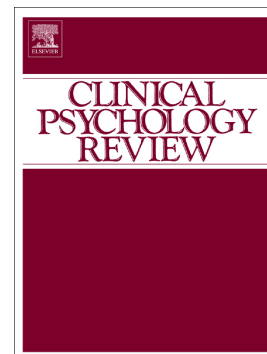


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Intrusive memories of trauma: a target for research bridging cognitive science
and its clinical application

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Abstract

Intrusive memories of a traumatic event can be distressing and disruptive, and comprise a core clinical feature of post-traumatic stress disorder (PTSD). Intrusive memories involve mental imagery-based impressions that intrude into mind involuntarily, and are emotional. Here we consider how recent advances in cognitive science have fuelled our understanding of the development and possible treatment of intrusive memories of trauma. We conducted a systematic literature search in PubMed, selecting articles published from 2008 to 2018 that used the terms “trauma” AND (“intrusive memories” OR “involuntary memories”) in their abstract or title. First, we discuss studies that investigated internal (neural, hormonal, psychophysiological, and cognitive) processes that contribute to intrusive memory development. Second, we discuss studies that targeted these processes using behavioural/pharmacological interventions to reduce intrusive memories. Third, we consider possible clinical implications of this work and highlight some emerging research avenues for treatment and prevention, supplemented by new data to examine some unanswered questions. In conclusion, we raise the possibility that intrusive memories comprise an alternative, possibly more focused, target in translational research endeavours, rather than only targeting overall symptoms of disorders such as PTSD. If so, relatively simple approaches could help to address the need for easy-to-deliver, widely-scalable trauma interventions.

Keywords: Intrusive memory; Mental imagery; Post-traumatic Stress Disorder;
Psychological trauma; Treatment innovation; Cognitive science.

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1. Introduction: reviewing cognitive science for its clinical implications in the area of intrusive memories of trauma

In this review, we examine specific advances in cognitive science that pertain to the topic of intrusive memories of trauma. This review is part of a special issue, led and edited by Professor Bethany Teachman, which illustrates how advances in cognitive science have improved our understanding of the aetiology, maintenance, and reduction of psychopathology, while also highlighting the many questions that remain unanswered. Here, we demonstrate how combining research from different fields is starting to improve our understanding of the development and reduction of intrusive memories.

1.1. What are intrusive memories of trauma?

After suffering psychological trauma, people can repeatedly experience sensory-perceptual impressions of the event, which intrude involuntarily into consciousness (Ehlers & Steil, 1995; Michael, Ehlers, & Halligan, 2005). These “intrusive memories” typically take the form of visual images (e.g., pictures in the mind’s eye), but can also include sounds, smells, tastes and bodily sensations (Ehlers, Hackmann, & Michael, 2004), and come with a range of negative emotions associated with the “hotspots” in the trauma memory (Grey & Holmes, 2008). For example, after having a head-on collision in their car, a person may describe intrusive images of seeing “dust and smoke, debris everywhere” and hearing the “bang” of the airbags (Iyadurai et al., 2017, supplementary information).

1.2. Why are we interested in intrusive memories of trauma?

Over the course of their lifetime, most people will experience or witness a traumatic event (estimated up to 70%; Benjet et al., 2016), in which they are exposed to “actual or threatened death, serious injury, or sexual violence” (Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-5; American Psychiatric Association, 2013, p. 271). Intrusive memories are common following trauma exposure, especially in the first few days and weeks. For most people, they abate over time. For example, in a study of motor vehicle accident patients, 76% had intrusive memories in the first few weeks, dropping to 25% at 3 months, and 24% at 1 year (Mayou, Bryant, & Duthie, 1993). Therefore, the presence of early intrusive memories does not necessarily indicate that they will persist; for some they will, for others they will not.

Regardless of their time course, intrusive memories may in and of themselves be associated with clinical levels of distress and perceived functional impairment, either early after trauma or later. In other words, they may cause distress in their own right - even if they occur outside of a diagnosed psychological disorder. One example is in the case of sub-threshold Post-Traumatic Stress Disorder (PTSD), in which symptoms are associated with clinical impairment, even though the full disorder is not diagnosed (Zlotnick, Franklin, & Zimmerman, 2002). However, intrusive memories will not be associated with clinical impairment for everyone. Indeed, intrusive memories are

considered to lie on a continuum with non-clinical involuntary memory experiences in daily life (Berntsen, 2009).

For some people, intrusive memories from as early as the first few days are not only associated with clinical distress and functional impairment, but are also recognised as a symptom of a psychological disorder. Specifically, “recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)” are symptoms of both Acute Stress Disorder (ASD) from 3 days to 1 month post-trauma and PTSD from one month post-trauma (American Psychiatric Association, 2013). While intrusive memories occur across many other psychological disorders (Brewin, Gregory, Lipton, & Burgess, 2010; Holmes & Mathews, 2010), and hence hold transdiagnostic relevance to clinical psychology, in PTSD they comprise a core clinical feature.

Cognitive models of PTSD place intrusive memories of trauma at the hub of symptomatology (Brewin, 2014; Brewin & Holmes, 2003; Ehlers & Clark, 2000) – potentially acting as a driver of the other three symptom clusters (avoidance, negative alterations in cognitions and mood, and hyperarousal). For example, when they spring to mind, intrusive memories elicit high levels of emotional distress (Ehlers & Steil, 1995; Foa & Riggs, 1993), and can be “attention hijacking” (Clark & Mackay, 2015), with the potential to disrupt concentration and cause impairment in day-to-day functioning (Holmes et al., 2017). Network models of PTSD have demonstrated that intrusive memories are centrally connected to and likely to activate other symptoms of the disorder (Bryant et al.,

2017; see also Haag, Robinaugh, Ehlers, & Kleim, 2017). This has raised the suggestion that “clinically targeting an important core symptom, such as intrusive re-experiencing in PTSD... can produce downstream beneficial effects on other symptoms in a kind of therapeutic cascade” (McNally, 2012, p. 225).

However, as mentioned earlier, not all intrusive memories of trauma are associated with psychopathology; nor are all early intrusive memories associated with longer-term symptoms. One view is that intrusive memories after trauma may, at times, serve some adaptive function in the survival of the physical and psychological self (Krans, Näring, Becker, & Holmes, 2009). For example, they may act as “warning signals” to help prevent future harm (Ehlers et al., 2002) or may aid protection of self-coherence in autobiographical memory (Conway & Pleydell-Pearce, 2000; Conway, Singer, & Tagini, 2004). As yet, we are unable to accurately predict whether early intrusive memories following trauma are indicative of long-term poor prognosis or not. Such issues are common to secondary prevention endeavours and are discussed further in Section 5.2 on “Prevention and early intervention soon after trauma”.

1.3. What is the focus of this review?

In this review, we focus on intrusive memories as one key symptom that can arise after trauma. Specifically, we discuss how cognitive science has made notable theoretical contributions to our understanding of intrusive memory development and has opened up possible new intervention approaches.

Throughout the review, we consider intrusive memories as a clinical phenomenon

of interest in its own right, as well as an important symptom of psychopathology following trauma, i.e., in the broader context of ASD and PTSD.

Treatments following trauma need to be progressed in a number of ways. First, we currently lack mechanistic insights into the effectiveness of existing treatments (Kazdin, 2007), including those to address psychopathology after trauma; such mechanistic insights are crucial, given that not everyone benefits from existing treatments (Hoge & Chard, 2018; Holmes, Craske, & Graybiel, 2014). Second, preventive interventions after trauma are lagging behind (Roberts, Kitchiner, Kenardy, & Bisson, 2009; Sijbrandij, Kleiboer, Bisson, Barbui, & Cuijpers, 2015). Third, interventions that can be scaled up and adapted for global use are much-needed. A recent editorial has called for “a more substantive evolution in PTSD treatments” and suggested that “novel treatment approaches need to be aggressively pursued.” (Hoge & Chard, 2018, p. 344).

We suggest that focusing on intrusive memories of trauma may help in developing new approaches to therapeutic interventions through a targeted (precision) approach. Further, focusing on the single process of intrusive memory, rather than the whole disorder, allows us to bridge between cognitive science research and psychopathology research with greater precision, as cognitive science tends to examine specific processes in isolation under controlled conditions.

In this review we describe some key theories, methods and findings from cognitive science that have offered insights into the development and reduction of

intrusive memories of trauma, rather than PTSD as a whole. We refer the reader to other excellent reviews on cognitive factors in PTSD (Elwood, Hahn, Olatunji, & Williams, 2009; Hayes, Vanelzakker, & Shin, 2012) and on intrusive memories in the context of PTSD specifically (Brewin, 2011, 2014; Brewin et al., 2010; Ehlers, 2010; Ehlers et al., 2004).

Our review focuses on recent studies (within the last decade) that have investigated causal associations, and that highlight distal and proximal internal factors, such as neural, hormonal, psychophysiological and cognitive processes. First, we discuss studies that investigated processes that contribute to intrusive memory development, followed by studies that targeted these processes using behavioural/pharmacological interventions to reduce intrusive memories. Next, we consider possible clinical implications of this work and highlight some emerging research avenues, which are supplemented by new data to examine some unanswered questions. We finish with a discussion of some of the merits and limitations of the research reviewed. In conclusion, we raise the possibility that intrusive memories comprise an alternative, possibly more focused, target in translational research endeavours, rather than only targeting overall symptoms of PTSD.

2. Method: systematic literature search

A search of PubMed was conducted to identify articles published from 2008 to 2018 (for pragmatic reasons we chose the last decade), using the terms “trauma” AND (“intrusive memories” OR “involuntary memories”) in their

abstract or title. The 112 articles resulting from this search, as well as relevant references cited in those articles, were selectively reviewed. Titles and abstracts were used to screen articles suitable for inclusion. Articles were selected if they were peer-reviewed; published in English; presented data obtained from human participants; and intrusive memories of (experimental) trauma was one of the outcome measures and reported separately from other PTSD symptoms (i.e., not only as part of the PTSD re-experiencing symptom cluster score, as this encompasses other symptoms such as nightmares and physiological reactivity). Furthermore, we only selected studies that either used prospective correlational designs or experimental manipulations to obtain insights into factors that might causally contribute to the development and change in intrusive memories. We excluded genetic, cross-sectional correlational, qualitative, uncontrolled pilot studies and case studies. Of the 112 articles resulting from the search, 52 articles met the inclusion criteria. An additional 24 eligible articles were identified via cross-references, yielding 76 articles in total.

3. Insights from cognitive science on the development of intrusive memories

In this section we aim to present an overview of studies that built on insights from cognitive science to study individual differences in the development of intrusive memories of trauma. Most of these studies used prospective correlational designs in non-clinical populations (using experimental analogues of trauma); a few studies used such designs in at-risk or clinical populations.

As an experimental model of exposure to psychological trauma, most of these studies employed variations of the trauma film paradigm (Holmes & Bourne, 2008; Horowitz, 1969; James, Lau-Zhu, Clark, et al., 2016). This is a widely-used method for inducing analogue trauma symptoms, by asking participants to view video footage with traumatic content. Numerous studies have demonstrated that film stimuli with traumatic content can induce intrusive memories that share characteristics with those experienced following actual trauma (Holmes & Bourne, 2008; Horowitz, 1969; James, Lau-Zhu, Clark, et al., 2016). However, there are limitations of the trauma film paradigm, as with any experimental model, which we raise later in the discussion (section 6).

Assessments of intrusive memories varied across studies. Most studies used ambulatory assessments over multiple days after the experimental trauma using, for example, a daily diary or an app in which participants recorded their intrusive memories as they occurred. Some studies additionally measured intrusions in the laboratory (Lau-Zhu, Holmes, & Porcheret, 2018) using tasks designed to evoke intrusions (e.g., presenting blurred still images from the film). Other studies only used retrospective measures in which participants indicated retrospectively how often they had experienced intrusions, or how much distress their intrusions had caused, over a certain period (days or weeks). These measures included the Clinician Administered PTSD Scale-IV (Blake et al., 1995), the intrusion subscale of the Impact of Event Scale—Revised (Weiss & Marmar, 1997), and the PTSD Checklist for DSM-5 (Weathers et al., 2013).

In this section, on the development of intrusive memories, we first describe brain imaging studies examining neural mechanism, followed by studies investigating the role of hormones. We then describe studies looking at psychological and physiological factors, and finally studies examining the role of cognitive processing styles.

3.1. Neural mechanisms underlying the development of intrusive memory

While brain imaging studies have captured the involuntary *recall* of a traumatic event in real time (e.g., in patients with PTSD), investigating the neural mechanisms during *encoding* of a real-life traumatic event (i.e., peri-traumatic mechanisms that could be involved in intrusive memory development) is impossible. Such investigations therefore rely on using experimental trauma analogues. Despite the wealth of brain imaging research in the broader field of emotional memory (LaBar & Cabeza, 2006), only a few studies identified here (all using functional magnetic resonance imaging, fMRI) looked at brain mechanisms underlying the formation of involuntary intrusive memories of experimental trauma. In this section we only discuss prospective studies that focused on *predicting* intrusive memory recall, excluding studies that focused on neural correlates of involuntary memory recall, or brain abnormalities in established PTSD, as they can de facto provide little information about *development*.

In one study (Bourne, Mackay, & Holmes, 2013), 22 non-clinical volunteers viewed a traumatic film during fMRI scanning and then filled in a week-long

intrusion diary. For each individual, the film was subsequently divided into scenes that resulted in later intrusions ('intrusive scenes'); intrusions for *other* participants, but not that particular individual ('potential scenes'); and scenes from neutral clips that did not cause intrusions in any of the participants ('control scenes'). Clusters of brain activation in response to 'intrusive scenes' compared to 'potential scenes' during film viewing were identified in the left inferior frontal gyrus and bilateral middle temporal gyrus. This finding was recently replicated (Clark, Mackay, Woolrich, & Holmes, 2016), suggesting that distinct neural traces for intrusive memories are already (partially) formed during exposure to experimental trauma. In a re-analysis of the data, these activation patterns were used in a machine learning approach to predict which moments in the film would come back as intrusions in the subsequent week, which was possible with high accuracy both within individuals (97.3% accuracy), and across individuals (68.0% accuracy) (Clark et al., 2014).

Another study (Battaglini et al., 2016) used visual stills (e.g., of mutilated bodies and neutral objects) as analogue trauma, with a concurrent task to induce either visual (matching the target still to one of two smaller images) or verbal (semantic judgment of the target still as "natural" or "artificial") processing of the pictures. Brain activation was compared between individuals with a subsequent low (0-1) versus high (>5) intrusion score assessed two days later using the Impact of Event Scale. In the high versus low intrusion group, verbal processing of negative stills revealed clusters of activation in the left amygdala, bilateral

hippocampal gyrus, dorsal anterior cingulate cortex, and bilateral inferior frontal gyrus, while visual processing of negative stills only showed activation in the bilateral inferior frontal gyrus. This finding suggests there may be different neural mechanisms underlying verbal and visual processing *during* trauma that make an individual susceptible to developing intrusions.

In the final study (Gvozdanic, Stämpfli, Seifritz, & Rasch, 2017), using a between-subjects design, participants were presented either with a neutral film clip or an aversive film clip (a rape scene). Within three hours after encoding, neural responses to implicit memory stimuli (unattended neutral cues from both films) and explicit memory stimuli (an audiotape of someone retelling the traumatic scene) were assessed. In the group who viewed the aversive film, greater activity in the retrosplenial cortex during the implicit task, and in the posterior cingulate cortex during the explicit task, predicted *fewer* subsequent intrusions in a diary. These findings indicate that neural responses to early retrieval in the immediate aftermath of experimental trauma can predict the formation of intrusive memories.

3.2. The role of stress and sex hormones

The role of hormones in memory, and emotional memory in particular, has received considerable attention over the past few decades. For example, research suggests that the stress hormone cortisol may impair the recall of declarative (*non-intrusive*) emotional memories, while both cortisol and noradrenaline (also involved in the stress response) are thought to enhance the encoding and

consolidation of emotional events (e.g., Holz, Lass-Hennemann, Streb, Pfaltz, & Michael, 2014; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Extending these insights to *involuntary* memory, several studies have specifically addressed the relationship between hormonal changes at the time of (experimental) trauma and subsequent intrusive memories. The studies described below examined the role of the stress hormone cortisol, as well as the female sex hormones estradiol (a form of estrogen) and progesterone.

In a sample of healthy participants, salivary cortisol was collected pre-, peri- and post-viewing of an aversive film (Chou, La Marca, Steptoe, & Brewin, 2014a). *Lower* cortisol levels *post-film* predicted greater vividness of intrusions (recorded in a seven-day diary). However, *higher* cortisol levels *peri-film* predicted greater frequency of intrusions, but only among individuals with greater sympathetic activation (i.e., those who showed heart rate acceleration in response to acoustic startle probes). This suggests that the effect of cortisol on intrusive memory development may be dependent on time of assessment (or of cortisol administration in pharmacological intervention studies) relative to the aversive learning experience (Joëls, Fernandez, & Roozendaal, 2011; Schwabe & Wolf, 2014). Another study (Cheung, Chervonsky, Felmingham, & Bryant, 2013) similarly found that *lower* cortisol levels *after* viewing negative images during a cold water pressor test (immersion of hand in ice cold water) predicted more subsequent intrusive memories, but only in men. Meanwhile, higher general levels of estradiol predicted more intrusive memories in women.

A further study (Wegerer, Kerschbaum, Blechert, & Wilhelm, 2014) looked at the role of estradiol in women with a natural menstrual cycle (during early follicular or luteal cycle phase), in a conditioned-intrusion paradigm. The paradigm included a differential fear conditioning procedure with short violent film clips as unconditioned stimuli (US), followed by a fear extinction phase. Women with lower levels of estradiol showed stronger intrusive memories (greater number, duration and distress) of the violent clips, assessed over 3 days, and this relationship was at least partially explained by the conditioned responding (skin conductance) observed during fear extinction. The different findings in relation to estradiol may be attributed to whether the study sample included women on hormonal contraceptives (Cheung et al., 2013) or not (Wegerer et al., 2014).

Some studies found an association between progesterone and intrusive memories. Women reported having had more intrusive memories of an emotional film (measured using a retrospective estimate) if they viewed it during the luteal phase relative to the non-luteal phase of their menstrual cycle, i.e., when progesterone levels are high (Ferree & Cahill, 2009; Ferree, Kamat, & Cahill, 2011), and progesterone level was positively correlated with intrusive memory frequency (Ferree et al., 2011). However, other studies, discussed above in the context of estradiol, failed to find an association between progesterone and intrusive memories of experimental trauma (Cheung et al., 2013; Wegerer et al., 2014). It should be noted that studies on sex hormones are complicated by the

fact that influences of estradiol and progesterone can be hard to disentangle in naturally cycling women (high progesterone levels mainly occur in the presence of increased estradiol levels). One study even found that it was the *ratio* of estradiol-to-progesterone, rather than estradiol or progesterone alone, that was negatively correlated with the frequency of intrusive memories (Soni, Curran, & Kamboj, 2013).

No studies resulting from our literature search used a *prospective* design to examine the role of sex hormones on intrusive memory development after *real-life* trauma. However, we found it noteworthy that one *cross-sectional* study suggested that women who were exposed to real-life trauma during the mid-luteal phase of their menstrual cycle (again, when progesterone levels are high) were more than three times more likely to experience intrusive memories in the acute period (7-10 days) after trauma than women in the non-luteal phase (Bryant et al., 2011).

3.3. Psychological and psychophysiological predictors

A number of studies have identified ‘psychological’ or ‘affective’ factors associated with intrusive memory development. Both stable (trait) as well as transient (state) factors have been examined. Investigation of traits reveals information about individual differences in susceptibility for developing intrusive memories (i.e., more distal factors), while state factors reveal information about circumstances at a particular moment that increase the likelihood of experiencing intrusive memories in the future (i.e., more proximal factors). As will be

discussed, certain states (e.g., high autonomic arousal in response to stressful events) may be associated with certain traits (e.g., high trait anxiety), and the distinction may therefore be somewhat arbitrary. However, whereas trait factors may be difficult to influence, state factors may point to malleable targets for interventions early after trauma.

Several studies using experimental models of trauma have found a clear association between ‘negative emotionality’ traits and intrusive memory development. For example, greater general disgust propensity predicted a higher number of intrusive memories of graphic film footage (Bomyea & Amir, 2012). In another study, trait anxiety, depression and trait dissociation were all positive correlated with intrusion frequency in the week after trauma-film viewing (Laposa & Alden, 2008). Further, this study found that film-induced changes in anxiety, as well as post-film state anxiety, were associated with intrusion frequency, and state anxiety mediated the relationship between the trait factors (anxiety, depression and dissociation) and intrusions. In a follow-up study, post-film anxiety levels again predicted intrusions (Laposa & Rector, 2012). Feelings of guilt (experimentally manipulated using a staged computer crash and related loss of data) also predicted the number of intrusive memories of the event and intrusion-related distress (Bub & Lommen, 2017).

Complementing these findings, a meta-analysis of 16 experiments using the trauma film paradigm (n = 458, all no-task control condition; Clark, Mackay, & Holmes, 2015) showed that an *absence* of intrusions was predicted by a low self-

reported emotional response to the trauma film (composite negative mood change score, including emotions such as fear and sadness), as well as low trait anxiety and low depression levels. In line with this, one study using structural equation modelling (Regambal & Alden, 2009) found that greater emotional reactivity during a distressing film was associated with greater intrusive memory frequency over the subsequent week. Interestingly, non-clinical participants who scored high, compared to low, on measures of vulnerability for hypomanic experience (e.g., elated, energetic), also showed elevated numbers of intrusive memories after viewing a film with traumatic content (Malik, Goodwin, Hoppitt, & Holmes, 2014), suggesting that perhaps not negative emotionality per se, but any type of altered emotional processing may influence intrusive memory development.

Finally, changes in state psychological factors such as those discussed above are usually accompanied by physiological stress responses (e.g., changes in skin conductance). For example, both greater mood change and higher physiological reactivity have been found to predict more intrusions immediately after an aversive film (Ripley, Clapp, & Beck, 2017) and also in the 24 hours after a virtual reality analogue trauma (an unexpected emergency situation simulated in an underground parking lot; Schweizer et al., 2017). In women, lower heart rate variability (regarded as a sign of less adaption to environmental changes) *prior* to watching a stressful film predicted more intrusive memories of the film (Rombold-Bruehl et al., 2017), while peri-film decreases in heart rate predicted the frequency of image-based (rather than verbal) intrusive memories (Chou, La

Marca, Steptoe, & Brewin, 2014b) (see also Holmes, Brewin, & Hennessy, 2004). Relatedly, two studies showed that enhanced conditionability to neutral cues presented in between (Wegerer, Blechert, Kerschbaum, & Wilhelm, 2013) or during (Streb, Conway, & Michael, 2017) distressing film clips predicted subsequent intrusive memories (a combination of number, duration and distress). Finally, skin conductance responses to a distressing film have been found to moderate the relationship between psychological traits (anxiety sensitivity) and intrusive memories (Olatunji & Fan, 2015). That is, the number of intrusions significantly increased with greater skin conductance responses at high levels of general anxiety sensitivity, but not at low and moderate levels of anxiety sensitivity.

Together, these studies suggest a complex interplay between psychological and physiological processes in response to analogue trauma, which result in the occurrence of intrusive memories following these events. The next section will focus on cognitive processes during (analogue) trauma and how they may contribute to the formation of intrusive memories.

3.4. The role of cognitive processing styles

A number of cognitive processes have been implicated in intrusive memory development. The first two studies examined the role of mental imagery. A mental image can be defined as “the same sort of representation that is produced during the first phases of perception, but is created from stored representations in memory not from on-line sensory input.” (Kosslyn, 2005, p. 852). Intrusive

memories are mental imagery-based (J. Pearson, Naselaris, Holmes, & Kosslyn, 2015). In one study, the vividness of general mental imagery, assessed before analogue trauma, predicted the number, vividness and emotional distress associated with image-based intrusive memories of the analogue trauma, recorded over five days (Morina, Leibold, & Ehring, 2013). However, another study found a negative relationship between a questionnaire measure of spontaneous use of (non-emotional) imagery in daily life and intrusions of analogue trauma (Krans, Näring, Speckens, & Becker, 2011). Potentially, general *spontaneous use of imagery* and the *vividness of imagery* rely on different mechanisms (D. G. Pearson, Deeproose, Wallace-Hadrill, Burnett Heyes, & Holmes, 2013).

A number of studies examined the link between the development of intrusive memories after a trauma film and memory contextualisation, i.e., the binding of items in memory with each other and with their surrounding context (Bisby & Burgess, 2017). Across various studies, weaker memory contextualisation was associated with more subsequent intrusive memories (Marks, Steel, & Peters, 2012; T. D. Meyer et al., 2013; T. Meyer, Krans, van Ast, & Smeets, 2017). Further, indirect evidence for the association between weaker memory contextualisation and increased intrusions came from two studies that investigated the acute effects of alcohol (low and high doses) versus placebo, given prior to viewing a trauma film, on subsequent intrusive memories. Both studies found an inverted 'U' dose-response on the number of intrusive

memories, with a low dose of alcohol increasing intrusions relative to placebo, while a high dose decreased intrusions (Bisby et al., 2009; Bisby et al., 2010). These findings were interpreted within a dual representation model of intrusive memory development (Brewin et al., 2010), whereby the low dose of alcohol impaired the contextual memory system but not the image-based memory system, while the high dose was hypothesised to impair both memory systems. Conversely, one study found that *greater* contextual memory was associated with more intrusions of experimental trauma (D. G. Pearson, 2012). This inconsistency seems to be best explained by how different studies defined ‘context’, as ‘context’ may be operationalised as primarily perceptual (e.g., physical environment), or conceptual (meaning of an experience through verbal information; e.g., Krans, Pearson, Maier, & Moulds, 2016). With this in mind, findings regarding memory contextualization seem to indicate that intrusive memory development is associated with poor perceptual integration, and increased (negative) conceptual processing (D. G. Pearson, Ross, & Webster, 2012; Zhang, van Ast, Klumpers, Roelofs, & Hermans, 2018). As an example of how negative conceptual processing may enhance intrusive memory development, a number of experimental studies have found that rumination (versus, for example, distraction) after a trauma film increased the experience of intrusions and intrusion-related distress (Ball & Brewin, 2012; Ehring, Fuchs, & Klasener, 2009; Hawkins & Cogle, 2013; Zetsche, Ehring, & Ehlers, 2009).

Attentional processes also seem to be an important factor in intrusive memory development. Studies have shown that biased attentional processing of trauma-related cues after exposure to analogue trauma predicted higher subsequent intrusive memory frequency (Schäfer, Zvielli, Höfler, Wittchen, & Bernstein, 2018). That is, reaction times in a dot-probe task were slower on trials with trauma-related cues compared to other threat-related and neutral cues, and a stronger bias predicted more intrusions. The general ability to control thoughts (suppress memory retrieval or resist pro-active interference in working memory, i.e., ignore irrelevant information) has been associated with fewer (Nixon, Cain, Nehmy, & Seymour, 2009; Verwoerd, Wessel, de Jong, Nieuwenhuis, & Huntjens, 2011) or less distressing (Streb, Mecklinger, Anderson, Lass-Hennemann, & Michael, 2016) intrusive memories following a trauma film. It is notable that the general ability to suppress memory retrieval may differ from thought suppression as a coping strategy in response to intrusive memories – the latter of which has been associated with more subsequent intrusive memories (Regambal & Alden, 2009; mentioned in section 3.3 above). Although no evidence for a direct relationship between self-reported attentional control and intrusive memories has been found (Hagenaars & Putman, 2011), attentional control did moderate the relationship between self-assessed tonic immobility (i.e., ‘freezing’ in response to an aversive film) and intrusive memories. The degree to which spontaneous and/or deliberate ‘thought suppression’, ‘memory control

ability' and 'attentional control' rely on overlapping or distinct mechanisms may be an interesting topic for future research.

One further study examined other cognitive factors highlighted in cognitive models of PTSD (e.g., Ehlers & Clark, 2000), and found that peri-traumatic dissociation, data driven processing, and lack of self-referent processing were all positively associated with the development of intrusive memories (Laposa & Rector, 2012).

3.5. Summary and theoretical links with PTSD research

The studies reviewed in this section provided numerous insights into the neural, hormonal, psychophysiological and cognitive factors that contribute to intrusive memory development. Neuroimaging studies have shown that neural factors during encoding of an event, not solely factors during consolidation and retrieval of a memory, are important for the future occurrence of intrusive memories. This is consistent with the finding that peri-traumatic processes at the time of trauma are an important predictor of subsequent PTSD symptoms (Ozer, Best, Lipsey, & Weiss, 2003). While current evidence suggests that the inferior frontal gyrus, retrosplenial cortex and the posterior cingulate cortex may be involved in intrusive memory formation, further studies are needed. In addition, whilst there have been a number of imaging studies looking at consolidation processes occurring in the immediate aftermath of an emotional experience, such as post-encoding rest-periods in fear conditioning paradigms (e.g., Hermans et al., 2016), this review identifies a gap in the literature regarding the relationship

between neural processes occurring early after encoding and subsequent intrusive memories.

Research reviewed on the effects of hormones on the development of intrusive memories focused on cortisol and sex hormones. Studies reveal a complex picture of the interplay between cortisol and both internal factors (e.g., sympathetic activation) and external factors (e.g., time of assessment). With regard to sex hormones, studies in women suggest that lower estrogen levels are associated with stronger intrusive memories (assessed by frequency, distress and duration), and that the luteal phase of the menstrual cycle (when progesterone levels are high) is associated with a higher frequency of intrusive memories. These findings have important implications for understanding sex differences in propensity to develop intrusive memories of trauma, and possibly anxiety and stress disorders in general. For example, higher rates of PTSD are seen in women compared to men (R. C. Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) and a meta-analysis showed that women are more vulnerable to re-experiencing symptoms (Tolin & Foa, 2006).

Research into psychological and psychophysiological factors involved in intrusive memory development show that negative emotionality (both as a trait and a state); heightened emotional arousal at the time of trauma; and lower heart rate variability (regarded as a sign of less adaption to environmental changes) are all associated with the formation of intrusive memories. These findings appear consistent with what is already understood about pre- and peri-traumatic risk

factors for PTSD; in particular that emotional state during and immediately after trauma, and psychiatric history, are predictors of later PTSD symptoms (Brewin, Andrews, & Valentine, 2000; Ozer et al., 2003).

Finally, in terms of cognitive processing styles, studies suggest that enhanced perceptual and data-driven processing, accompanied by poorer contextual memory integration, play a crucial role in the development of intrusions. This again seems consistent with the wider PTSD literature, in which a hypothesized shift from contextual towards perceptual-based processing during trauma is a key feature of cognitive models of PTSD (Ehlers & Clark, 2000; Brewin et al., 2010). Findings also suggest that individuals who engage more in vivid mental imagery may do so because their cognitive processing style is highly perceptual (as opposed to semantic/conceptual), leading to a stronger consolidation of sensory information and a higher likelihood of experiencing intrusions of an event.

4. Insights from cognitive science on the reduction of intrusive memories

In this next section we highlight recent studies that have capitalised on insights from cognitive science to reduce the distress, vividness and/or frequency of intrusive memories. These studies typically exploit principles of memory malleability, by interfering with memory during the transient time windows in which memory is labile and vulnerable to alteration (McGaugh, 2000; Nader, 2003). We start the section with a brief summary of basic principles of memory plasticity, and the neurobiological processes underlying so-called memory

consolidation and reconsolidation. In the subsequent sections we discuss different approaches that directly or indirectly target these putative processes. We discuss pharmacological and endogenous, behavioural (sleep and cognitive task interference), and cognitive manipulations to reduce intrusive memories of experimental and/or real-life trauma.

4.1. Basic principles of memory plasticity

Most of the knowledge about the malleability of memory accumulated in the last two decades comes from experimental research in non-human animals (Josselyn, Köhler, & Frankland, 2015; Tonegawa, Liu, Ramirez, & Redondo, 2015). Following acquisition, memory is thought to undergo a time-dependent process of stabilisation necessary for the memory to persist, referred to as memory ‘consolidation’ (McGaugh, 1966, 2000), which may be further divided into ‘synaptic’ and ‘systems’ consolidation. ‘Synaptic consolidation’ refers to a strengthening of local neural circuits via a cascade of molecular processes involving protein synthesis and the formation of new synaptic connections, and is thought to occur minutes to hours after information encoding; ‘systems consolidation’ refers to the reorganization of long-term memory over distributed brain circuits, occurring over days to years after initial encoding (Dudai, 2012). In the current review, most work has focused on the time window that is thought to overlap mainly with synaptic consolidation, in which memories are susceptible to interference (McGaugh, 1966, 2000).

So far, only one study has directly investigated the molecular processes underlying memory consolidation (Das et al., 2016), by targeting N-Methyl D-Aspartate (NMDA) receptors, which play an important role in synaptic consolidation. Nitrous oxide, also known as ‘laughing gas’, blocks NMDA receptors, thus potentially interfering with synaptic consolidation. Das et al. (2016) found that individuals who inhaled nitrous oxide for 30 minutes immediately after trauma film viewing, relative to those who inhaled medical air (control condition) for the same duration, showed a steeper (quicker) reduction in intrusive memory frequency over one week. While the applicability of laughing gas as an intervention soon after trauma may require further research, this study provides important evidence that the mechanisms underlying memory stabilisation may be disrupted using relatively simple procedures, in ways that are quite similar across different types of memory and even different species (see Visser, Lau-Zhu, Henson, & Holmes, 2018 for further detail).

Rather than there being a ‘one-off’ opportunity in which memory is malleable, relatively recent research indicates that even consolidated memories are not fixed. Upon retrieval, memories can re-enter a transient labile state, where they are again vulnerable to modification (e.g., Alberini & LeDoux, 2013; Nader & Hardt, 2009; Sara, 2000). The re-stabilisation of a memory is a putative process termed memory ‘reconsolidation’, and requires de-novo protein synthesis (Nader, Schafe, & LeDoux, 2000). This suggests that there may be an additional window of opportunity to interfere with the storage of trauma memories. Indeed,

it has been suggested that “novel pharmacological and psychotherapeutic approaches that target memory reconsolidation...need to be moved toward the top of the priority list” (Hoge & Chard, 2018, p. 344).

4.2. Pharmacological and endogenous manipulations

To influence intrusive memories, a number of studies have targeted brain processes via indirect manipulations, for example by administering the stress hormone cortisol, or by increasing endogenous stress hormones using behavioural manipulations. In a randomized double-blind placebo-controlled study (Graebener, Michael, Holz, & Lass-Hennemann, 2017), female participants received either a low dose of cortisol (20 mg) or placebo for three days following negative film viewing (i.e., outside the consolidation window). Contrary to the prediction that cortisol may inhibit memory retrieval, the cortisol group did not report fewer subsequent intrusions than the placebo group. Similar null findings were obtained in a randomised, double-blind, placebo-controlled crossover study in 30 female inpatients with PTSD (Ludäscher et al., 2015): hydrocortisone administration for a week did not show any effect on the frequency or intensity of intrusive memories (but see Sijbrandij et al., 2015, discussed in section 4.6 below).

Administration of cortisol (20 mg) *prior* to film viewing in a sample of 60 women also had no effect on the frequency or vividness of intrusive memories (Rombold, Wingenfeld, Renneberg, Schwarzkopf, et al., 2016). However, another study by the same group found that activity of the noradrenergic system

prior to film viewing did have an effect on intrusive memories (Rombold, Wingenfeld, Renneberg, Hellmann-Regen, et al., 2016). In this study, participants received either 10 mg of yohimbine (which stimulated noradrenergic activity), 0.15 mg of clonidine (which inhibited noradrenergic activity), or placebo, 60 minutes prior to viewing a distressing film. The yohimbine group showed a delayed decline in intrusive memories in the four days after film viewing. Interestingly, yohimbine increased endogenous cortisol levels, providing indirect evidence for the hypothesised role of cortisol in the *consolidation* of intrusive memory.

Another study aimed to increase endogenous stress hormones using a behavioural manipulation (Bryant, McGrath, & Felmingham, 2013). Participants experienced either a cold pressor test (immersion of their hand in ice cold water for 3 minutes; high-stress group) or submerged their hand in warm water for the equivalent time (low-stress group) immediately after viewing aversive and neutral images. Findings showed relatively enhanced free recall and greater intrusions two days later (using the Impact of Event Scale intrusion subscale) in the high-stress group. Further, in women, but not men, an increase in adrenergic and glucocorticoid response – from baseline to the behavioural manipulation – predicted more intrusive memories (Bryant et al., 2013). A follow-up study (Cheung, Garber, & Bryant, 2015) used a similar approach, but induced stress immediately before memory *reactivation* two days after the trauma film. Results showed that the ‘stress + reactivation’ group had higher intrusion scores than

both the ‘reactivation only’ or ‘stress only’ groups, suggesting that acute stress enhances intrusive memories only when the memory trace is reactivated shortly afterwards. Only in the ‘stress + reactivation’ group did higher cortisol level predict a higher intrusion score. As the stress induction occurred *before* the reactivation of the memory, it is unclear whether reactivation acted to destabilise the memory, or instead served as a new learning experience in a stressful context. Thus, whether the effects can be explained by reconsolidation-update mechanisms or some other account remained unclear.

4.3. Targeting sleep

Sleep is thought to enhance memory consolidation, particularly for emotional relative to neutral materials (Nishida, Pearsall, Buckner, & Walker, 2009; Payne, Chambers, & Kensinger, 2012; Payne, Stickgold, Swanberg, & Kensinger, 2008; Wagner, Gais, & Born, 2001). Thus, the prevention of sleep (i.e., sleep deprivation) has been postulated as a tool for weakening the initial consolidation of unwanted (intrusive) memories. Three experimental studies directly tested this hypothesis using the trauma film paradigm followed by a prolonged period of wake before sleep. One study employed total overnight sleep deprivation for 24 hours in a hospital environment (Porcheret, Holmes, Goodwin, Foster, & Wulff, 2015), and showed that the manipulation reduced the number of intrusive memories reported in the initial few days ($n = 44$, ~75% female per group). In contrast, another study employed day-wake of at least 8 hours (Kleim, Wysokowsky, Schmid, Seifritz, & Rasch, 2016), and instead reported the day-

wake group to have more intrusive memories towards the end of the week ($n = 71$, 100% female). Further, a recent study (Woud et al., 2018) found that after viewing a trauma film, participants who had a 90 minute nap rather than watching a neutral film experienced *fewer* intrusive memories later as indexed in a daily intrusion diary and by the Impact of Event Scale intrusion subscale ($n = 105$, 69% female). To clarify these findings, future research should systematically investigate the impact of the duration of wake and whether or not natural sleep cycles are disrupted (as is the case for full sleep deprivation, but not day-wake), as well as the impact of gender differences.

4.4. Cognitive task interference

A series of studies have investigated the use of cognitive task interference as a strategy to reduce intrusive memories. This rationale is based on three key insights from neuroscience and cognitive psychology: 1) memory can be disrupted shortly after an event, or upon retrieval (see section on ‘Basic principles of memory plasticity’, and Visser et al., 2018); 2) working memory has limited capacity (Baddeley, 2003); and 3) intrusive memories of an event include mental imagery, which requires working memory resources (Andrade, Kavanagh, & Baddeley, 1997; Baddeley & Andrade, 2000). Therefore, visuospatial tasks, which occupy working memory, may compete for working memory resources with visual imagery. The effects of such “dual-task” or “concurrent task” interference on intrusive memory development have been demonstrated in a number of experiments for time periods when memories are assumed to be labile,

that is, either *during* trauma film viewing (Holmes et al., 2004), or within minutes to hours *after* film viewing. In the latter, film reminder cues preceded the cognitive task to orientate the participant to film content (Holmes, James, Coode-Bate, & Deeprose, 2009; Holmes, James, Kilford, & Deeprose, 2010).

Within the last decade, the use of computer game play has been examined as a form of cognitive interference task for intrusive memories of trauma. A series of studies have used the computer game ‘Tetris’, which has been shown to be associated with visuospatial working memory function (Lau-Zhu, Holmes, Butterfield, & Holmes, 2017). In one experiment, participants who completed a brief reminder task for a trauma film and then played Tetris, either 30 minutes (Experiment 1) or 4 hours (Experiment 2) after viewing the film, reported fewer intrusive memories in the subsequent week (in a daily diary) compared to participants in a reminder-only group without Tetris game-play (Holmes, James, et al., 2010). The same study showed that, compared with individuals in the visuospatial Tetris and reminder-only groups, individuals who played a verbal-based computer game called ‘Pub Quiz’ reported comparable (Experiment 2) or even increased (Experiment 1) numbers of intrusive memories, despite both games being rated by participants as equally enjoyable/distracting (Holmes, James, et al., 2010). In both these experiments, interference tasks were administered within hours of the film, during the purported time-window of memory consolidation (McGaugh, 2000). Before film viewing, when the memory

is not yet established, a similar procedure does not appear to be effective in reducing intrusions (James, Lau-Zhu, Tickle, Horsch, & Holmes, 2016).

Tetris game play may also be used to reduce intrusive memories for established (24 hours old) memory of experimental trauma (James et al., 2015), based on the hypothesis that this could enable interference with memory *reconsolidation* (Nader & Hardt, 2009). In this study, individuals who underwent a memory reactivation procedure for the film 24 hours after trauma film viewing and then played Tetris had fewer intrusive memories than a no-reactivation/no-Tetris group (Experiment 1). A second experiment replicated these findings (James et al., 2015), and further showed that neither memory reactivation nor Tetris game-play alone were sufficient to reduce intrusive memory frequency (Experiment 2). This finding is in line with the idea that both memory reactivation (hypothesised to initiate reconsolidation processes and render memory malleable, in this case showing still pictures for the film) and Tetris game play (to interfere with memory for the film) were needed to reduce the number of intrusive memories of a previously consolidated (analogue) trauma memory. The notion of memory reconsolidation has proved useful in inspiring new avenues for intervention for older memories of trauma, even though some potential limitations have been raised (Treanor, Brown, Rissman, & Craske, 2017).

While multiple types of visuospatial game (not just Tetris) may hold potential to reduce visual image-based intrusions, selecting tasks that are

effective may not be straightforward. A GamePlay app thought to tax visuospatial working memory, compared to a no-task control condition, did not show any effects on intrusions, regardless of whether or not trauma retrieval cues were presented prior to game play (Asselbergs et al., 2018). However, it is unclear whether such an app sufficiently taxed working memory. Other tasks that at face value do not appear to be visuospatial have been found to be effective in reducing intrusions too, such as a word game (Hagenaars, Holmes, Klaassen, & Elzinga, 2017) and counting backwards in 3's (Krans, Näring, & Becker, 2009). Further research is needed to disentangle which elements of a task are crucial to observe cognitive interference.

Findings using derivations of the trauma film paradigm add to our understanding of less common but equally distressing forms of intrusive memories of trauma. Tabrizi and Jansson (2016) investigated cognitive task interference for *auditory* intrusive memories of experimental trauma. The frequency of auditory intrusive memories of an auditory (analogue) trauma was compared in four groups, each testing different hypothesized parts of working memory interference: visuospatial sketchpad (modelling specific shapes in clay); phonological loop (verbal; counting backwards from 10 to 1); executive processes (verbal; counting backwards in 3's from specified numbers) and no-task. Results were in line with a modality-specific view of memory processing: individuals in the two verbal groups reported fewer auditory intrusive memories in the subsequent week compared with visuospatial and no-task groups.

Researchers have started to translate these experimental findings to clinical settings. An early translational study with PTSD patients indicated that concurrent eye movements, relative to counting or no task, reduced the vividness and emotionality of established trauma memories in PTSD patients (Lilley, Andrade, Turpin, Sabin-Farrell, & Holmes, 2009). More recent studies have focused on early intervention by administering a task within 6 hours after a real-world trauma (Horsch et al., 2017; Iyadurai et al., 2017). One proof-of-principle randomised controlled study investigated mothers who had undergone an emergency caesarean section. Women who received usual care plus a cognitive task procedure involving 15 minutes of Tetris game-play – whilst still in their hospital bed (i.e., the same context in which the trauma occurred) – reported fewer intrusive memories and a trend towards reduced re-experiencing symptoms after one week, compared to those who received usual care only (using intention-to-treat analysis). At one month, groups differed in PTSD diagnosis (intervention group: 4.2%, versus control group: 30.4%; using per protocol analysis) and avoidance symptoms, although these were not primary outcomes, and the small sample is noted.

Another proof-of-principle randomised controlled study tested a similar behavioural intervention with individuals who had experienced a traumatic motor vehicle accident (Iyadurai et al., 2017). Seventy-one patients waiting in a hospital emergency department were randomized to either the behavioural intervention (a trauma reminder cue – briefly recalling the worst moments of the accident – and

then 20 minutes of Tetris game-play) or an attention-placebo control (filling in a simple written activity log for an equivalent length of time). Intention-to-treat analyses showed medium effect sizes for the reduction in the number of intrusive memories in the week after the accident (primary outcome: 62% reduction) and in intrusion symptom score at one week (secondary outcome) in the intervention compared to control group, but small to negligible effect sizes for other PTSD symptoms (and anxiety and depression symptoms) at one week and one month. Again, tests of replication are required, as well as studies designed to test longer-term outcomes.

4.5. Changing cognitive processing styles

Instead of interfering with the memory by, for example, using competing tasks, other studies have examined whether the experience of the memory itself may be changed. In two studies, a computerized programme was used to train participants to re-evaluate intrusive memory symptoms *after* (Woud, Holmes, Postma, Dalgleish, & Mackintosh, 2012) or *prior* to (Woud, Postma, Holmes, & Mackintosh, 2013) viewing a trauma film. The training involved participants viewing scripted vignettes that either resolved positively (positive training, i.e., “intrusive memories are normal”) or negatively (negative training, i.e., “having intrusions means I am going mad”). Positive reappraisal training led to fewer intrusive memories (Woud et al., 2012) and less intrusion-related distress (Woud et al., 2013). Relatedly, a recent study (Krans, Brown, & Moulds, 2018) found that participants who were instructed to recall autobiographical memories of

success (high self-efficacy condition) relative to memories of failure (low self-efficacy condition) reported fewer intrusive memories of a distressing film in the following week, regardless of whether the manipulation was administered before or after film viewing.

Two studies showed beneficial effects of training participants to process information in a concrete (“How did it happen?”) versus abstract (“Why did it happen?”) style *prior* to traumatic film viewing: training a concrete processing style resulted in fewer intrusive memories over the subsequent week (White & Wild, 2016) and reduced the relationship between trait rumination and intrusive memory frequency (Schaich, Watkins, & Ehring, 2013). However, training a concrete versus abstract thinking style *after* analogue trauma did not affect intrusion frequency (Ehring, Szeimies, & Schaffrick, 2009). This suggests that certain cognitive styles can be trained, and that such training, when delivered preventively, may protect against developing intrusions.

Other post-trauma cognitive processes may also be targeted, via techniques that have either been developed in the laboratory or derived from established treatments. For example, directing attention away from trauma reminders after a trauma film, using a form of attention bias modification training, resulted in fewer film-related intrusive memories reported in a diary over the subsequent three days (Verwoerd, Wessel, & de Jong, 2012). Further, changing the valence of distressing memories, through either imaginal exposure or autobiographical memory elaboration, also neutralised the valence of trauma-associated cues (i.e.,

evaluative conditioning effects) soon after traumatic picture stories, and reduced subsequent intrusive memory frequency (Ehlers, Mauchnik, & Handley, 2012). Finally, imagery rescripting, believed to promote change via re-evaluating the meaning of the trauma memory, when applied 30 minutes after a trauma film, resulted in fewer intrusive memories over the subsequent week compared to two control interventions: imagery re-experiencing and positive imagery (Hagenaars & Arntz, 2012).

4.6. Summary and theoretical links with PTSD research

Research reviewed in this section capitalised on insights from cognitive science to reduce the frequency, distress, and/or duration of intrusive memories. These studies typically exploited principles of memory malleability, by interfering with memory during the transient time windows in which memory is labile and vulnerable to alteration (McGaugh, 2000; Nader & Hardt, 2009). However, the level at which they interfered differed widely (Visser et al., 2018). One study showed molecular processes underlying memory consolidation can be targeted at the receptor level, using laughing gas to block NMDA receptors, leading to a steeper decline in intrusive memories over the week. Other studies have used hormonal manipulations, such as administrations of hydrocortisone to reduce intrusive memory recall. Whilst hormonal manipulation studies reviewed here did not reveal any effect on intrusive memories, a previous meta-analysis of randomised controlled trials did find a small beneficial effect of hydrocortisone on overall PTSD diagnosis (Sijbrandij et al., 2015).

Studies that used sleep manipulations shortly after (analogue) trauma have revealed mixed results. The possible differential impact of wake versus (partial or full) sleep deprivation on intrusive memory frequency, as well as why the effects of staying awake become apparent at different times, is an important area for further investigation, as these studies are clearly at an early stage. Possible factors to explore are the duration of wake and whether natural sleep cycles are disrupted (as is the case for full sleep deprivation, but not day-wake).

A number of studies used cognitive task interference to reduce the frequency of intrusive memories. Questions remain as to whether such interventions depends on modality-specific interference specifically (as suggested in Deeproose, Zhang, Dejong, Dalgleish, & Holmes, 2012; Holmes et al., 2009; Holmes, James, et al., 2010) or generally taxing working memory (as suggested in Engelhard, van den Hout, & Smeets, 2011; Tadmor, McNally, & Engelhard, 2016; Van den Hout & Engelhard, 2012), and what other characteristics of the task are crucial to obtain effects. Finally, a number of studies suggest that it is possible to influence characteristics of intrusive memories by changing cognitive styles and appraisals about trauma-related symptoms, or by directly changing the valence of trauma-related cues.

Most of the studies described in this section involved non-clinical samples following experimental trauma. However, within studies investigating clinical samples following real trauma there was some heterogeneity (e.g., female inpatients with PTSD, patients in a hospital emergency department after a motor

vehicle accident). Future studies may examine generalisability of findings across different samples.

5. Clinical implications and future directions

We have discussed a broad spectrum of research in the last decade in which cognitive science has shed light on the specific symptom of intrusive memories of a traumatic event: how they develop and some strategies by which they can be reduced. In this section we take a step back to consider possible implications of this research for clinical practice in the field of psychological trauma. As the possibility of reducing intrusive memories after trauma raises novel questions about how individuals experience intrusive memories, this section is supplemented by brief survey data, which may help open up questions and further thinking in this area to link cognitive science to clinical developments.

We select three key areas that we consider as priorities for the future: a) understanding the mechanisms of trauma treatments, b) prevention and early intervention following trauma, and c) supporting vulnerable populations of trauma survivors on a large scale. These are highlighted in line with a recently commissioned paper on the future of psychological treatments research (Holmes et al., 2018). In each of these three areas we highlight emerging lines of research, as informed by the literature review, that have the potential to move the field forwards.

5.1. Mechanisms of treatment

Understanding treatment mechanisms is critical to target treatments more efficiently: indeed, this goal has been identified as a priority for psychological treatment research in general (Holmes et al., 2018; Kazdin, 2007). For trauma in particular, there has been a call to better understand the essential components of effective trauma-focused treatments, and to explore modularity of treatments whereby specific techniques can be employed rather than a full manualized protocol (Hoge & Chard, 2018). Leading evidence-based psychological interventions for PTSD include trauma-focused cognitive behavioural therapy, prolonged exposure therapy, and eye movement desensitization and reprocessing (American Psychological Association, 2017; National Institute for Health and Clinical Excellence, 2005; World Health Organization, 2013a). What these have in common is that the treatment targets problematic aspects of the trauma memory, whether by techniques such as exposure (Foa & Kozak, 1986), restructuring (Ehlers & Clark, 2000), or dual-task interference (Van den Hout & Engelhard, 2012). A clinically successful outcome is not for someone to forget or erase the trauma memory (Holmes, Sandberg, & Iyadurai, 2010) but to be able to deliberately recall the traumatic event without being overwhelmed, and without having frequent, distressing *intrusive* memories of the trauma.

In this review we have highlighted how cognitive science studies have manipulated key characteristics of intrusive memories (frequency, vividness, and distress) by intervening at multiple levels of mechanism: from interventions that

target molecular processes (section 4.1), through pharmacological interventions (section 4.2) and behavioural interventions (section 4.4), all the way to cognitive/affective manipulations such as imagery rescripting (section 4.5). These studies point to multiple mechanistic pathways through which established trauma interventions might take effect. For example, trauma-focused cognitive behavioural therapy may at once reduce endogenous stress hormones through techniques such as imaginal exposure, whilst also changing cognitive processing of trauma memories using techniques such as imagery rescripting. Critically, a cognitive science approach suggests that we may be able to employ different intervention techniques to target the same processes, with implications for flexible use of specific treatment *components* rather than entire manualized treatments. Such patient-tailored treatment approaches offer an alternative to a one-size-fits-all approach.

The studies reviewed here have predominantly tested manipulations derived from laboratory research, with a minority testing those derived from therapeutic interventions (e.g., imagery rescripting). Understanding treatment mechanisms requires bi-directional translation between laboratory and clinic. For example, a series of rigorous laboratory studies have examined the effects of eye movements, a key technique in eye movement desensitization and reprocessing, on the vividness and emotionality of aversive (non-intrusive) memories. These experiments have demonstrated that the efficacy of such techniques can be explained in the context of working memory theory, whereby eye-movements

occupy limited cognitive resources during memory retrieval, resulting in the storage of less vivid/emotional memory representations (see Van den Hout & Engelhard, 2012 for an overview).

In addition to understanding treatment mechanisms, we need to understand individual differences in treatment effect. Trials of PTSD treatments are beginning to examine potential moderators of treatment efficacy, such as social problems or emotion regulation (Cloitre, Petkova, Su, & Weiss, 2018; Ehlers et al., 2013). However, there is a great deal yet to be understood regarding the influence of individual differences and demographic factors (such as age, gender and ethnicity) on treatment outcome. Taking a symptom-focused approach might help to hone precision approaches. For example, trait vividness of general mental imagery has been associated with the occurrence of intrusive memories (Morina et al., 2013). Thus, by focusing on the impact of potential moderators on single symptoms in the laboratory, we may be able to test factors that are not routinely collected in clinical trials, but that may be useful in understanding why symptoms arise or treatments work for some but not others.

5.2. Prevention and early intervention soon after trauma

Prevention of mental illness is high on the mental health agenda internationally (World Health Organization, 2013b) yet progress has been slow. A unique feature of trauma-related disorders ASD and PTSD is that, unlike other mental disorders in DSM-5, they are linked to a specific onset event (Criterion A; American Psychiatric Association, 2013). This opens up the opportunity to

employ prevention strategies soon after the occurrence of the traumatic event (known as “secondary prevention”). Previously, a prominent approach to secondary prevention was psychological debriefing (also known as critical incident stress debriefing): a structured intervention designed to target PTSD as a whole, delivered within the first few days of a trauma. This approach typically includes recalling the trauma and talking about it in detail with a therapist or counsellor (Rose, Bisson, Churchill, & Wessely, 2002). However, this intervention has been shown to be ineffective, and possibly even harmful (Rose et al., 2002), and therefore it is not recommended in evidence-based clinical practice.

Another psychological intervention – a prolonged exposure therapy based on fear extinction training (involving imaginal and behavioural exposure) – has shown preventive effects on PTSD in an early stage trial (Rothbaum et al., 2012) and future research is awaited. Data are not described for intrusions specifically; rather, the focus is on PTSD as a whole. This intervention also involved talking through the trauma in detail, which does not hold appeal to some people. The feasibility and practical implications of administering such therapist-delivered interventions soon after trauma requires further empirical examination. A number of pharmacological candidates have also been tested, with only hydrocortisone showing promise in randomised controlled trials (Sijbrandij et al., 2015). There remains a need for safe, effective and feasible preventive treatments that can be administered in the early aftermath of trauma.

Cognitive science research opens some new potential avenues for prevention, by focusing on intrusive memories of trauma (rather than several symptom clusters at once) and seeking to precisely modify this target outcome. By intervening in the first few hours after trauma and targeting memory consolidation, some studies suggest it may be possible to reduce the frequency of intrusive memories over the subsequent days. The wide range of interventions reviewed here include nitrous oxide (section 4.2), sleep deprivation (section 4.3), competing cognitive tasks (section 4.4), and imagery rescripting (section 4.6), and we suspect many more are possible, targeting different mechanisms at different levels. Further, those studies that provided early tests of interventions following real (rather than experimental) trauma, showed moderate effect sizes on intrusive memory frequency in the first week post-trauma (e.g., Cohen's d of 0.65 in Horsch et al., 2017; Cohen's d of 0.67 in Iyadurai et al., 2017). These effect sizes are encouraging, but as the reproducibility literature cautions, are likely to be high given they are the first studies of their kind. As the pool of translational studies in this area increases, we will be able to better evaluate the potential clinical impact of these interventions.

As discussed in the introduction, not all intrusive memories of trauma are associated with psychopathology; nor are all early intrusive memories associated with longer-term symptoms. Therefore, as is the case for most areas of secondary prevention in health, we may not know if a given individual would have needed the preventive treatment, as only a subsample would have developed longer-term

difficulties. Such observations raise the issue of whether preventive approaches should be offered to all individuals (“universal prevention”), even though some people will not “need” it, or only be applied to those at high risk after screening (“selective prevention” or “indicated prevention”; World Health Organization, 2002). In the area of trauma, we would need to develop more precise predictive tools to aid screening for risk factors, and attempts to do this are underway (e.g., Carlson, Palmieri, & Spain, 2017; Russo, Katon, & Zatzick, 2013). From a pragmatic and clinical point of view, the prevention of acute or early-term distress (even if it did not have additional, longer term benefits), may be an approach valued by some patients, particularly if it is brief, cost-effective, and without negative side effects. However, further research on this perspective is warranted.

There is the possibility that for some people, intervening early may not only be unnecessary, but could even lead to adverse outcomes. It could be the case that early interventions may compromise natural resilience after trauma. This is of particular relevance given the important finding, as mentioned above, that the talking therapy “critical incident stress debriefing” was ineffective and could even lead to poorer symptom outcome (Rose et al., 2002). Indeed, critical incident stress debriefing has been identified on a provisional list of potentially harmful therapies (Lilienfeld, 2007). Assessment of negative or iatrogenic effects in psychological therapy is often neglected (Barlow, 2010; Holmes et al., 2018). In the area of trauma, the public demand for prompt intervention that can arise

after a crisis must be balanced against issues related to treatment effectiveness and the risk of unintended iatrogenic harm. Examining whether any new treatments, such as those to reduce intrusive memories, have adverse effects (and for whom) should therefore be part of the wider research agenda.

5.2.1. Functional impact of early intrusive memories of real-life trauma: a network perspective and new data

Intrusive memories can be associated with functional impairment. For example, we know that older intrusive memories can be experienced as highly distressing by PTSD patients (e.g., Ehlers & Steil, 1995), can be associated with avoidance of situations that induce intrusions (e.g., Ehlers & Clark, 2000), and interfere with concentration (e.g., in refugees: Holmes et al., 2017). We also know that the frequency of early intrusive memories can be associated with later emotional adjustment. For example, following childbirth the frequency of involuntary memories, and whether they were experienced as distressing or enjoyable, was associated with the presence of post-traumatic stress symptoms at six weeks (Bridson, Isaac, & Slade, 2015).

Interestingly, emerging network studies have examined the links between early intrusive memories and other early and late post-traumatic stress symptoms. Network models view mental disorders, including PTSD, as dynamic systems with multiple links between symptoms (e.g., Borsboom & Cramer, 2013). Recent network analysis of acute and chronic post-traumatic stress symptoms has found early intrusive memories (as well as physiological reactivity) to be centrally

linked to other PTSD symptoms in injured, hospitalized trauma survivors (Bryant et al., 2017) and to be a strong predictor of later PTSD in assault survivors (Haag et al., 2017).

A commentary on Bryant et al. (2017) summarised that “intrusions and physiological reactivity to reminders of the trauma scored high on centrality metrics, indicating that activation of these 2 symptoms are especially likely to activate other symptoms in the network. Conversely, successful early intervention targeting these symptoms would likely prevent the full syndrome of PTSD from emerging.” (McNally, 2017, p. 125). However, we note that these findings may not necessarily generalise to *all* individuals exposed to trauma (including, for example, those who are not physically injured). It remains to be tested whether reducing intrusive memories in the early phase post-trauma can have longer-term effects, and even impact on other PTSD symptoms.

What is more, little data seems available regarding the functional impact of early stage intrusive memories outside of a clinical diagnosis of ASD or PTSD. Presented for the first time here in this review, we conducted a pragmatic survey of 350 individuals at a local university (see also Table 2 in section 5.3). We note that limitations to this pragmatic survey study include retrospective self-report assessment and a small sample size, but hope the data might open further research nearer the time of traumatic events. One hundred and eighteen respondents to the survey indicated that they had experienced a traumatic event,

81 (68.6%) of whom reported they had experienced intrusive memories in the first week after their traumatic event (see Table 1).

Table 1. Online Survey Questions and Responses Regarding Experiences of Intrusive Memories in the First Week after a Traumatic Event (N=81)

Survey question	Responses	
How distressing were your intrusive memories in the first week after the traumatic event?	No distress	2.5%
	Minimal distress	13.9%
	Distress clearly present	40.5%
		26.6%
	Pronounced distress	16.5%
How much difficulty did you have in dismissing the memories i.e. putting them out of your mind and thinking about something else?	Extreme distress	
	No difficulty	3.7%
	Some difficulty	40.7%
	Considerable difficulty	43.2%
How much did your intrusive memories		12.4%
	Extreme difficulty	
	No adverse impact	9.9%

in the first week after the traumatic	Mild impact	25.9%
event affect your functioning (social,	Moderate impact	30.9%
occupational, or other important areas	Severe impact	23.5%
e.g. relationships with other people,	Extreme impact	9.9%
social life, work, parenting, schoolwork, housework, volunteer work etc.)?		

Note. Participants were university staff and students who received the online survey via an email from their department/college. Results are from a subset of respondents (23.1%) who indicated that they had experienced intrusive memories in the first week after a traumatic event (N=81, out of a total sample of N=350). See Appendix for methodology.

Results from the survey suggest that in the first week after a trauma, >80% of respondents reported that their intrusive memories were clearly distressing and >60% of respondents indicated they had moderate to extreme impact on everyday functioning (see Table 1, and see Appendix for methodology). We hope these findings stimulate further research to answer questions such as whether reducing intrusive memory frequency soon after trauma may be a means to reducing subjective distress and improving functioning in this early period. For example, some people may suffer negative effects of intrusive memories to the extent that they are compromised in their ability to engage in activities that might be helpful for their recovery, such as seeking social support, accessing medical care,

engaging in breastfeeding after a traumatic childbirth, or filing a car insurance claim. For these people, reducing the frequency of associated early intrusive memories may provide some benefit and even allow them to recover more effectively. Others, for whom there is neither distress nor functional impairment, would not be predicted to benefit from a reduction in intrusion frequency. As discussed earlier, potential adverse effects should also always be monitored.

5.3. Scalable interventions: trauma is a global issue

Trauma is ubiquitous worldwide, and traumatic events such as war, terrorist attacks, and natural disasters feature frequently in the media. The sheer scale requires new and innovative strategies to treat and mitigate the potential consequences for psychopathology. We need interventions that are low-intensity, require few resources to deliver, are culturally adaptive, and are accessible to many (Holmes et al., 2018).

Therapist-delivered psychological treatments are difficult to deliver to large numbers of people in different parts of the world. Innovative strategies for disorders such as anxiety and depression involve training community health workers (Patel, Chowdhary, Rahman, & Verdelli, 2011), and this remains to be done following trauma. As a case in point, the refugee crisis worldwide is expanding (Abbott, 2016; United Nations High Commissioner for Refugees, 2015). Refugee host countries (even in Europe) lack the capacity and infrastructure to deploy evidence-based face-to-face psychological treatments at the scale needed, potentially alongside interpreters (Ullmann et al., 2015). The

number of psychological treatments tested with refugee populations is low (Nickerson, Bryant, Silove, & Steel, 2011), and while initial evidence indicates that trauma-focused approaches work across cultures (Nose et al., 2017), cultural acceptability of these interventions is important (Hassan et al., 2015). As another example, workers who experience regular exposure to traumatic incidents as part of their jobs, such as emergency department staff, crisis responders, paramedics, firefighters and the police, are often unable to access time-intensive psychological treatments. Here there is a need for brief, low-intensity interventions that are feasible and acceptable alongside a pressured working environment.

Cognitive science-informed interventions may offer one way forwards, amongst other approaches. From the studies reviewed here, a few approaches in particular hold potential to be disseminated widely and speedily by those who are not specialised in trauma-focused care, and in a non-invasive (e.g., not pharmacological) manner. For example, simple cognitive task interventions (Horsch et al., 2017; Iyadurai et al., 2017), or possibly even sleep deprivation (Porcheret et al., 2015), may be feasible to use in the early aftermath of trauma. However, whether people would be willing to undertake such interventions is an important question. Findings from two proof-of-concept trials reviewed earlier (section 4.4) provided some support for the acceptability of a computer game intervention following a motor vehicle accident (Iyadurai et al., 2017) and emergency caesarean section (Horsch et al., 2017). Table 2 below shows new

survey data, which suggests that such novel approaches may be acceptable for many people (see Appendix for methodology).

Table 2. Online survey questions and responses regarding participants' willingness to receive novel treatment approaches soon after a traumatic event (N = 350)

Survey question	Responses	
	Yes	No
Would you be willing to receive a treatment delivered via mobile phone?	80.2%	19.8%
Would you be willing to play a computer game for 10-20 minutes as part of a treatment to reduce intrusive memories?	85.7%	14.3%
Would you be willing to stay awake on the first night after a traumatic experience if it could reduce your intrusive memories over the course of a week?	67.1%	32.9%

Note. Participants were university staff and students who received the online survey via an email from their department/college. See Appendix for further details.

6. Discussion: Linking cognitive science and implications for psychopathology in the area of intrusive memories of trauma

In the context of this special issue on how recent advances in cognitive science have contributed to our understanding of the aetiology, maintenance and reduction of psychopathology, we have reviewed how cognitive science research in the last 10 years has informed our understanding of the development and reduction of intrusive memories of trauma. We have chosen to focus on intrusive memories as a clinical phenomenon of interest in its own right, as well as a core clinical feature of PTSD and ASD. We note, as a limitation, that there may be other relevant papers that were not identified by our search terms. Given the complexity and heterogeneity of a full mental health diagnosis such as PTSD, a precise mapping between cognitive processes and broad symptom clusters can be a challenge. Instead, most experimental studies (such as those discussed here) use a reductionist approach to obtain mechanistic insights into the cognitive processes that contribute to a single symptom, in this case intrusive memories of a traumatic event. In this discussion we consider a number of issues that cut across the studies reviewed, with implications for translation between laboratory-based experimental paradigms and the clinical context.

6.1. Translational merit and limitations of experimental models of trauma

The vast majority of studies in this review used an experimental analogue of real-life trauma, such as film material, static pictures, virtual reality, and

laboratory scenarios. A benefit of experimental models is that they enable variables around the time of trauma to be examined and manipulated under controlled conditions, which is rarely possible in the case of real-life trauma. However, there are clear limitations to the ecological validity of this approach. For example, viewing a trauma film (such as those used in Holmes, James, et al., 2010; James et al., 2015) is by no means equivalent to experiencing real-life trauma, as some individuals may, for instance, choose to view distressing films recreationally (i.e., a non-traumatic experience). Thus, experimental findings should be corroborated with prospective studies following real-life trauma. Reporting in prospective clinical studies on intrusive memories specifically would help toward this aim (in this review, only 4 out of the 76 studies identified followed real-life trauma). Early-stage translational work moving similar protocols used in the laboratory to the clinic are starting to show promise. An example since this review was conducted is for older intrusive memories after complex trauma (H. Kessler et al., in press). We note that repeated or extreme *indirect* exposure to aversive events in the line of work (such as police having to view electronic media or pictures of real murder or abuse) is now included as a diagnostic criterion for a traumatic event in the DSM5 (American Psychiatric Association, 2013, p. 271). Relatedly, studies looking at media viewing of real trauma have shown that repeated and enduring viewing of scenes in media footage, for example of the Boston Marathon bombings, is associated with acute

stress symptoms (Holman, Garfin, & Silver, 2014). Such studies highlight the importance of further understanding this form of media-based exposure.

6.2. Assessment of intrusive memories

Across the studies reviewed, assessment of intrusive memories was predominantly self-report, for example, using a daily diary or retrospective questionnaire. Self-report measures may be susceptible to demand characteristics, in that participants may respond based on how they believe they are expected to respond. However, some studies reviewed here have indicated that expectations did not differ between experimental groups (e.g., Holmes, James, et al., 2010), and/or that expectations did not predict intrusion outcomes (Iyadurai et al., 2017; James et al., 2015). Further, routine clinical assessments that serve the basis for diagnosis and treatment (including for psychopathology where intrusive memories are implicated, such as PTSD) are also based on self-report, sometimes months or years after the trauma. Intrusive memories entail conscious awareness of the memory springing back to mind – a form of involuntary *explicit* memory (Berntsen, 2009; Visser et al., 2018) – and thus by definition require self-report.

Nevertheless, experiential phenomena such as intrusive memories can be measured in more than one way, for example by ‘provoking’ them in the laboratory so that they are at least reported under more controlled conditions (Lau-Zhu et al., 2018). They may also be complemented with physiological outcomes, such as heart rate and skin conductance response to trauma cues (e.g., Kunze, Arntz, & Kindt, 2015; Meyer et al., 2014; Streb, Conway, & Michael,

2017; Wegerer, Blechert, Kerschbaum, & Wilhelm, 2013), performance-based tasks that assess their putative underlying cognitive processes, such as perceptual priming (Holz et al., 2014; Sündermann, Hauschildt, & Ehlers, 2013) or memory/attention biases (Nixon, Cain, Nehmy, & Seymour, 2009; Schäfer, Zvielli, Höfler, Wittchen, & Bernstein, 2018; Verwoerd, Wessel, & de Jong, 2012; Verwoerd, Wessel, de Jong, & Nieuwenhuis, 2009).

The studies discussed within this review typically measured intrusive memories in terms of their frequency, either using ambulatory measures, such as reporting the occurrence of an intrusion when it happens in a diary, or retrospective clinical measures of PTSD symptom frequency and severity, such as the Clinician Administered PTSD Scale-IV or variations of the PTSD Checklist for DSM-5. Compared to ambulatory measurements, these retrospective questionnaires provide relatively coarse information and do not take into account that the occurrence of intrusive memories may be highly context dependent (Kleindienst et al., 2017); however, their use in clinical practice as well as research permits bi-directional translation. Only a few studies examined other characteristics of intrusive memories, such as distress or duration (e.g., Streb et al., 2017; Wegerer et al., 2013). Given that intrusion distress and “nowness” (the extent to which they are experienced as occurring in the present moment) have been indicated as predictors of later PTSD (Michael, Ehlers, Halligan, & Clark, 2005), assessing various characteristics of intrusive memories as outcomes in experimental studies may be fruitful for clinical translation.

Finally, the majority of studies assessed intrusive memories in the first few days after (real or experimental) trauma. It may be useful to examine intrusive memories after longer time periods, given that we know they naturally decline over time for most people. For example, many participants in experimental studies report zero intrusive memories after a few days (e.g., Butler, Wells, & Dewick, 1995; Das et al., 2016; James et al., 2015). However, intrusive memories do not decline within a week for everyone; neither after analogue trauma (e.g., see James et al., 2015, Figure 2), nor after real-life trauma (e.g., see Horsch et al., 2017; Iyadurai et al., 2017, Figure 3 and 2 respectively). Thus, longer time periods are needed to better understand their time course, and what factors contribute to them persisting or not. This is critical for considering translational implications of these studies for PTSD treatment and prevention.

6.3. Reproducibility of research

The cognitive science of intrusive memories is at an early stage, and there is still a relatively small body of work in this area compared to other forms of memory. Throughout the work reviewed above, as in all psychological science, it remains important to consider reproducibility. Open science will clearly help in this regard (Nosek et al., 2015). Studying intrusive memories in the laboratory requires detailed experimental psychopathology paradigms, often requiring multiple laboratory sessions, for which extensive training is typically required to reproduce findings. Suggestions to aid researchers in their pursuit of adequate tests of replication include: sharing protocols which are accompanied by an

agreed set of minimum training standards in their use (e.g., for trauma film viewing, any intervention procedure, intrusive memory monitoring, and data checking); training of the experimenter involving a scientist on the original study, as well as pre-specified protocol-adherence checks, in order to monitor adherence to the original protocol of the study; and training in how to score and interpret measures.

6.4. Issues of individual difference and diversity

From the studies reviewed, it is hard to draw any strong conclusions about the impact of diversity (which includes but is not limited to age, gender, ethnicity, socioeconomic status and so forth) on the aetiology and reduction of intrusive memories. The majority of studies were conducted in Western European, American and Australian regions, and many used student samples. Furthermore, studies looking at the role of hormones in intrusive memory development often use all-male or all-female samples in order to reduce variance, as some hormones (e.g., cortisol) have been shown to have differential effects in men or women (e.g., Bryant et al., 2013). Therefore, embracing the complexity of individual differences is a critical area for future research. We also need to question our basic assumptions about the way we study experimental trauma in cognitive science, for example, the personal relevance of the trauma film footage to different cultural groups, ages, genders, etc., and its impact in generating intrusive memories. This may be particularly relevant for studies where only a low rate of intrusive memories is observed, rendering them liable to floor effects;

a film that worked to generate intrusive memories in one country or time may not transfer to another. Careful work to develop appropriate stimulus materials needs to be undertaken in consultation with specific study populations.

7. Conclusion

Research and clinical practice in the field of psychological trauma continues to focus predominantly on full mental health disorders, such as PTSD. This review has demonstrated how focusing on a single core symptom - here intrusive memories of a traumatic event - can offer novel opportunities for bridging the gap between cognitive science and therapeutic interventions. With the expanding experimental literature, the time is now ripe for accelerating translational links, and building on emerging real-world data to help address the global burden of trauma.

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Appendix

An online survey of views about intrusive memories after a traumatic event in university staff and students: Method

In examining the literature for this review there appeared little data that captured individuals' subjective experiences of having intrusive memories after a traumatic event(s) outside of the context of this being a symptom of PTSD. The Online Intrusive Memory Survey was designed to identify the subjective impact of intrusive memories on functioning and concentration in everyday life, in a sample of volunteers. The survey further sought to examine the acceptability of potential novel intervention strategies identified within the literature review, such as the use of acute sleep deprivation or engaging in simple computer games, to reduce intrusive trauma memories.

Participants. Participants were 432 adult staff and students at the University of Oxford, contacted via departments and colleges, who clicked on a link to take part in the online survey. Of those, 350 individuals completed the survey and

were included in the analysis. The sample consisted of 231 females (66%); 56.4% of the sample were 18-30 years; 33.9% were 31-50 years and 9.4% were over 51.

Materials. The survey comprised 10-24 questions, in 2 sections. In Section 1, participants were asked whether they had ever experienced a traumatic event. A traumatic event was defined using PTSD Criterion A (1 through 4) from the DSM-5 (American Psychiatric Association, 2013, p. 271). Participants were asked whether they had experienced an intrusive memory of that event. If participants answered 'no' they were directed to Section 2 of the survey (answering a total of 10 questions). If participants answered 'yes' they continued with Section 1 of the survey (answering a total of 13 - 24 questions). Survey questions shown in Table 2 were preceded by the statement: "People can experience large numbers of intrusive memories of a traumatic event over the course of a week. At present, we have no simple treatments to offer people, which do not require seeing a professional, to reduce the number of intrusive memories they experience in the course of a week."

Procedure. Online survey information and the website address to access the survey were emailed to colleges and departments of the University of Oxford, who then forwarded the details to their students and staff. Participants were informed that they could stop the survey at any time, and that they did not have to answer any question that they did not wish to, and that their responses were anonymous. Upon reading the survey information, participants gave their informed consent online and then could view and answer the survey questions.

Participants were offered the option of being entered into a prize draw. The survey was administered online using Qualtrics software (Qualtrics, 2015). Ethical approval for the study was obtained from the University of Oxford Central University Research Ethics Committee (CUREC; Ethics Code: R46724/RE001).

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Iyadurai's DPhil (PhD) was funded by a NIHR Doctoral Research Fellowship and completed at the University of Oxford. During her DPhil, she developed a simple intervention to reduce intrusive memories after trauma, and tested it in a clinical trial in a hospital emergency department [1]. Prior to this, Iyadurai worked as a Senior Clinical Psychologist in Neuropsychology. She completed a Doctorate in Clinical Psychology at the University of Manchester.

[1]. Iyadurai, L., Blackwell, S. B., Meiser-Stedman, R., Watson, P. C., Bonsall, M. B., Geddes, J. R., Nobre, A. C., & Holmes, E. A. (2017) Preventing intrusive memories after trauma via a brief intervention involving Tetris

computer game play in the emergency department: a proof-of-concept

randomized controlled trial. *Molecular Psychiatry*, doi: 10.1038/mp.2017.23

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References

- Abbott, A. (2016). The troubled mind of migrants. *Nature*, 538, 158-160.
- Alberini, C. M., & LeDoux, J. E. (2013). Memory Reconsolidation. *Current Biology*, 23, R746-R750.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- American Psychological Association. (2017). Clinical practice guideline for the treatment of PTSD.
- Andrade, J., Kavanagh, D. J., & Baddeley, A. D. (1997). Eye-movements and visual imagery: A working memory approach to the treatment of post-traumatic stress disorder. *British Journal of Clinical Psychology*, 36, 209-223.
- Asselbergs, J., Sijbrandij, M., Hoogendoorn, E., Cuijpers, P., Olie, L., Oved, K., . . . Riper, H. (2018). Development and testing of TraumaGameplay: an iterative experimental approach using the trauma film paradigm. *European Journal of Psychotraumatology*, 9, 1424447.
- Baddeley, A. D. (2003). Working memory: looking back and looking forward. *Nature Reviews Neuroscience*, 4, 829-839.
- Baddeley, A. D., & Andrade, J. (2000). Working memory and the vividness of imagery. *Journal of Experimental Psychology-General*, 129, 126-145.

- Ball, S. C., & Brewin, C. R. (2012). The effect of rumination on intrusive images and mood: An experimental investigation using the trauma film paradigm. *Journal of Experimental Psychopathology*, *3*, 297-309.
- Barlow, D. H. (2010). Negative effects from psychological treatments: A perspective. *American Psychologist*, *65*, 13-20.
- Battaglini, E., Liddell, B., Das, P., Malhi, G., Felmingham, K., & Bryant, R. A. (2016). Intrusive Memories of Distressing Information: An fMRI Study. *PloS one*, *11*, e0140871.
- Benjet, C., Bromet, E., Karam, E. G., Kessler, R. C., McLaughlin, K. A., Ruscio, A. M., . . . Koenen, K. C. (2016). The epidemiology of traumatic event exposure worldwide: results from the World Mental Health Survey Consortium. *Psychological Medicine*, *46*, 327-343.
- Berntsen, D. (2009). *Involuntary autobiographical memories. An introduction to the unbidden past*. New York: Cambridge University Press.
- Bisby, J. A., Brewin, C. R., Leitz, J. R., & Curran, H. V. (2009). Acute effects of alcohol on the development of intrusive memories. *Psychopharmacology*, *204*, 655-666.
- Bisby, J. A., & Burgess, N. (2017). Differential effects of negative emotion on memory for items and associations, and their relationship to intrusive imagery. *Current Opinion in Behavioral Sciences*, *17*, 124-132.
- Bisby, J. A., King, J. A., Brewin, C. R., Burgess, N., & Curran, H. V. (2010). Acute effects of alcohol on intrusive memory development and viewpoint

dependence in spatial memory support a dual representation model.

Biological psychiatry, 68, 280-286.

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

Bomyea, J., & Amir, N. (2012). Disgust propensity as a predictor of intrusive cognitions following a distressing film. *Cognitive Therapy and Research*, 36, 190-198.1

Borsboom, D., & Cramer, A. O. .J. (2013). Network Analysis: An Integrative Approach to the Structure of Psychopathology. *Annual review of clinical psychology*, 9, 91-121.

Bourne, C., Mackay, C. E., & Holmes, E. A. (2013). The neural basis of flashback formation: the impact of viewing trauma. *Psychological Medicine*, 43, 1521-1533.

Brewin, C. R. (2011). The nature and significance of memory disturbance in posttraumatic stress disorder. *Annual review of clinical psychology*, 7, 203-227.

Brewin, C. R. (2014). Episodic memory, perceptual memory and their interaction: Foundations for a theory of posttraumatic stress disorder. *Psychological bulletin*, 140, 69-97.

- Brewin, C. R., Andrews, B., & Valentine, J. D. (2000). Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. *Journal of Consulting and Clinical Psychology, 68*, 748-766.
- 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*, 210-232.
- Brewin, C. R., & Holmes, E. A. (2003). Psychological theories of posttraumatic stress disorder. *Clinical psychology review, 23*, 339-376.
- Briddon, E., Isaac, C., & Slade, P. (2015). The association between involuntary memory and emotional adjustment after childbirth. *British Journal of Health Psychology, 20*, 889-903.
- Bryant, R. A., Creamer, M., O'Donnell, M., Forbes, D., McFarlane, A. C., Silove, D., & Hadzi-Pavlovic, D. (2017). Acute and chronic posttraumatic stress symptoms in the emergence of posttraumatic stress disorder: A network analysis. *JAMA Psychiatry, 74*, 135-142.
- Bryant, R. A., Felmingham, K. L., Silove, D., Creamer, M., O'Donnell, M. L., & McFarlane, A. C. (2011). The association between menstrual cycle and traumatic memories. *Journal of Affective Disorders, 131*, 398-401.
- Bryant, R. A., McGrath, C., & Felmingham, K. L. (2013). The Roles of Noradrenergic and Glucocorticoid Activation in the Development of Intrusive Memories. *PloS one, 8*, e62675.

- Bub, K., & Lommen, M. J. J. (2017). The role of guilt in Posttraumatic Stress Disorder. *European Journal of Psychotraumatology*, *8*, 1407202.
- Butler, G., Wells, A., & Dewick, H. (1995). Differential effects of worry and imagery after exposure to a stressful stimulus: A pilot study. *Behavioural and Cognitive Psychotherapy*, *23*, 45-56.
- Carlson, E. B., Palmieri, P. A., & Spain, D. A. (2017). Development and preliminary performance of a risk factor screen to predict posttraumatic psychological disorder after trauma exposure. *General Hospital Psychiatry*, *46*, 25-31.
- Cheung, J., Chervovsky, L., Felmingham, K. L., & Bryant, R. A. (2013). The role of estrogen in intrusive memories. *Neurobiology of learning and memory*, *106*, 87-94.
- Cheung, J., Garber, B., & Bryant, R. A. (2015). The role of stress during memory reactivation on intrusive memories. *Neurobiology of learning and memory*, *123*, 28-34.
- Chou, C-Y., La Marca, R., Steptoe, A., & Brewin, C. R. (2014a). Biological responses to trauma and the development of intrusive memories: an analog study with the trauma film paradigm. *Biological psychology*, *103*, 135-143.
- Chou, C-Y., La Marca, R., Steptoe, A., & Brewin, C. R. (2014b). Heart rate, startle response, and intrusive trauma memories. *Psychophysiology*, *51*, 236-246.

- Clark, I. A., & Mackay, C. E. (2015). Mental imagery and post-traumatic stress disorder: a neuroimaging and experimental psychopathology approach to intrusive memories of trauma. *Frontiers in Psychiatry, 6*, 1-12.
- Clark, I. A., Mackay, C. E., & Holmes, E. A. (2015). Low emotional response to traumatic footage is associated with an absence of analogue flashbacks: An individual participant data meta-analysis of 16 trauma film paradigm experiments. *Cognition and emotion, 29*, 702-713.
- Clark, I. A., Mackay, C. E., Woolrich, M. W., & Holmes, E. A. (2016). Intrusive memories to traumatic footage: the neural basis of their encoding and involuntary recall. *Psychological Medicine, 46*, 505-518.
- Clark, I. A., Niehaus, K. E., Duff, E. P., Di Simplicio, M. C., Clifford, G. D., Smith, S. M., . . . Holmes, E. A. (2014). First steps in using machine learning on fMRI data to predict intrusive memories of traumatic film footage. *Behaviour Research and Therapy, 62*, 37-46.
- Cloitre, M., Petkova, E., Su, Z., & Weiss, B. J. (2018). Patient characteristics as a moderator of posttraumatic stress disorder treatment outcome: combining symptom burden and strengths. *BJPsych Open, 2*, 101-106.
- Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self- memory system. *Psychological Review, 107*, 261-288.
- Conway, M. A., Singer, J. A., & Tagini, A. (2004). The self and autobiographical memory: Correspondance and coherence. *Social Cognition, 22*, 491-529.

- 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*, *46*, 1749-1759.
- Deepröse, C., Zhang, S., Dejong, H., Dalgleish, T., & Holmes, E. A. (2012). Imagery in the aftermath of viewing a traumatic film: using cognitive tasks to modulate the development of involuntary memory. *Journal of Behavior Therapy and Experimental Psychiatry*, *43*, 758-764.
- Dudai, Yadin. (2012). The restless engram: consolidations never end. *Annual Review of Neuroscience*, *35*, 227-247.
- Ehlers, A. (2010). Understanding and Treating Trauma Memories in Posttraumatic Stress Disorder. *Zeitschrift für Psychologie*, *218*, 141-145.
- Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy*, *38*, 319-345.
- Ehlers, A., Grey, N., Wild, J., Stott, R., Liness, S., Deale, A., . . . Clark, D. M. (2013). Implementation of Cognitive Therapy for PTSD in routine clinical care: Effectiveness and moderators of outcome in a consecutive sample. *Behaviour Research and Therapy*, *51*, 742-752.
- Ehlers, A., Hackmann, A., & Michael, T. (2004). Intrusive re-experiencing in post-traumatic stress disorder: Phenomenology, theory, and therapy. *Memory*, *12*, 403-415.

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*, 995-1002.

Ehlers, A., Mauchnik, J., & Handley, R. (2012). Reducing unwanted trauma

memories by imaginal exposure or autobiographical memory elaboration:

An analogue study of memory processes. *Journal of Behavior Therapy and Experimental Psychiatry*, *43*, S67-S75.

Ehlers, A., & Steil, R. (1995). Maintenance of intrusive memories in

posttraumatic stress disorder: a cognitive approach. *Behavioural and*

Cognitive Psychotherapy, *23*, 217-249.

Ehring, T., Fuchs, N., & Klasener, I. (2009). The effects of experimentally

induced rumination versus distraction on analogue posttraumatic stress

symptoms. *Behavior Therapy*, *40*, 403-413.

Ehring, T., Szeimies, A-K., & Schaffrick, C. (2009). An experimental analogue

study into the role of abstract thinking in trauma-related rumination.

Behaviour Research and Therapy, *47*, 285-293.

Elwood, L. S., Hahn, K. S., Olatunji, B. O., & Williams, N. L. (2009). Cognitive

vulnerabilities to the development of PTSD: a review of four

vulnerabilities and the proposal of an integrative vulnerability model.

Clinical Psychology Review, *29*, 87-100.

Engelhard, I. M., van den Hout, M. A., & Smeets, M. A. M. (2011). Taxing

working memory reduces vividness and emotional intensity of images

- about the Queen's Day tragedy. *Journal of Behavior Therapy and Experimental Psychiatry*, 42, 32-37.
- Ferree, N. K., & Cahill, L. (2009). Post-event spontaneous intrusive recollections and strength of memory for emotional events in men and women. *Consciousness and Cognition*, 18, 126-134.
- Ferree, N. K., Kamat, R., & Cahill, L. (2011). Influences of menstrual cycle position and sex hormone levels on spontaneous intrusive recollections following emotional stimuli. *Consciousness and Cognition*, 20, 1154-1162.
- Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, 99, 20-35.
- Foa, E. B., & Riggs, D.S. (1993). Post-traumatic stress disorder in rape victims. In J. Oldham, M.B. Riba, & A. Tasman (Eds.), *American Psychiatric Press Review of Psychiatry* (Vol. 12, pp. 273-303). Washington, DC: American Psychiatric Press.
- 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, 1132-1143.
- Grey, N., & Holmes, E. A. (2008). "Hotspots" in trauma memories in the treatment of post-traumatic stress disorder: a replication. *Memory*, 16, 788-796.

- Gvozdanovic, G. A., Stämpfli, P. , Seifritz, E. , , & Rasch, B. (2017). Neural correlates of experimental trauma memory retrieval. *Human Brain Mapping, 38*, 3592-3602.
- Haag, C., Robinaugh, D. J., Ehlers, A., & Kleim, B. (2017). Understanding the emergence of chronic posttraumatic stress disorder through acute stress symptom networks. *JAMA Psychiatry, 74*, 649-650.
- Hagenaars, M. A., & Arntz, A. (2012). Reduced intrusion development after post-trauma imagery rescripting; an experimental study. *Journal of Behavior Therapy and Experimental Psychiatry, 43*, 808-814.
- Hagenaars, M. A., Holmes, E. A., Klaassen, F., & Elzinga, B. (2017). Tetris and word games affect intrusive memories when applied after memory reactivation 4 days post analogue trauma. *European Journal of Psychotraumatology, 8*, 1386959
- Hagenaars, M. A., & Putman, P. (2011). Attentional control affects the relationship between tonic immobility and intrusive memories. *Journal of Behaviour Therapy and Experimental Psychiatry, 42*, 379-383.
- Hales, S. A., Deeprose, C., Goodwin, G. M., & Holmes, E. A. (2011). Cognitions in bipolar disorder versus unipolar depression: imagining suicide. *Bipolar Disorders, 13*, 651-661.
- Hassan, G., Kirmayer, L. J., Mekki-Berrada, A., Quosh, C., el Chammay, R., Deville-Stoetzel, J. B., . . . Ventevogel, P. (2015). Culture, Context and the Mental Health and Psychosocial Wellbeing of Syrians: A Review for

Mental Health and Psychosocial Support staff working with Syrians Affected by Armed Conflict. Geneva, Switzerland: United Nations High Commissioner for Refugees [UNHCR].

Hawkins, K. A., & Cogle, J. R. (2013). The effects of nicotine on intrusive memories in nonsmokers. *Experimental and Clinical Psychopharmacology*, *21*, 434-442.

Hayes, J. P., Vanelzakker, M. B., & Shin, L. M. (2012). Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Frontiers in Integrative Neuroscience*, *6*, 89.

Hermans, E. J., Kanen, J. W, Tambini, A., Fernández, G., Davachi, L., & Phelps, E. A. (2016). Persistence of amygdala–hippocampal connectivity and multi-voxel correlation structures during awake rest after fear learning predicts long-term expression of fear. *Cerebral Cortex*, *27*, 3028-3041.

Hoge, C. W., & Chard, K. M. (2018). A window into the evolution of trauma-focused psychotherapies for posttraumatic stress disorder. *JAMA*, *319*, 343-345.

Holman, E. A., Garfin, D. R., & Silver, R. C. (2014). Media's role in broadcasting acute stress following the Boston marathon bombings. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 93-98.

- Holmes, E. A., & Bourne, C. (2008). Inducing and modulating intrusive emotional memories: a review of the trauma film paradigm. *Acta Psychologica, 127*, 553-566.
- Holmes, E. A., Brewin, C. R., & Hennessey, R. G. (2004). Trauma films, information processing, and intrusive memory development. *Journal of Experimental Psychology: General, 133*, 3-22.
- Holmes, E. A., Craske, M. G., & Graybiel, A. M. (2014). Psychological Treatments: a call for mental-health science. Clinicians and neuroscientists must work together to understand and improve psychological treatments. *Nature, 511*, 287-289.
- Holmes, E. A., Ghaderi, A., Eriksson, E., Lauri, K. O., Kukacka, O. M., Mamish, M., . . . Visser, R. M. (2017). "I can't concentrate": a feasibility study with young refugees in Sweden on developing science-driven interventions for intrusive memories related to trauma. *Behavioural and Cognitive Psychotherapy, 45*, 97-109.
- Holmes, E. A., Ghaderi, A., Harmer, C., Ramchandani, P. G., Cuijpers, P., Morrison, A. P., . . . Craske, M. G. (2018). Psychological treatments research in tomorrow's science: seeing further. *Lancet Psychiatry, 5*, 237-286
- 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*, e4153.

- 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*, e13706.6
- Holmes, E. A., & Mathews, A. (2010). Mental imagery in emotion and emotional disorders. *Clinical Psychology Review*, *30*(3), 349-362. doi: 10.1016/j.cpr.2010.01.001
- Holmes, E. A., Sandberg, A., & Iyadurai, L. (2010). Erasing trauma memories: Is this what the science suggests or even what we want to do? [Letter to the editor]. *British Journal of Psychiatry Online*, *190*, 81a.
- Holz, E., Lass-Hennemann, J., Streb, M., Pfaltz, M., & Michael, T. (2014). Effects of Acute Cortisol Administration on Perceptual Priming of Trauma-Related Material. *PloS ONE*, *9*, e104864.
- Horowitz, M. J. (1969). Psychic trauma. Return of images after a stressful film. *Archives of General Psychiatry*, *20*, 552-559.
- Horsch, A., Vial, Y., Favrod, C., Harari, M. M., Blackwell, S. E., Watson, P., . . . Holmes, E. A. (2017). Reducing intrusive traumatic memories after emergency caesarean section: a proof-of-principle randomized controlled study. *Behaviour Research and Therapy*, *94*, 36-47.
- Iyadurai, L., Blackwell, S. B., Meiser-Stedman, R., Watson, P. C., Bonsall, M. B., Geddes, J. R., . . . Holmes, E. A. (2017). Preventing intrusive memories after trauma via a brief intervention involving Tetris computer game play

- in the emergency department: a proof-of-concept randomized controlled trial. *Molecular Psychiatry*, 23, 674-682.
- James, E. L., Bonsall, M. B., Hoppitt, L., Tunbridge, E. M., Geddes, J. R., Milton, A. L., & Holmes, E. A. (2015). Computer game play reduces intrusive memories of experimental trauma via reconsolidation update mechanisms. *Psychological Science*, 261201-2015.
- 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, E. L., Lau-Zhu, A., Tickle, H., Horsch, A., & Holmes, E. A. (2016). Playing the computer game Tetris prior to viewing traumatic film material and subsequent intrusive memories: examining proactive interference. *Journal of Behavior Therapy and Experimental Psychiatry*, 53, 25-33.
- Joëls, M., Fernandez, G., & Roozendaal, B. (2011). Stress and emotional memory: a matter of timing. *Trends in Cognitive Sciences*, 15, 280-288.
- Josselyn, S. A., Köhler, S., & Frankland, P. W. (2015). Finding the engram. *Nature Reviews Neuroscience*, 16, 521.
- Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annual Review of Clinical Psychology*, 3, 1-27.
- Kessler, H., Holmes, E. A., Blackwell, S. E., Schmidt, A. C., Schweer, J. M., Bückner, A., . . . Kehyayan, A. (in press). Reducing Intrusive Memories of

Trauma Using a Visuospatial Interference Intervention with Inpatients with Complex Post-traumatic Stress Disorder. *Journal of Consulting and Clinical Psychology*.

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995).

Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, 52, 1048-1060.

Kleim, B., Wysokowsky, J., Schmid, N., Seifritz, E., & Rasch, B. (2016). Effects of sleep after experimental trauma on intrusive emotional memories. *Sleep*, 39, 2125-2132.

Kleindienst, N., Priebe, K., Petri, M., Hecht, A., Santangelo, P., Bohus, M., & Schulte-Herbrüggen, O. (2017). Trauma-related memories in PTSD after interpersonal violence: an ambulatory assessment study. *European Journal of Psychotraumatology*, 8, 1409062.

Kosslyn, S. M. (2005). Reflective thinking and mental imagery: A perspective on the development of posttraumatic stress disorder. *Development and Psychopathology*, 17, 851-863.

Krans, J., Brown, A. D., & Moulds, M. L. (2018). Can an experimental self-efficacy induction through autobiographical recall modulate analogue posttraumatic intrusions? *Journal of Behavior Therapy and Experimental Psychiatry*, 58, 1-11.

Krans, J., Näring, G., & Becker, E. S. (2009). Count out your intrusions: effects of verbal encoding on intrusive memories. *Memory*, 17, 809-815.

- Krans, J., Näring, G., Becker, E. S., & Holmes, E. A. (2009). Intrusive trauma memory: A review and functional analysis. *Applied Cognitive Psychology*, *23*, 1076-1088.
- Krans, J., Näring, G., Speckens, A., & Becker, E. S. (2011). Eyewitness or earwitness: the role of mental imagery in intrusion development. *International Journal of Cognitive Therapy*, *4*, 154-164.
- Krans, J., Pearson, D. G., Maier, B., & Moulds, M. L. (2016). Contextual representations of negative images modulate intrusion frequency in an intrusion provocation paradigm. *Journal of Behavior Therapy and Experimental Psychiatry*, *53*, 52-58.
- LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience*, *7*, 54-64.
- Laposa, J. M., & Alden, L. E. (2008). The effects of pre-existing vulnerability factors on laboratory analogue trauma experience. *Journal of Behavior Therapy and Experimental Psychiatry*, *39*, 424-435.
- Laposa, J. M., & Rector, N. A. (2012). The prediction of intrusions following an analogue traumatic event: Peritraumatic cognitive processes and anxiety-focused rumination versus rumination in response to intrusions. *Journal of Behavior Therapy and Experimental Psychiatry*, *43*, 877-883.
- Lau-Zhu, A., Holmes, E. A., Butterfield, S., & Holmes, J. (2017). Selective association between Tetris game play and visuospatial working memory: a preliminary investigation. *Applied Cognitive Psychology*, *31*, 438-445.

- Lau-Zhu, A., Holmes, E. A., & Porcheret, K. (2018). Intrusive memories of trauma in the laboratory: Methodological developments and future directions. *Current Behavioral Neuroscience Reports*, 5, 61-71
- Lilienfeld, S. O. (2007). Psychological Treatments That Cause Harm. *Perspectives on Psychological Science*, 2, 53-70.
- Lilley, S. A., Andrade, J., Turpin, G., Sabin-Farrell, R., & Holmes, E. A. (2009). Visuospatial working memory interference with recollections of trauma. *British Journal of Clinical Psychology*, 48, 309-321.
- Ludäscher, P., Schmahl, C., Feldmann Jr, R. E., Kleindienst, N., Schneider, M., & Bohus, M. (2015). No evidence for differential dose effects of hydrocortisone on intrusive memories in female patients with complex post-traumatic stress disorder – a randomized, double-blind, placebo-controlled, crossover study. *Journal of Psychopharmacology*, 29, 1077-1084.
- Malik, A., Goodwin, G. M., Hoppitt, L., & Holmes, E. A. (2014). Hypomanic experience in young adults confers vulnerability to intrusive imagery after experimental trauma: relevance for bipolar disorder. *Clinical Psychological Science*, 2, 675-684.
- Marks, E. M., Steel, C., & Peters, E. R. (2012). Intrusions in trauma and psychosis: information processing and phenomenology. *Psychological Medicine*, 42, 2312-2323.

- Mayou, R., Bryant, B., & Duthie, R. (1993). Psychiatric consequences of road traffic accidents. *British Medical Journal*, *307*, 647-651.
- McGaugh, J. L. (1966). Time-dependent processes in memory storage. *Science*, *153*, 1351-1358.
- McGaugh, J. L. (2000). Memory - a century of consolidation. *Science*, *287*, 248-251.
- McNally, R. J. (2012). The Ontology of Posttraumatic Stress Disorder: Natural Kind, Social Construction, or Causal System? *Clinical Psychology: Science and Practice*, *19*, 220-228.
- McNally, R. J. (2017). Networks and nosology in posttraumatic stress disorder. *JAMA Psychiatry*, *74*, 124-125.
- Meyer, T., Krans, J., van Ast, V., & Smeets, T. (2017). Visuospatial context learning and configuration learning is associated with analogue traumatic intrusions. *Journal of Behavior Therapy and Experimental Psychiatry*, *54*, 120-127.
- Meyer, T., Smeets, T., Giesbrecht, T., Quaedflieg, C. W. E. M., Girardelli, M. M., Mackay, G. R. N., & Merckelbach, H. (2013). Individual differences in spatial configuration learning predict the occurrence of intrusive memories. *Cognitive, Affective, & Behavioral Neuroscience*, *13*, 186-196.
- Michael, T., Ehlers, A., & Halligan, S. L. (2005). Perceptual priming for trauma-related material in posttraumatic stress disorder. *Emotion*, *5*, 103-112.

- 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.
- Morina, N., Leibold, E., & Ehring, T. (2013). Vividness of general mental imagery is associated with the occurrence of intrusive memories. *Journal of Behavior Therapy and Experimental Psychiatry*, *44*, 221-226.
- Nader, K. (2003). Memory traces unbound. *Trends in Neurosciences*, *26*, 65-72.
- Nader, K., & Hardt, O. (2009). A single standard for memory: The case for reconsolidation. *Nature Reviews Neuroscience*, *10*, 224-234.
- Nader, K., Schafe, G. E., & LeDoux, J. E. (2000). The labile nature of consolidation theory. *Nature Reviews Neuroscience*, *1*, 216-219.
- National Institute for Health and Clinical Excellence. (2005). Post-traumatic stress disorder (PTSD): the management of PTSD in adults and children in primary and secondary care. London: National Institute for Health and Clinical Excellence.
- Nickerson, A., Bryant, R. A., Silove, D., & Steel, Z. (2011). A critical review of psychological treatments of posttraumatic stress disorder in refugees. *Clinical Psychology Review*, *31*, 399-417.
- Nishida, M., Pearsall, J. , Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex*, *19*, 1158-1166.

- Nixon, R. D. V., Cain, N., Nehmy, T., & Seymour, M. (2009). The influence of thought suppression and cognitive load on intrusions and memory processes following an analogue stressor. *Behavior Therapy, 40*, 368-380.
- Nose, M., Ballette, F., Boghelli, I., Turrini, G., Purgato, M., Tol, W., . . . Barbui, C. (2017). Psychosocial interventions for post-traumatic stress disorder in refugees and asylum seekers resettled in high-income countries: systematic review and meta-analysis. *PloS one, 12*, e0171030.
- Nosek, B. A., Alter, G., Banks, G. C., Borsboom, D., Bowman, S. D., Breckler, S. J., . . . Yarkoni, T. (2015). Promoting an open research culture. *Science, 348*, 1422-1425.
- Olatunji, B. O., & Fan, Q. (2015). Anxiety sensitivity and post-traumatic stress reactions: Evidence for intrusions and physiological arousal as mediating and moderating mechanisms. *Journal of Anxiety Disorders, 34*, 76-85.
- Ozer, E. J., Best, S. R., Lipsey, T. L., & Weiss, D. S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. *Psychological Bulletin, 129*, 52-73.
- Patel, V., Chowdhary, N., Rahman, A., & Verdeli, H. (2011). Improving access to psychological treatments: lessons from developing countries. *Behaviour Research and Therapy, 49*, 523-528.
- Payne, J. D., Chambers, A. M., & Kensinger, E. A. (2012). Sleep promotes lasting changes in selective memory for emotional scenes. *Frontiers in Integrative Neuroscience, 21*, 1-11.

- Payne, J. D., Stickgold, R., Swanberg, K., & Kensinger, E. A. (2008). Sleep preferentially enhances memory for emotional components of scenes. *Psychological Science, 19*, 781-788.
- Pearson, D. G. (2012). Contextual representations increase analogue traumatic intrusions: Evidence against a dual-representation account of peri-traumatic processing. *Journal of Behavior Therapy and Experimental Psychiatry, 43*, 1026-1031.
- Pearson, D. G., Deepro, C., Wallace-Hadrill, S. M. A., Burnett Heyes, S., & Holmes, E. A. (2013). Assessing mental imagery in clinical psychology: A review of imagery measures and a guiding framework. *Clinical Psychology Review, 33*, 1-23.
- Pearson, D. G., Ross, F. D. C., & Webster, V. L. (2012). The importance of context: evidence that contextual representations increase intrusive memories. *Journal of Behavior Therapy and Experimental Psychiatry, 43*, 573-580.
- Pearson, J., Naselaris, T., Holmes, E. A., & Kosslyn, S. M. (2015). Mental imagery: functional mechanisms and clinical applications. *Trends in cognitive sciences, 19*, 590-602.
- Porcheret, K., Holmes, E. A., Goodwin, G. M., Foster, R. G., & Wulff, K. (2015). Psychological impact of an analogue traumatic event reduced by sleep deprivation. *Sleep, 38*, 1017-1025.

Qualtrics. (2015). Qualtrics Software, version 07.16. Provo, Utah, USA:

Qualtrics.

Regambal, M. J., & Alden, L. E. (2009). Pathways to intrusive memories in a trauma analogue paradigm: a structural equation model. *Depression and Anxiety, 26*, 155-166.

Ripley, A. J., Clapp, J. D., & Beck, J. G. (2017). A prospective examination of risk factors in the development of intrusions following a trauma analog. *Behaviour Research and Therapy, 94*, 71-80.

Roberts, N. P., Kitchiner, N. J., Kenardy, J., & Bisson, J. I. (2009). Multiple session early psychological interventions for the prevention of post-traumatic stress disorder. *Cochrane Database of Systematic Reviews, Art. No.: CD006869(3)*.

Rombold-Bruehl, F., Otte, C., Renneberg, B., Schmied, A., Zimmermann-Viehoff, F., Wingefeld, K., & Roepke, S. (2017). Lower heart rate variability at baseline is associated with more consecutive intrusive memories in an experimental distressing film paradigm. *The World Journal of Biological Psychiatry, 1-6*.

Rombold, F., Wingefeld, K., Renneberg, B., Hellmann-Regen, J., Otte, C., & Roepke, S. (2016). Influence of the noradrenergic system on the formation of intrusive memories in women: an experimental approach with a trauma film paradigm. *Psychological Medicine, 46*, 2523-2534.

- Rombold, F., Wingefeld, 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.
- Rose, S. C., Bisson, J., Churchill, R., & Wessely, S. (2002). Psychological debriefing for preventing post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews, Art. No.: CD000560(2)*.
- Rothbaum, B. O., Kearns, M. C., Price, M., Malcoun, E., Davis, M., Ressler, K. J., . . . Houry, D. (2012). Early intervention may prevent the development of posttraumatic stress disorder: a randomized pilot civilian study with modified prolonged exposure. *Biological Psychiatry, 72*, 957-963.
- Russo, J., Katon, W., & Zatzick, D. (2013). The development of a population-based automated screening procedure for PTSD in acutely injured hospitalized trauma survivors. *General Hospital Psychiatry, 35*, 485-491.
- Sara, S. J. (2000). Retrieval and reconsolidation: toward a neurobiology of remembering. *Learning & Memory, 7*, 73-84.
- Schäfer, J., Zvielli, A., Höfler, M., Wittchen, H-U., & Bernstein, A. (2018). Trauma, attentional dysregulation, and the development of posttraumatic stress: An investigation of risk pathways. *Behaviour Research and Therapy, 102*, 60-66.
- Schaich, A., Watkins, E. R., & Ehring, T. (2013). Can concrete training buffer against the negative effects of rumination on PTSD? An experimental

- analogue study. *Journal of Behavior Therapy and Experimental Psychiatry*, 44, 396-403.
- Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: An update and integration. *Neuroscience & Biobehavioral Reviews*, 36, 1740-1749.
- Schwabe, L., & Wolf, O. T. (2014). Timing matters: temporal dynamics of stress effects on memory retrieval. *Cognitive Affective and Behavioral Neuroscience*, 14, 1041-1048.
- Schweizer, T., Schmitz, J., Plempe, L., Sun, D., Becker-Asano, C., Leonhart, R., & Tuschen-Caffier, B. (2017). The impact of pre-existing anxiety on affective and cognitive processing of a Virtual Reality analogue trauma. *PLoS ONE*, 12, e0190360.
- 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, 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.
- Streb, M., Conway, M. A., & Michael, T. (2017). Conditioned responses to trauma reminders: How durable are they over time and does memory

- integration reduce them? *Journal of Behavior Therapy and Experimental Psychiatry*, 57, 88-95.
- Streb, M., Mecklinger, A., Anderson, M. C., Lass-Hennemann, J., & Michael, T. (2016). Memory control ability modulates intrusive memories after analogue trauma. *Journal of Affective Disorders*, 192, 134-142.
- Sündermann, O., Hauschildt, M., & Ehlers, A. (2013). Perceptual processing during trauma, priming and the development of intrusive memories. *Journal of Behavior Therapy and Experimental Psychiatry*, 44, 213-220.
- Tabrizi, F., & Jansson, B. (2016). Reducing involuntary memory by interfering consolidation of stressful auditory information: A pilot study. *Journal of Behavior Therapy and Experimental Psychiatry*, 50, 238-244.
- Tadmor, A., McNally, R. J., & Engelhard, I. M. (2016). Reducing the negative valence of stressful memories through emotionally valenced, modality-specific tasks. *Journal of Behavior Therapy and Experimental Psychiatry*, 53, 92-98.
- Tolin, D. F., & Foa, E. B. (2006). Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. *Psychological Bulletin*, 132, 959-992.
- Tonegawa, S., Liu, X., Ramirez, S., & Redondo, R. (2015). Memory Engram Cells Have Come of Age. *Neuron*, 87, 918-931.
- Treanor, M., Brown, L. A., Rissman, J., & Craske, M. G. (2017). Can memories of traumatic experiences or addiction be erased or modified? A critical

review of research on the disruption of memory reconsolidation and its application. *Perspectives on Psychological Science*, 12, 290-035.

Ullmann, E., Barthel, A., Taché, S., Bornstein, A, Licinio, J., & Bornstein, S. R. (2015). Emotional and psychological trauma in refugees arriving in Germany in 2015. *Molecular Psychiatry*, 20, 1483-1484.

United Nations High Commissioner for Refugees. (2015). Mid-Year Trends 2015: from <http://www.unhcr.org/>

Van den Hout, M. A., & Engelhard, I. M. (2012). How does EMDR work? *Journal of Experimental Psychopathology*, 3, 724-738.

Verwoerd, J., Wessel, I., & de Jong, P. J. (2012). Fewer intrusions after an attentional bias modification training for perceptual reminders of analogue trauma. *Cognition & Emotion*, 26, 153-165.

Verwoerd, J., Wessel, I., de Jong, P., Nieuwenhuis, M., & Huntjens, R. (2011). Pre-Stressor interference control and intrusive memories. *Cognitive Therapy and Research*, 35, 161-170.

Visser, R. M., Lau-Zhu, A., Henson, R. N., & Holmes, E. A. (2018). Multiple memory systems, multiple time points: how science can inform treatment to control the expression of unwanted emotional memories. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 373. pii:

20170209

- Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning and Memory*, 8, 112-119.
- Weathers, F. W., Litz, B. T., Keane, T. M. , Palmieri, P. A. , Marx, B. P., & Schnurr, P. P. . (2013). The ptsd checklist for dsm-5 (pcl-5). *National Center for PTSD* <http://www.ptsd.va.gov/>
- Wegerer, M., Blechert, J., Kerschbaum, H., & Wilhelm, F. H. (2013). Relationship between fear conditioning and aversive memories: evidence from a novel conditioned-intrusion paradigm. *PloS ONE*, 8, e79025.
- Wegerer, M., Kerschbaum, H., Blechert, J., & Wilhelm, F. H. (2014). Low levels of estradiol are associated with elevated conditioned responding during fear extinction and with intrusive memories in daily life. *Neurobiology of Learning and Memory*, 116, 145-154.
- Weiss, D. S., & Marmar, C. R. (1997). The Impact of Event Scale - Revised. In J. P. Wilson & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD: A handbook for practitioners* (pp. 399-411). New York: Guilford Press.
- White, R., & Wild, J. (2016). “Why” or “How”: The Effect of Concrete Versus Abstract Processing on Intrusive Memories Following Analogue Trauma. *Behavior Therapy*, 47, 404-415.
- World Health Organization. (2002). *Prevention and Promotion in Mental Health*. Geneva, Switzerland: World Health Organization.

- World Health Organization. (2013a). Guidelines for the management of conditions specifically related to stress. Geneva, Switzerland: World Health Organization.
- World Health Organization. (2013b). Investing in mental health: Evidence for action. Geneva, Switzerland: World Health Organization.
- Woud, M. L., Cwik, J. C., Blackwell, S. E., Kleim, B., Holmes, E. A., Adolph, D., . . . Margraf, J. (2018). Does napping enhance the effects of Cognitive Bias Modification-Appraisal training? An experimental study. *PloS ONE*, *13*, e0192837.
- Woud, M. L., Holmes, E. A., Postma, P., Dalgleish, T., & Mackintosh, B. (2012). Ameliorating intrusive memories of distressing experiences using computerized reappraisal training. *Emotion*, *12*, 778-784.
- Woud, M. L., Postma, P., Holmes, E. A., & Mackintosh, B. (2013). Reducing analogue trauma symptoms by computerized reappraisal training - Considering a cognitive prophylaxis? *Journal of Behavior Therapy and Experimental Psychiatry*, *44*, 312-315.
- Zetsche, U., Ehring, T., & Ehlers, A. (2009). The effects of rumination on mood and intrusive memories after exposure to traumatic material: An experimental study. *Journal of Behavior Therapy and Experimental Psychiatry*, *40*, 499-514.
- Zhang, W., van Ast, V., Klumpers, F., Roelofs, K., & Hermans, E. J. (2018). Memory Contextualization: The Role of Prefrontal Cortex in Functional

Integration across Item and Context Representational Regions. *Journal of Cognitive Neuroscience*, 30, 579-593.

Zlotnick, C., Franklin, C. L., & Zimmerman, M. (2002). Does "subthreshold" posttraumatic stress disorder have any clinical relevance? *Comprehensive Psychiatry*, 43, 413-419.

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Highlights

- Intrusive memories of trauma can be distressing and disruptive in their own right
- Intrusive memories are a core clinical feature of posttraumatic stress disorder
- Cognitive science offers insights on the aetiology of intrusive memories
- Targeting intrusive memories has implications for prevention and scalable treatment
- Focusing on one symptom, instead of a whole disorder, has translational benefits