

understanding the pathophysiology of post-traumatic stress disorder: Implications for targeted pharmacological treatment. *CNS Drugs*, *27*, 221-232.

Beck, A.T., Steer, R.A., Ball, R., & Ranieri, W. (1996). Comparison of Beck

Depression Inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment*, *67*(3), 588-597.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for The Beck Depression Inventory Second Edition (BDI-II).* San Antonio, USA: Psychological Corporation.

Berntsen, D. (2007). Involuntary autobiographical memories: Speculations, findings,

and an attempt to integrate them. In J. H. Mace (Ed.), *Involuntary memory* (pp. 20-49). Oxford, England: Blackwell.

Bisby, J. A., King, J. A., Brewin, C. R., Burgess, N., & Curran, V. H. (2010). Acute

effects of alcohol on intrusive memory development and viewpoint dependence in spatial memory support a dual representation model. *Biological Psychiatry*, *68*(3), 280–286.

Bond, A., & Lader, M. (1974). The use of analogue scales in rating subjective

feelings. *British Journal of Medical Psychology*, *47*, 211-218.

Bremner, J.D., Narayan, M., Staib, L.H., Southwick, S.M., McGlashan, T., & Charney, D.S. (1999a). Neural correlates of memories of childhood sexual abuse in women with and without post-traumatic stress disorder. *American Journal of Psychiatry*, *156*, 1787-1795.

Bremner, J.D., Staib, L., Kaloupek, D., Southwick, S.M., Soufer, R., & Charney, D.S. (1999b). Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without post-traumatic stress disorder: A positron emission tomography study. *Biological Psychiatry*, *45*, 806-816.

Bremner, J.D., Randall, P., Scott, T.M., Bronen, R.A., Seibyl, J.P., Southwick, S.M., …Innis, R.B. (1995). MRI-based measurement of hippocampal volume in patients with combat-related post-traumatic stress disorder. *American Journal of Psychiatry*, *152*(7), 973-981.

Brewin, C.R. (2001). Memory processes in post-traumatic stress disorder. *International Review of Psychiatry*, *13*, 159-163.

Brewin, C.R. (2015). Re-experiencing traumatic events in PTSD: New avenues in research on intrusive memories and flashbacks. *European Journal of Psychotraumatology*, *6*(1), 27180-27184.

Brewin, C.R., & Burgess, N. (2014). Contextualisation in the revised dual representation theory of PTSD: A response to Pearson and colleagues. *Journal of Behavior Therapy and Experimental Psychiatry*, *45*, 217-219.

Brewin, C.R., Dalgleish, T., & Joseph, S. (1996). A dual representation theory of post-traumatic stress disorder. *Psychological Review*, *103*, 670-686.

Brewin, C.R., Gregory, J.D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. *Psychological Review*, *117*(1), 210-232.

Brewin, C.R., & Holmes, E.A. (2003). Psychological theories of post-traumatic

stress disorder. *Clinical Psychology Review*, *23*, 339-376.

Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The

Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and

research. *Psychiatry Research*, *28*, 193-213.

Cahill, L., Babinsky, R., Markowitsch, H.J., & McGaugh, J.L. (1995). The amygdala

and emotional memory. *Nature*, *377*, 295-296.

Cahill, L., Hurer, R.J., Fallon, J., Alhire, M.I., Tang, C., Keator, D., …McGaugh, J.L.

(1996). Amygdala activity at encoding correlated with long-term free recall of

emotional information. *Proceedings of the National Academy of Sciences of

the United States of America*, *23*, 8016-8021.

Cahill, L., Prins, B., Weber, M., & McGaugh, J.L. (1994). B-adrenergic activation

and memory for emotional events. *Nature*, *371*, 702-704.

Cahill, L., & van Stegeren, A. (2003). Sex-related impairment of memory for

emotional events with beta-adrenergic blockade. *Neurobiology of Learning

and Memory*, *79*(1), 81-88.

Carlson, E.B., & Putnam, F.W. (1993). An update on the Dissociative Experiences

Scale. *Dissociation*, *6*(1), 16-27.

Chamberlain, S.R., Muller, U., Blackwell, A.D., Robbins, T.W., & Sahakian, B.J.

(2006). Noradrenergic modulation of working memory and emotional memory

in humans. *Psychopharmacology*, *188*(4), 397-407.

Das, R.K., Tamman, A., Nikolova, V., Freeman, T.P., Bisby, J.A., Lazzarino, A.I., &

Kamboj., S.K. (2016). Nitrous oxide speeds the reduction of distressing

intrusive memories in an experimental model of psychological trauma.

Psychological Medicine, *1*, 1-11.

Ehlers, A., & Clark, D. M. (2000). A cognitive model of post-traumatic stress disorder. *Behaviour Research and Therapy*, *38*(4), 319-345.

Eichenbaum, H. (2004). Hippocampus: Cognitive processes and neural representations that underlie declarative memory. *Neuron*, *44*(1), 109-120.

Elzinga, B.M., & Bremner, J.D. (2002). Are the neural substrates of memory the final common pathway in post-traumatic stress disorder (PTSD)? *Journal of Affective Disorders*, *70*(1), 1-17.

European Medicines Agency. (2015). *Guideline on adjustment for baseline covariates in clinical trials.* London, England: Author.

Euston, D.R., Gruber, A.J., & McNaughton, B.L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron*, *76*(6), 1057-1070.

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*, 1149-1160.

Ferry, B., Roozendaal, B., & McGaugh, J.L. (1999). Basolateral amygdala noradrenergic influences on memory storage are mediated by an interaction between β- and α1-adrenoceptors. *The Journal of Neuroscience*, *19*, 5119-5123.

Foa, E.B., & Rothbaum, B.O. (1998). Treating the trauma of rape: Cognitive-Behavioral Therapy for PTSD. New York, NY: Guilford Press.

Ghacibeh, G.A., Shenker, J.I., Shenal, B., Uthman, B.M., & Heilman, K.M. (2006). The influence of vagus nerve stimulation on memory. *Cognitive and Behavioral Neurology*, *19*, 119-122.

Goldstein, L.E., Rasmusson, A.M., Bunney, B.S., & Roth, R.H. (1996). Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal

cortical monoamine responses to psychological stress in the rat. *Journal of Neuroscience*, *16*(15), 4787-4798.

Gong, A.T. (2018). *Intrusive memories following a single dose of hydrocortisone: Examining the effects of hydrocortisone on intrusive memories in healthy volunteers* (Unpublished doctoral dissertation). University College London, England.

Graebener, A. H., Michael, T., Holz, E., & Lass-Hennemann, J. (2017). Repeated cortisol administration does not reduce intrusive memories – A double blind placebo controlled experimental study. *European Neuropsychopharmacology*, *27*(11), 1132-1143.

Guyenet, P.G. (2006). The sympathetic control of blood pressure. *Nature Reviews Neuroscience*, *7*, 335-346.

Hackmann, A. (1998). Working with images in clinical psychology. In A. S. Bellack & M. Hersen (Eds.), *Comprehensive clinical psychology* (Vol. 6, pp. 301-318). New York, NY: Elsevier.

Hackmann, A., Ehlers, A., Speckens, A., & Clark, D.M. (2004). Characteristics and content of intrusive memories in PTSD and their changes with treatment. *Journal of Traumatic Stress, 17,* 231-240.

Hatfield, T., & McGaugh, J.L. (1999). Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. *Neurobiology of Learning and Memory*, *71*, 232-239.

Hendrickson, R.C., & Raskind, M.A. (2016). Noradrenergic dysregulation in the pathophysiology of PTSD. *Experimental Neurology*, *284*, 181-195.

Hoge, E.A., Worthington, J.J., Nagurney, J.T., Chang, Y., Kay, E.B., Feterowski, C.M., …Pitman, R.K. (2012). Effect of acute posttrauma propranolol on PTSD

outcome and physiological responses during script-driven imagery. *CNS Neuroscience & Therapeutics*, *18*, 21-27.

Holmes, E.A., Brewin, C.R., & Hennessy, R.G. (2004). Trauma films, information processing, and intrusive memory development. *Journal of Experimental Psychology: General*, *133*(1), 3-22.

Holmes, E.A., James, E.L., Coode-Bate, T., & Deeprose, C. (2009). Can playing the computer game "Tetris" reduce the build-up of flashbacks for trauma? A proposal from cognitive science. *PLoS ONE*, *4*(1), e4153. doi:10.1371/journal. pone.0004153

Holmes, E.A., James, E.L., Kilford, E.J., & Deeprose, C. (2010). Key steps in developing a cognitive vaccine against traumatic flashbacks: Visuospatial Tetris versus Verbal Pub Quiz. *PLoS ONE*, *5*(11), e13706. doi:10.1371/journal.pone. 0013706

Hurlemann, R., Walter, H., Rehme, A.K., Kukolja, J., Santoro, S.C., Schmidt, C., Schnell, K., et al. (2010). Human amygdala reactivity is diminished by the β-noradrenergic antagonist propranolol. *Psychological Medicine*, *40*(11), 1839-1848.

IBM Corp. (2016). IBM SPSS Statistics (Version 24.0) [Windows]. Armonk, NY.

James, E.L., Lau-Zhu, A., Clark, I.A., Visser, R.M., Hagenaars, M.A., & Holmes, E.A. (2016). The trauma film paradigm as an experimental psychopathology model of psychological trauma: Intrusive memories and beyond. *Clinical Psychology Review*, *47*, 106-142.

James, G.D., Yee, L.S., Harshfield, G.A., Blank, S.G., & Pickering, T.G. (1986). The influence of happiness, anger, and anxiety on the blood pressure of borderline hypertensives. *Psychosomatic Medicine*, *48*(7), 502-508.

Joels, M., & Baram, T.Z. (2009). The neuro-symphony of stress. *Nature Reviews: Neuroscience*, *10*(6), 459-466.

Kemp, A., & Manhan-Vaughan, D. (2008). β-adrenoreceptors comprise a critical element in learning-facilitated long-term plasticity. *Cerebral Cortex*, *18*, 1326-1334.

Kreibig, S.D. (2010). Autonomic nervous system activity in emotion: A review. *Biological Psychology*, *84*, 394-421.

Kukolja, J., Klingmuller, D., Maier, W., Fink, G.R., & Hurlemann, R. (2011). Noradrenergic-glucocorticoid modulation of emotional memory encoding in the human hippocampus. *Psychological Medicine*, *41*, 2167-2176.

LeDoux, J. (1996). *The emotional brain.* New York, NY: Simon & Schuster.

Lemieux, A.M., & Coe, C.L. (1995). Abuse-related post-traumatic stress disorder: Evidence for chronic neuroendocrine activation in women. *Psychosomatic Medicine*, *57*, 105-115.

Liang, K.C., Juler, R.G., & McGaugh, J.L. (1986). Modulating effects of posttraining epinephrine on memory: Involvement of the amygdala noradrenergic system. *Brain Research*, *368*(1), 125-133.

Lonergan, M.H., Olivera-Figueroa, L.A., Pitman, R.K., & Brunet, A. (2013). Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: a meta-analysis. *Journal of Psychiatry and Neuroscience*, *38*, 222-231.

Lovallo, W.R. (2016). *Stress and health: Biological and psychological interactions. (3rd ed.).* Thousand Oaks, CA: SAGE Publications.

Lupien, S.J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T.E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition*, *65*, 209-237.

Maheu, F.S., Joober, R., Beaulieu, S., & Lupien, S.J. (2004). Differential effects of adrenergic and corticosteroid hormonal systems on human short- and long-term declarative memory for emotionally arousing material. *Behavioral Neuroscience*, *118*(2), 420-428.

McClelland, J.L., McNaughton, B.L., & O'Reilly, R.C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, *102*(3), 419-457.

McGaugh, J.L. (2000). Memory – a century of consolidation. *Science*, *287*, 248-251.

McGaugh, J.L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience*, *27*, 1-28.

McGhee, L.L., Maani, C.V., Garza, T.H., Desocio, P.A., Gaylord, K.M., & Black, I.H. (2009). The effect of propranolol on post-traumatic stress disorder in burned service members. *Journal of Burn Care Research*, *30*, 92-97.

McIntyre, C.K., & Roozendaal, B. (2007). Adrenal stress hormones and enhanced memory for emotionally arousing experiences. In F. Bermúdez-Rattoni (Ed.), *Neural plasticity and memory: From genes to brain imaging* (pp.265-284)*.* Boca Raton, FL: CRC Press/Taylor & Francis.

Metcalfe, J., & Jacobs, W.J. (1998). Emotional memory: The effects of stress on "cool" and "hot" memory systems. In D.L. Medin (Ed.), *The psychology of learning and motivation: Advances in research and theory (Vol. 38, pp.187-222)*. San Diego, CA: Academic Press.

Michael, T., Ehlers, A., Halligan, S.L., & Clark, D.M. (2005). Unwanted memories of

    assault: What intrusion characteristics are associated with PTSD? *Behaviour*

    Research and Therapy, 43, 613–628.

Mitte, K. (2008). Memory bias for threatening information in anxiety and anxiety

    disorders: A meta-analytic review. *Psychological Bulletin*, *134*(6), 886-911.

Monfils, M. H., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009). Extinction-

    reconsolidation boundaries: Key to persistent attenuation of fear memories.

    Science, 324, 951–955.

Nagengast, S.L., Baun, M.M., Megel, M., & Leibowitz, J.M. (1997). The effects of

    the presence of a companion animal on physiological arousal and behavioral

    distress in children during a physical examination. *Journal of Pediatric*

    Nursing, *12*(6), 323-330.

Nicholson, E.L., Bryant, R.A., & Felmingham, K.L. (2014). Interaction of

    noradrenaline and cortisol predicts negative intrusive memories in post-

    traumatic stress disorder. *Neurobiology of Learning and Memory*, *112*, 204-

    211.

Payne, J.D., & Nadel, L. (2004). Sleep, dreams, and memory consolidation: The

    role of the stress hormone cortisol. *Learning & Memory*, *11*, 671-678.

Pervanidou, P., Kolaitis, G., Charitaki, S., Lazaropoulou, C., Papassotiriou, I.,

    Hindmarsh, P., …Chrousos, G.P. (2007). The natural history of

    neuroendocrine changes in pediatric post-traumatic stress disorder (PTSD)

    after motor vehicle accidents: Progressive divergence of noradrenaline and

    cortisol concentrations over time. *Biological Psychiatry*, *62*, 1095-1102.

Phan, K.L., Wager, T., Taylor, S.F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, *16*(2), 331-348.

Pitman, R.K., Sanders, K.M., Zusman, R.M., Healy, A.R., Cheema, F., Lasko, N.B., Cahill, L., et al. (2002). Pilot study of secondary prevention of post-traumatic stress disorder with propranolol. *Biological Psychiatry*, *51*, 189-192.

Ramos, B.P., & Arnsten, A.F. (2007). Adrenergic pharmacology and cognition: Focus on the prefrontal cortex. Pharmacology & Therapeutics, 113(3), 523-536.

Reynolds, M., & Brewin, C.R. (1999). Intrusive memories in depression and post-traumatic stress disorder. *Behaviour Research and Therapy*, *37*(3), 201-215.

Rombold, F., Wingenfeld, K., Renneberg, B., Schwarzkopf, F., Hellmann-Regen, J., Otte, C., & Roepke, S. (2016). Impact of exogenous cortisol on the formation of intrusive memories in healthy women. *Journal of Psychiatric Research*, *83*, 71-78.

Roozendaal, B., Barsegyan, A., & Lee, S. (2008). Adrenal stress hormones, amygdala activation, and memory for emotionally arousing experiences. *Progress in Brain Research*, *167*, 79-97.

Roozendaal, B., McEwen, B.S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience*, *10*(6), 423-433.

Roozendaal, B., Okuda, S., van der Zee, E.A., & McGaugh, J.L. (2006). Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences*, *103*(17), 6741-6746.

Shaffer, F., & Ginsberg, J.P. (2017). An overview of heart rate variability metrics and norms. *Frontiers in Public Health*, *5*, 258. doi:10.3389/fpubh.2017.00258

Shin, L.M., Rauch, S.L., & Pitman, R.K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences*, *1071*, 67-79.

Sijbrandij, M., Kleiboer, A., Bisson, J.I., Barbui, C., & Cuijpers, P. (2015). Pharmacological prevention of post-traumatic stress disorder and acute stress disorder: a systematic review and meta-analysis*. Lancet Psychiatry*, *2*(5), 413-421.

Soni, M., Curran, V.H., & Kamboj, S.K. (2013). Identification of a narrow post-ovulatory window of vulnerability to distressing involuntary memories in healthy women. *Neurobiology of Learning and Memory*, *104*, 32-38.

Southwick, S.M., Bremner, J.D., Rasmusson, A., Morgan, C.A., III, Arnsten, A., & Charney, D.S. (1999). Role of norepinephrine in the pathophysiology and treatment of post-traumatic stress disorder. *Biological Psychiatry*, *46*, 1192-1204.

Southwick, S.M., Davis, M., Horner, B., Cahill, L., Morgan, C.A., III, & Gold, P.E., et al. (2002). Relationship of enhanced norepinephrine activity during memory consolidation to enhanced long-term memory in humans. *American Journal of Psychiatry*, *159*, 1420-1422.

Southwick, S.M., Krystal, J.H., Morgan, C.A., Johnson, D., Nagy, L.M., Nicolaou, A., …Charney, D.S. (1993). Abnormal noradrenergic function in post-traumatic stress disorder. *Archives of General Psychiatry*, *50*, 266-274.

Smith, A., Brice, C., Nash, J., Rich, N., & Nutt, D.J. (2003). Caffeine and central noradrenaline: Effects on mood, cognitive performance, eye movements and cardiovascular function. *Journal of Psychopharmacology*, *17*(3), 283-292.

Spielberger, C.D. (1983). *Manual for the State-Trait Anxiety Inventory (STAI).* Palo Alto, CA: Consulting Psychologists Press.

Stein, M.B., Kerridge, C., Dimsdale, J.E., & Hoyt, D.B. (2007). Pharmacotherapy to prevent PTSD: Results from a randomized controlled proof-of-concept trial in physically injured patients. *Journal of Traumatic Stress*, *20*(6), 923-932.

Strange, B.A., & Dolan, R.J. (2004). β-adrenergic modulation of emotional memory-evoked human amygdala and hippocampal responses. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 11454-11458.

Thayer, J.F., Ahs, F., Fredrickson, M., Sollers, J.J., & Wager, T.D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Reviews*, *36*, 747-756.

Ulrich-Lai, Y.M., & Herman, J.P. (2009). Neural regulation of endocrine and autonomic stress. *Nature Reviews Neuroscience*, *10*(6), 397-409.

van Cauter, E., & Turek, F.W. (1995). Endocrine and other biological rhythms. In L.J. De Groot, (Ed.), *Endocrinology* (pp. 2487-2548). Philadelphia, PA: Saunders.

van der Kolk, B. A., & Fisler, R. (1995). Dissociation and the fragmentary nature of traumatic memories: Overview and exploratory study. *Journal of Traumatic Stress*, 8, 505-525.

van Stegeren, A.H. (2008). The role of the noradrenergic system in emotional memory. *Acta Psychologica*, *127*, 532-541.

van Stegeren, A.H. (2009). Imaging stress effects on memory: A review of neuroimaging studies. *Canadian Journal of Psychiatry*, *54*(1), 16-27.

van Stegeren, A. H., Everaerd, W., Cahill, L., McGaugh, J. L., & Gooren, L. J. (1998). Memory for emotional events: Differential effects of centrally versus peripherally acting beta-blocking agents. *Psychopharmacology*, *138*(3-4), 305-310.

van Stegeren, A.H., Goekoop, R., Everaerd, W., Scheltens, P., Barkhof, F., & Kuijer, J. P. et al. (2005). Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. *Neuroimage*, *24*, 898-909.

van Stegeren, A. H., Wolf, O.T., Everaerd, W., Scheltens, P., Barkhof, F., & Rombouts, S.A.R.B. (2007). Endogenous cortisol level interacts with noradrenergic activation in the human amygdala. *Neurobiology of Learning and Memory*, *87*, 57-66.

Vyas, A., Mitra, R., Rao, B.S.S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience*, *22*(15), 6810-6818.

Watson, D., Clark, L.A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063-1070.

Wolf, O.T. (2008). The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychologica*, *127*, 513-531.

Yehuda, R., Southwick, S.M., Giller, E.L., Xiaowan, M.A., & Mason, J.W. (1992).

　　Urinary catecholamines excretion and severity of PTSD symptoms in Vietnam

　　Veterans. *Journal of Nervous and Mental Disorders*, *180*, 321-325.

Zald, D.H. (2003). The human amygdala and the emotional evaluation of

　　sensory stimuli. *Brain Research Reviews*, *41*(1), 88–123.

PART 3: Critical Appraisal

(2753 words)

Introduction

This critical appraisal explores several conceptual and practical issues encountered in the research. First, it will address issues associated with the use of an analogue trauma paradigm and particular memory measures (intrusion diary, free/cued recall tasks). It will then explore further implications of current findings in research and clinical contexts. It will conclude with personal reflections on the research process.

Issues Associated with Aspects of Study Methodology

1   Use of Analogue Trauma Paradigm

The exposure of healthy participants to traumatic events in order to determine the efficacy of potential interventions for trauma is not ethical. Yet, studies conducted with clinical populations are subject to a variety of methodological difficulties – for example, difficulties in obtaining access to suitable samples, reliably determining the events that meet Post-traumatic Stress Disorder (PTSD) criteria and validating the occurrence of these events (Corcoran, Green, Goodman, & Krinsley, 2000), and considering the costs and benefits of participants' involvement (Newman & Kaloupek, 2009). Alternative methodologies such as fear conditioning do not mirror the complexity of actual traumatic experiences (James et al., 2016). Analogue trauma paradigms, which induce some trauma symptoms in healthy individuals (such as the use of 'trauma films' or other ways of presenting traumatic stimuli, e.g. pictures), have recently begun to fill this gap. These offer a more ethically-acceptable way to probe the processes involved in trauma memory consolidation and reconsolidation, and test interventions purporting to aid the primary and secondary prevention of PTSD symptoms (e.g. Holmes, James, Kilford, & Deeprose, 2010).

Notwithstanding their numerous merits, the use of an analogue trauma paradigm in this study raised several important issues which merit consideration. One of these was the extent to which the one-off viewing of a 'trauma film' paralleled actual traumatic experiences – even if the events portrayed in the film were considered traumatic events, and even if repeated indirect media exposure to such events has been acknowledged as a potential cause of PTSD (both as per DSM-5 PTSD diagnostic criteria; American Psychiatric Association, 2013). It is worth noting that James et al.'s (2016) review of relevant literature concluded that although repeated indirect exposure to traumatic events can be associated with more severe PTSD symptoms compared to direct exposure to the same events, more investigation of indirect trauma exposure is also needed (e.g. individual differences which increase/decrease vulnerability to PTSD after indirect trauma exposure).

Further, the ability of the 'trauma film' to result in a (small) number of intrusions (Das et al., 2016) is difficult to completely reconcile with theories such as the Dual Representation Theory (DRT), which suggest that moderate levels of emotional distress result in more strongly-encoded contextual representations which are also closely associated with strongly-encoded sensory representations. In principle, such encoding should prevent intrusions, as sensory representations will be retrieved alongside information regarding their contexts (Brewin, Gregory, Lipton, & Burgess, 2010). Yet, if intrusions caused by the film are accompanied by contextual information/only weakly associated with a sense of reliving, this raises queries about the extent to which these parallel intrusions caused by real-world trauma, given already-apparent differences between the two in their frequency and persistence over time. On the other hand, if intrusions arising from the film and those arising from real-world trauma are equivalent, this poses questions about the factors which trigger shifts from healthy emotional memory encoding to traumatic

memory encoding (e.g. psychological/emotional distress, socialised cognitive evaluations regarding the implications of the event); also, is there a line between 'normal' film-viewing and indirect media exposure to traumatic events (i.e. does the viewing of all violent events, fictional or otherwise, constitute some form of indirect trauma along a continuum of severity), and where does it lie if so?

Theories which propose that intrusive memories lie on a spectrum of severity (Brewin, 2015) suggest that it is appropriate to extrapolate findings from analogue trauma paradigms to actual trauma. However, further methodological research comparing analogue trauma, real-world direct trauma and real-world indirect trauma and their effects (e.g. degrees of distress, patterns/characteristics of subsequent symptomatology, fit with theoretical models of PTSD) would increase understanding of overlaps and differences between these. This would aid conclusions about the extent to which findings from the analogue trauma paradigm can be generalised to real-world trauma. Further, Bailey, Dawson, Dourish, and Nutt (2011) outline several requirements that an experimental model of anxiety should meet (e.g. the need for it to have a measurable endpoint, be translatable to clinic settings in its current form, and have measurable psychological and physical effects). It remains to be seen if the analogue trauma paradigm meets applicable criteria. These issues underline the necessity for effects observed in this study to be replicated in clinical populations before conclusions can be confidently drawn.

Of course, any attempt to evoke a trauma response – regardless of the means by which this is done, and the severity of distress caused – also requires the consideration of associated ethical issues. While participants were expected to have an emotional response, steps were taken to regulate the psychological impact of the film: for example, ensuring that participants were aware of the nature of the film beforehand and their right to withdraw at any point in the experiment (as one

participant later did during the film), and excluding participants with trauma histories and psychiatric conditions.

2   Use of Intrusion Diary and Free Recall/Cued Recall Tasks

Likewise, issues related to the use of a daily online diary to monitor intrusions had to be thought about and discussed. The desire for greater accuracy had to be balanced against the amount of effort required of participants. A daily online intrusion diary ostensibly increases accuracy compared to retrospective self-report measures completed only after a delay (e.g. 1 week or 1 month). More frequent prompts to complete the diary at randomly-spaced intervals over the day might have increased the number of intrusions recorded, since such probes increase individuals' awareness of intrusions (Takarangi, Strange, & Lindsay, 2014), but may have increased effort required and decreased compliance. Furthermore, it is difficult to assess participants' compliance to instructions and the accuracy of their reports, particularly in view of forgetting over the day and potential memory/response biases. While random variation would likely have reduced the impact of this on between-group differences, and there were minimal amounts of missing data, additional methodological research studying the impact of prompt frequency on the number/characteristics of intrusive memories reported may aid future research decisions. Convergent measures could also be administered at the end of the period (James et al., 2016).

Also, the use of free recall and cued recall measures (i.e. both generally, and the tasks particular to this study) rests on assumptions regarding their validity in assessing voluntary memory for film content, and regarding their sensitivity to the process of voluntary retrieval. Different types of measures and retrieval cues (e.g.

different sets of cued recall prompts) could be used to determine if additional findings are consistent with hypotheses.

Additional implications of study findings

1   Further research implications

Beyond the trauma- and memory-related implications of the analogue trauma paradigm mentioned in the empirical paper (see Part 2, Discussion, Section 4), it may also be extended in a variety of ways to investigate the occurrence of intrusive thoughts, both in healthy populations as well as in the context of other psychiatric conditions (e.g. depression). For example, differences in individuals' susceptibility to film-related intrusive memories given pre-existing psychopathology, and the kinds of intrusive memories which such individuals are more susceptible to, could be examined (e.g. by comparing individuals suffering from such psychopathology with those who are not, or by using mood induction procedures; Kučera & Haviger, 2012). The characteristics of intrusions (e.g. vividness) caused by films that evoke different types of strong affect (e.g. sadness, anger, happiness) could also be studied to determine the specificity of effects observed in this study.

The weak relationship between trait mood and intrusions suggests that the influence of the former on the latter is minimal. This is inconsistent with the proposal that individuals with more severe depression/anxiety symptoms are more susceptible to experiencing intrusive memories (e.g. contributed to by cognitive patterns such as rumination; Brewin et al., 2010). This discrepancy might have been contributed to by the fact that intrusive memories reported in previous studies were related to life events of considerable personal relevance (e.g. death, abuse), and had been encoded prior to the depressive episode (and thus likely reactivated and reconsolidated multiple times). These differences suggest interesting potential

avenues for research on the characteristics/mechanisms of intrusive memories retrieval in individuals with depression, with implications for our understanding of the relationship between depression and intrusive memories.

2   Further clinical implications

Of course, given ongoing concerns about generalisability, it would be premature to position propranolol as an alternative to current treatments. Nonetheless, when considering the potential implementation of such a treatment in NHS settings, several issues may need to be taken into account. Firstly, at face value, the news that a single dose of propranolol has the potential to treat intrusive memories will likely be welcome in the NHS, given the relatively low cost of a single dose of propranolol and the current financial climate. However, more detailed analysis of the benefits and costs of propranolol treatment is required – for example, weighing up the combined cost of propranolol and the cost of the staff time required to administer it, against potentially small effects on intrusive memories/lack of effects on other PTSD symptoms. Propranolol also needs to be compared to other treatments that – while perhaps more resource-intensive – might be able to treat more symptoms of PTSD to greater effect. Further, the extent to which propranolol administration can realistically take place immediately after trauma is questionable, as trauma victims might not have direct access to healthcare professionals. This emphasises the need for more research on propranolol's specific effects on intrusive memories, its effects on other PTSD symptoms, and the timeframe in which it disrupts intrusive memory consolidation in clinical populations. This will facilitate informed decisions on feasibility and usefulness.

Personal Reflections

1   Practicalities of the Research Process

This study confronted me with several practical issues inherent in real-world research that might be of particular relevance for the inexperienced researcher.

1.1   Complexities of collaboration.

This research involved collaboration with another Doctorate in Clinical Psychology trainee and several Master's students – and, speaking more broadly, with our supervisors. This had several advantages in line with those proposed by Rigby and Edler (2005): members of the group brought different complementary strengths and expertise to the endeavour (e.g. bodies of theoretical and technical knowledge, planning experience, qualities such as orientation to detail and pragmatism). This benefited both our individual learning, as well as the quality of the research (e.g. through the process of reaching a consensus about the most appropriate ways to go about the work, being able to ask for assistance if one was unsure about a particular task). In addition, experiment planning and data collection was less time-consuming for each of us simply by virtue of more people being involved. Nevertheless, the micro- and macro-processes occurring in collaborative work are complex, and the costs of collaboration were apparent. For example, efforts had to be made to generate and preserve a constructive, creative dynamic within the team. The roles each person played had to be negotiated and adjusted as time went on; we also had to take steps to standardise experiment administration across group members and ensure that everyone was familiar with technical procedures which one person in the group had learnt. Technology (e.g. WhatsApp groups, Skype, Google Drive) was helpful in facilitating communication and sharing of resources while minimising additional burdens on time/resources. Further, I was

conscious of the potential tendency to conform to peer pressure rather than taking a stand on issues or querying the bases for particular decisions, and of the negative effects this might have on the quality of research. There was a need to act against anxiety and actively monitor my agreement with outcomes of discussions.

1.2   The enormity of 'small' decisions.

There was a large number of 'small' decisions that had to be made even within the setup of a general research design – for example, drug dosage, the timing of drug administration/checks on drug effects, the nature of filler tasks, and the amount of remuneration participants were offered. Moreover, the number and types of inclusion and exclusion criteria were infinitely extendable, leaving the decision regarding an appropriate endpoint open. These decisions were especially stressful because we were conscious of their potential effects on recruitment and study findings, and of the consequences of attempting to reverse them once data collection had begun. Within this, the importance of a broad familiarity with the relevant literature (e.g. factors that might affect outcome measures, the time at which the intervention would have effects) was clear, without which some issues might not even have entered consideration. There was also a need to continually consider where we stood on the balance between doing too little (at the expense of rigour) and too much (at the expense of resources, participant effort and generalisability).

1.3   Dealing with unexpected events.

The involvement of humans (e.g. participants, experimenters, other researchers using the same laboratory) led inevitably to various practical issues which I had not foreseen. For example, one participant stated partway through a

session that she needed to leave early; errors were nearly made in the data-importing process for eyetracking data; rooms were double-booked. These problems had to be flexibly dealt with in the moment to minimise their impact on findings. This highlighted the necessity for preparation and rehearsal of procedures ahead of the actual experiment – while these did not necessarily prevent such situations, familiarity with what was expected at each stage and the rationale for these steps allowed us more cognitive resources to deal with unexpected events. Ensuring that we possessed multiple copies of the data also helped to reduce the potential consequences of experimenter error.

2   Psychological versus Pharmacological Interventions

Interestingly, despite my excitement about the findings of this study and their consistency with hypotheses I had arrived at previously, I noticed that I also experienced emotions of surprise and anxiety. Upon reflection, I realised that I entertained concurrent contradictory beliefs about the efficacy of pharmacological treatments in PTSD, drawn from the different contexts in which I operated (Pearce, 1994). As a researcher, I had believed that propranolol would have an effect on intrusive memories given prior evidence, and was happy to receive further confirmation of this belief. However, as a trainee clinical psychologist, I knew that the primary treatment for trauma symptoms was trauma-focused psychological therapies (National Institute for Clinical Excellence, 2005), and that medication was not routinely prescribed for PTSD – although I also knew that psychological and pharmacological interventions used in combination could enhance benefits for mental health beyond what each could achieve. At the same time, as a self-appointed 'educated consumer' of popular media, media representations of MDMA as a potential "remedy" for PTSD symptoms – which had simultaneously downplayed the role of therapy despite concurrent administration of the two in trials

– were fresh in my mind, as were previous popular statements that propranolol could "cure fear" (both of which I had recoiled from). Perhaps I had come to assume the privileged status of psychological therapies in the treatment of PTSD symptoms, and to believe that the putative effects of drugs on PTSD were gross oversimplifications of the 'truth'. Thus, the demonstrated impact of propranolol on intrusive memories seemed almost 'too good to be true'.

These findings challenged my assumptions. They reminded me that the treatment of psychological disorders is not a competition or a zero-sum game, and that the end of interventions is to reduce human distress. Not only can psychological and pharmacological therapies be used in combination to maximise effects (e.g. reducing intrusive memories using propranolol, then treating the remaining symptoms with psychological therapies), but crossovers between the two fields can also catalyse further helpful research (e.g. potential effects of propranolol on intrusive memories can be postulated based on psychological theories and tested empirically).

Conclusion

Overall, this research highlighted the advantages of the analogue trauma experimental paradigm. However, it also underlined the issues associated with the use of this, the intrusion diary and particular voluntary recall tasks. These require further exploration to disentangle. At the same time, this research generated potential avenues for research – on intrusions and their relationships with mood and psychopathology, and on the feasibility of propranolol's use in healthcare settings. Personally, it highlighted the practicalities of collaboration, decision-making, and managing unexpected events. It also revealed my contradictory beliefs and challenged my assumptions regarding the treatment of psychological disorders.

References

Bailey, J.E., Dawson, G.R., Dourish, C.T., & Nutt, D.J. (2011). Validating the inhalation of 7.5% CO2 in healthy volunteers as a human experimental medicine: A model of generalized anxiety disorder (GAD). *Journal of Psychopharmacology*, *25*(9), 1192-1198.

Brewin, C.R., Gregory, J.D., Lipton, M., & Burgess, N. (2010). Intrusive images in psychological disorders: Characteristics, neural mechanisms, and treatment implications. *Psychological Review*, *117*(1), 210-232.

Corcoran, C.B., Green, B.L., Goodman, L.A., & Krinsley, K.E. (2000). Conceptual and Methodological Issues in Trauma History Assessment. In Shalev A.Y., Yehuda R., McFarlane A.C. (eds.) *International Handbook of Human Response to Trauma. Springer Series on Stress and Coping.* Boston, MA: Springer.

Holmes, E.A., James, E.L., Kilford, E.J., & Deeprose, C. (2010). Key steps in developing a cognitive vaccine against traumatic flashbacks: Visuospatial Tetris versus Verbal Pub Quiz. *PLoS ONE*, *5*(11), e13706. doi:10.1371/journal.pone. 0013706

James, E.L., Lau-Zhu, A., Clark, I.A., Visser, R.M., Hagenaars, M.A., & Holmes, E.A. (2016). The trauma film paradigm as an experimental psychopathology model of psychological trauma: Intrusive memories and beyond. *Clinical Psychology Review*, *47*, 106-142.

Kučera, D., & Haviger, J. (2012). Using mood induction procedures in psychological research. *Procedia - Social and Behavioral Sciences*, *69*, 31-40.

National Institute for Clinical Excellence (2005*). Post-traumatic stress disorder: Management. NICE guideline (CG26).*

Newman, E., & Kaloupek, D. (2009). Overview of Research Addressing Ethical

    Dimensions of Participation in Traumatic Stress Studies: Autonomy and

    Beneficence. *Journal of Traumatic Stress*, *22*(6), 595-602.

Pearce, W.B. (1994). *Interpersonal Communication: Making Social Worlds.* New

    York, NY: Harper Collins College.

Rigby, J., & Edler, J. (2005). Peering inside research networks: Some observations

    on the effect of the intensity of collaboration on the variability of research

    quality. *Research Policy*, *34*(6), 784-794.

Takarangi, M.K.T., Strange, D., & Lindsay, D.S. (2014). Self-report may

    underestimate trauma intrusions. *Consciousness and Cognition*, *27*, 297-305.

Appendix 01: Studies excluded based on inclusion and exclusion criteria

Reason for exclusion	Number of studies
No primary data (e.g. reviews, conceptual papers)	15
Involved intervention (e.g. drug efficacy studies, psychotherapy studies)	42
Did not elicit specific information regarding individuals' exposure to traumatic event(s), and PTSD status and/or symptoms	6
Did not define ≥1 characteristic of dreams being measured	7
No specific measures of dreaming	58
Psychoanalytic orientation	1*
Total excluded	**129**

*Other papers written in a psychoanalytic orientation have been classified under other reasons for exclusion

Appendix 02: Standard tool used to assess research quality of papers (based on 'QualSyst' tool and Pluye et al., 2009)

Checklist for assessing the quality of quantitative studies

	Criteria	Yes (2)	Partial (1)	No (0)	N/A
1	Question / objective sufficiently described?				
2	Study design evident and appropriate?				
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?				
4	Subject (and comparison group, if applicable) characteristics sufficiently described?				
5	If interventional and random allocation was possible, was it described?				
6	If interventional and blinding of investigators was possible, was it reported?				
7	If interventional and blinding of subjects was possible, was it reported?				
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?				
9	Sample size appropriate?				
10	Analytic methods described/justified and appropriate?				
11	Some estimate of variance is reported for the main results?				
12	Controlled for confounding?				
13	Results reported in sufficient detail?				
14	Conclusions supported by the results?				

Checklist for assessing the quality of qualitative studies

	Criteria	Yes (2)	Partial (1)	No (0)
1	Question / objective sufficiently described?			
2	Study design evident and appropriate?			
3	Context for the study clear?			
4	Connection to a theoretical framework / wider body of knowledge?			
5	Sampling strategy described, relevant and justified?			
6	Data collection methods clearly described and systematic?			

7	Data analysis clearly described and systematic?			
8	Use of verification procedure(s) to establish credibility?			
9	Conclusions supported by the results?			
10	Reflexivity of the account?			

Additional criteria for assessing the quality of mixed methods designs

Criteria		Presence (1)	Absence (0)
1	Mixed methods design justified?		
2	Combination of qualitative and quantitative data collection-analysis techniques or procedures used?		
3	Qualitative and quantitative data or results integrated?		

Scoring guidelines

Items are scored depending on the degree to which each item is met ("yes" = 2, "partial" = 1, "no" = 0), and the total score obtained by each paper is then calculated as a percentage of its total possible score.

For quantitative studies:

> **Total sum** = (number of "yes" * 2) + (number of "partials" * 1)
> **Total possible sum** = 28 – (number of "N/A" * 2)
> **Summary score:** total sum / total possible sum   *Max. score = 1*

For qualitative studies:

> **Total sum** = (number of "yes" * 2) + (number of "partials" * 1)
> **Total possible sum** = 20
> **Summary score:** total sum / total possible sum   *Max. score = 1*

For mixed methods studies:

1) Evaluate quantitative and qualitative study components as per above.
2) Appraise mixed methods design:
> **Total sum** = number of "presence" * 1
> **Total possible sum** = 3
> **Summary score:** total sum / total possible sum   *Max. score = 1*

Appendix 03: Ethics approval letter

UCL RESEARCH ETHICS COMMITTEE
ACADEMIC SERVICES

31st October 2016

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

Dear Dr Kamboj

<u>**Notification of Ethical Approval**</u>
<u>**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**</u>

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 **30th 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) 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) 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.

Yours sincerely

Professor John Foreman
Chair, UCL Research Ethics Committee

Enc.

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

Appendix 04: Approval of ethics amendment

Amendment Approval Request Form

1	**Project ID Number:** 5583/002	**Name and Address of Principal Investigator:** Sunjeev Kamboj, Reader in Clinical Psychology Research Department of Clinical, Educational and Health Psychology, UCL

2	**Project Title:** 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

3	**Type of Amendment/s (tick as appropriate)** Research procedure/protocol (including research instruments) ☒ Participant group ☐ Sponsorship/collaborators ☐ Extension to approval needed (extensions are given for one year) ☐ Information Sheet/s ☐ Consent form/s ☐ Other recruitment documents ☐ Principal researcher/medical supervisor* ☐ Other ☐ *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 *

4	**Justification** (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).

5	**Details of Amendments** (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.

6	**Ethical Considerations** (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.

7	**Other Information** (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

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 05: Trainees' contribution to joint study

Another UCL Doctorate in Clinical Psychology trainee, two Master's degree students, and I jointly collected data. I and the other trainee independently analysed data from placebo controls and only one other treatment arm (i.e. propranolol or hydrocortisone). This paper's focus is comparisons between the propranolol and placebo groups.

Appendix 06: Study Information Sheet

<div style="border:1px solid black; padding:10px;">

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:
	Tel:

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

</div>

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 you 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 <u>do not take part</u> 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 capsules (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 <u>absolutely crucial</u> 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:

_____

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.

Appendix 07: Study consent form

<u>Informed consent for participants involved in memory consolidation research study using cortisol and propranolol</u>

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.:

Appendix 08: Emotion-related visual analogue scales (E-VAS's) assessing acute emotional states

Please indicate *how you feel right now* by marking the line below.

Your responses:

How **disgusted** do you feel right now?

| Not at all DISGUSTED | | | | | | | | Very DISGUSTED | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

How **frightened** do you feel right now?

| Not at all FRIGHTENED | | | | | | | | Very FRIGHTENED | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

How **angry** do you feel right now?

| Not at all ANGRY | | | | | | | | Very ANGRY | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

How **sad** do you feel right now?

| Not at all SAD | | | | | | | | Very SAD | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

How **happy** do you feel right now?

| Not at all HAPPY | | | | | | | | Very HAPPY | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

How **distressed** do you feel right now?

| Not at all DISTRESSED | | | | | | | | Very DISTRESSED | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

Appendix 09: Bodily Symptoms Scale (BSS)

1. Please rate the way you feel in terms of the dimensions given below
2. Regard the line as representing the full range of each dimension
3. Rate your feelings as they are AT THE MOMENT
4. Mark the line on a spot that most closely represents how you are feeling

Your responses:

No anxiety   Very severe anxiety

No depression   Very severe depression

No impairment to memory   Very severe impairment to memory

No palpitations or heart beating fast   Very severe palpitations or heart beating fast

No nausea or sickness   Very severe nausea or sickness

No feeling of being emotionally numb   Strong feeling of being emotionally numb

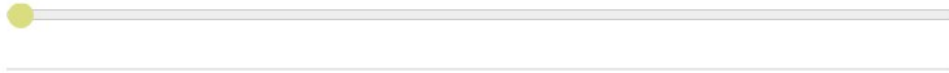No euphoria   Very strong euphoria

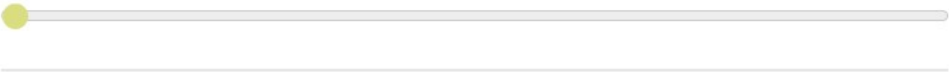No drowsiness   Very severe drowsiness

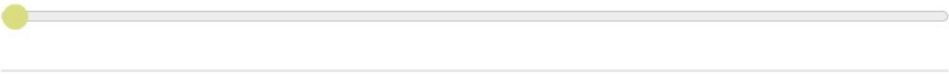No muscular tension   Very severe muscular tension

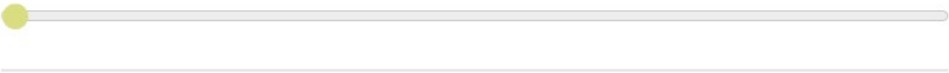No headache   Very severe headache

No loss of concentration   Very severe loss of concentration

No shaking or trembling   Very severe shaking or trembling

No confusion   Very severe confusion