

Reducing Intrusive Memories of
Real-World Stimuli via Memory Reconsolidation

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Abstract

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After a distressing event, intrusive memories often persist and, for some, become pathological and debilitating (e.g., Brewin et al., 2010). Methods that enhance extinction learning may translate to improved exposure-based interventions that target intrusive memories. One possible opportunity for enhancing extinction is through memory reconsolidation (Nader, Schafe, & LeDoux, 2000; Monfils, Cowsanage, Klann, & LeDoux, 2009; Schiller et al., 2010). A retrieved memory reactivated by conditioned stimulus (CS) presentation is thought to enter a labile state as proteins are synthesized, and the effects of new learning that occurs within the reconsolidation window (about 10 min to 6 hrs post-retrieval) is more robust (e.g., Nader et al., 2000). To date, memory reconsolidation research in humans has been limited by fear learning paradigms that lack ecological validity (e.g., Elsey & Kindt, 2017), and parameters of boundary conditions (e.g., memory strength, retrieval cue specificity, prediction error) remain unclear (e.g., Treanor, Brown, Rissman, & Craske, 2017).

In a two-study sequence, both behavioral and biological mechanisms underlying memory reconsolidation were examined, first in a non-clinical sample, and then in a sample of trauma-exposed individuals with and without current trauma-related intrusive memories. We used the film fear learning paradigm in order to elicit and then reduce film-related intrusive memories. Neutral and negative cues were used to explore differences in cue valence, given that previously, a negative CS retrieval cue elicited higher distress and more intrusive memories than non-retrieval conditions (Marks & Zoellner, 2014). Timing of cues were varied to examine any enhanced effects of extinction within the reconsolidation window. In Study 1, participants ($N = 173$) were randomized to one of four CS cueing conditions: Pre Neutral CS, Pre Negative CS, or Pre Scrambled cue, presented 10 min prior to extinction, or Delayed Neutral CS presented 10 min after extinction. Intrusive memories were assessed 24 hr and 72 hr after acquisition. There were no differences in intrusive memory frequency or distress 72 hr after acquisition between participants in the Pre Neutral and Pre Negative cue conditions, nor were there differences between the Pre Neutral and Pre Delayed conditions. Larger increases in sAA during acquisition, $b = .23$, and larger increases in cortisol and sAA together, $b = .25$, during acquisition predicted higher intrusive memory frequency 72 hr after acquisition. Larger cortisol increase, $b = .28$, and sAA increase, $b = .25$, during extinction also predicted intrusive memories 72 hr after acquisition, and a larger increase in sAA, $b = .27$, also predicted higher intrusive memory distress 72 hr after acquisition. Negative affect after acquisition predicted intrusive memory frequency and distress 72 hr after acquisition, $b = .35$ and $b = .44$ respectively.

Boundary conditions of reconsolidation as they relate to more ecologically valid stimuli and intrusive memories remain elusive. Study 2 sought to extend this work to a clinical sample, characterized by persistent intrusive memories, and to better understand the specific type of new

learning during extinction that may be required to initiate reconsolidation. Importantly, intrusive memories are a transdiagnostic construct present in a range of psychopathology (e.g., Brewin et al., 2010). Participants ($N = 14$) in the PTSD/MDD ($n = 11$) and control ($n = 3$) groups were randomized to one of three extinction conditions: an image extinction condition, where a brief 20 sec film segment that preceded the analogue trauma during acquisition is presented repeatedly in the absence of the analogue trauma, and a film extinction condition, where the acquisition segment is shown repeatedly, and an assessment only control condition, where participants do not engage in any kind of extinction procedure. All data from this study is preliminary. Patterns of intrusive memories 72 hr after acquisition suggest that, though intrusive memory frequency did not decrease $d = 0.08$, related distress did decrease, $d = 0.85$. Participants in the PTSD/MDD group reported more intrusive memories than the control group both 24 hr ($d = 1.12$) and 72 hr ($d = 0.54$) after acquisition. Intrusive memory frequency decreased in the assessment only ($d = 0.89$) but not in the extinction conditions 72 hr after acquisition ($d = 0.07$), but patterns of distress reduction from 24 to 72 hr post-acquisition appeared similar across conditions. Parameters of reconsolidation boundary conditions when more complex, ecologically valid stimuli and outcome measures are used remain unclear; neither cue valence nor timing of retrieval cue affected intrusive memories after extinction. Glucocorticoid and noradrenergic system activity predicted intrusive memories, illustrating the importance of these two systems in strengthening emotional memory. As efforts to push reconsolidation toward clinical settings continue, preliminary findings from Study 2 highlight the importance of capturing distressing and persistent intrusive memories and determining whether these intrusive memories are amenable to enhanced extinction, as these are the kinds of intrusive re-experiencing representative of psychopathology that are often missed in experimental paradigms.

Introduction

Intrusive re-experiencing refers to a broad range of ways in which the memory of a previously experienced event can resurface, from flashbulb-like images to nightmares, to thoughts accompanied by emotional distress when cued by some type of reminder of the event. More specifically, the term “intrusive memories” is often conceptualized as a particular form of intrusive re-experiencing. Intrusive memories are typically experienced as intense, brief, and vivid image-based recollections of a specific autobiographical event (e.g., Ehlers & Steil, 1995; Brewin & Holmes, 2003; Brewin Gregory, Lipton, & Burgess, 2010). They are predominantly involuntary, often coming to mind without any attempt at deliberate memory retrieval (e.g., Bernsten 1996), and they often include strong sensory-perceptual elements of the event (e.g., most threatening or salient images, sounds, smells; Conway & Pleydell-Pearce, 2000; Ehlers et al., 2002; Ehlers, Hackmann, & Michael, 2004). Importantly, intrusive memories are common after highly distressing events, and experiencing such memories is not necessarily pathological (e.g., Bernsten, 2001; Bywaters, Andrade, & Turpin, 2004; Shalev, 1992; Watkins, Grimm, & Kolts, 2004). Typically, these memories naturally diminish over time (McFarlane, 1988; Shalev, 1992; Steil & Ehlers, 2000). However, in a minority of individuals, intrusive memories persist and are considered pathological.

Persistent intrusive memories of the event are a hallmark symptom of posttraumatic stress disorder (PTSD; APA, 2013). That said, individuals with depression also commonly experience intrusive memories following stressful life events (e.g., death of a loved one) that often lead to depressive episodes (e.g., Williams, Watts, MacLeod, & Mathews, 1997) but do not lead to PTSD. Fittingly, distress associated with intrusive memories not only correlates with severity of PTSD symptoms (e.g., Hackmann, Ehlers, Speckens, & Clark, 2004) but also depressive

symptoms (e.g., Freeston, Ladouceur, Thibodeau, & Gagnon, 1992; Brewin, Reynolds, & Tata, 1999; Patel et al., 2007). Many commonalities in the content of intrusive memories exist across the disorders (e.g., Reynolds & Brewin, 1999), and multiple theoretical models work to explain the emergence and persistence of these memories over time.

Prominent Theoretical Models of Intrusive Memories

According to prominent models, intrusive memories are thought to form based on the way the event is encoded in memory (e.g., Conway & Pleydell-Pearce, 2000; Foa, Sketeeke, & Rothbaum, 1989; Brewin et al., 2010). In general, memories of emotional events tend to be more persistent and vivid (e.g., Christianson, 1992), which makes sense evolutionarily, given that emotional memories were often critical for survival. Thus, there may be unique neurobiological underpinnings of emotional memory encoding not seen in the encoding of other kinds of memory that allows these memories to persist longer and be more readily available for retrieval. Indeed, Phelps (2004) suggests an interaction between the amygdala and hippocampal lobe occurs during the encoding of emotional memory, wherein the amygdala is able to modulate the encoding and storage processes. Fittingly, when a memory undergoing consolidation is emotional in nature and the amygdala is more activated, the degree of amygdala activation during encoding is positively correlated with later memory recall (e.g., McGaugh, 2004). In other words, an individual higher in stress or distress as an event is being encoded, according to these theories of stress and memory, will likely encode a more persistent, durable memory due to greater amygdala activation modulating hippocampal encoding processes (e.g., Cahill & McGaugh, 1998; McGaugh, 2004; McGaugh, 2014; Phelps, 2004).

In a specific theoretical account of intrusive memories incorporating both cognitive and neurobiological processes, Brewin and colleagues (2010) and Brewin and colleagues (1996)

emphasize two different theorized types of memory representations. Sensory representations, or S-reps, are perceptual, sensory images that can only be retrieved involuntarily once a traumatic memory is encoded. In contrast, during encoding, contextualized representations (C-reps) correlate with where conscious attention is focused, and can be retrieved both involuntarily and voluntarily. C-reps can also be communicated and reappraised, unlike S-reps. In this model, when an emotional memory is encoded, both C-reps and S-reps are longer lasting than those of a neutral memory. For individuals who experience an extremely distressing event but recover naturally, the S-rep has a corresponding C-rep, which then allows for the memory to be filed in the autobiographical memory “library,” thus available for voluntary retrieval with a relatively low likelihood of involuntary retrieval. However, for some, the very durable S-rep may be cued for retrieval by a particular affective state or environmental cue associated with the original memory, thus causing involuntary retrieval. C-reps are thought to modulate this retrieval process, but the process can also occur in the alternate order. Intrusive memories may also arise when a C-rep involuntarily activates a corresponding S-rep, which then provides the vivid sensory and emotional components of the involuntarily retrieved memory. Brewin and colleagues (2010), in their revised theory that accounts for intrusive images across a wide range of psychological disorders, make a distinction between perceptual and episodic long-term memory storage and point to evidence of reduced bilateral inferior temporal cortex volume and lower activation of the parahippocampal gyrus (medial temporal lobe) in patients with flashbacks, arguing that these areas of the brain are implicated in processing of contextual visual and spatial information.

With a similar emphasis on sensory-perceptual encoding of emotional memories as Brewin and colleagues, Ehlers and Clark’s (2000) and Ehlers and colleagues’ (2004) model

emphasizes the roles of data-driven processing and lack of self-referent processing. According to their cognitive theory, intrusive memories develop in individuals who are primarily encoding sensory-perceptual details without the broader context and conceptual organization that helps make sense of the event as it is happening. In other words, an event encoded primarily as fragmented sensory details (e.g., a loud bang, an image of a face, darkness, and the sound of sirens) is much more likely to re-emerge as an intrusive memory than a memory of the same event encoded in a more conceptual, organized manner (e.g., “I walked into my house one night and was confronted by an armed robber. As he threatened me, he fired his gun into mid-air. I fled, called 911, and felt relief as the cops arrived.”). The former data-driven processing leads to the lack of self-referent processing, in that individuals are unable to place a memory with little conceptual detail or organization into their broader autobiographical memory base. Further, sensory perceptual details of immediately before and during the event, often poorly discriminated from other parts of the memory, are understood by the individual as “warning signals” of imminent danger (Ehlers et al., 2004) and will easily cue intrusive memories and other trauma responses. If an individual then negatively appraises an intrusive memory (e.g., “This must mean I am going crazy” or “I have permanently changed for the worse”), this likely leads to increases in negative emotions and subsequent maladaptive coping behaviors like thought suppression, avoidance of reminders that may cue intrusions, etc. that ultimately maintain intrusive memories long term. Within this model, Ehlers and colleagues did not posit specific neurobiological mechanisms implicated in the development and persistence of intrusive memories.

Alternatively to encoding based models, retrieval-based models suggest that greater access to the explicit memory of an event predicts intrusive memories and other PTSD

symptoms, rather than the manner of the event encoding (e.g., Conway, 2005; Rubin, Bernsten, & Bohni, 2008). According to these retrieval-based models, the more emotional the information encoded, regardless of modality of encoding, will lead to increased voluntary and involuntary recall of these memories following the event. Further, because emotional memories are more readily available for retrieval, these memories will be better rehearsed than neutral memories, making them increasingly more likely for future retrieval. In addition, and specific to involuntary distressing memories, retrieval is typically accompanied by an intense emotional response (fear, anger, sadness, etc.). If a memory is retrieved and paired with intense emotional responding, this then further increases the salience and strength of the memory as it is restored to long-term memory, and increases likelihood of future retrieval (e.g., Dolcos, LaBar, & Cabeza, 2005; LaBar & Cabeza, 2006). Neurobiologically, it is thought that when an emotional memory is retrieved, brain areas that were activated during initial encoding are reactivated and produce an affective state comparable to the affective state that was present during memory encoding (Buchanan, 2007). Specifically, activation of the amygdala and medial prefrontal cortex typically occurs, as well as hypothalamic and brainstem activation, eventually leading to a range of neurophysiological responses. It is worth noting that the experience of an affective state can serve as a cue for memory retrieval (e.g., the feeling of fear cuing an intrusive memory of a rape) in addition to an external reminder (e.g., a man who resembles the perpetrator). In both cases, the neurobiological activity is thought to closely resemble that of encoding (e.g., Smith, Stephan, Rugg, & Dolan, 2006; Dolcos et al., 2005).

Marks, Franklin, and Zoellner (2018) recently proposed a novel theoretical model of how intrusive memories are encoded and persist over time. The model sought to better incorporate the crucial role of memory retrieval processes, given that factors affecting retrieval in the weeks

and months after a distressing event have been largely neglected in the empirical intrusive memory literature. This shift in emphasis may better reflect the dynamic, reconstructive memory processes at play with intrusive memories. In our model, pre-existing factors such as pre-existing psychopathology and negative appraisal style likely place certain individuals at higher risk of developing intrusive memories after a distressing event. Certain characteristics of the event itself and experiences as the event happens also make someone more at risk for experiencing intrusive memories; events that are more personally relevant, either from an evolutionary or an emotional perspective, are more likely to elicit later intrusive memories. However, given that intrusive re-experiencing of a salient event is non-pathological, we are most interested in the range of factors that likely predict the persistence of intrusive memories. The phenomenon of retrieval-induced forgetting (e.g., Anderson, Bjork, & Bjork, 1994; Anderson, Bjork, & Bjork, 2000; MacLeod & Macrae, 2001; Barnier, Hung, & Conway, 2004) suggests that each time certain memory traces are retrieved (e.g., the moment where imminent danger becomes clear; Ehlers et al., 2002), the retrieval strength of those specific traces increases while the retrieval strength of other traces associated with that same memory decreases. If intrusive memories are experienced as distressing, the retrieval strength of that memory trace subsequently increases, as emotional memories have stronger retrieval strength than unemotional memories (e.g., Barnier et al., 2004). Heightened distress may be more likely following some kind of maladaptive or negative appraisal of the intrusive memory (e.g., “This must mean I am losing my mind.”). Furthermore, negative appraisals can also change how an event is remembered (e.g., Levine, 1997; Gross, 2002; Levine, Prohaska, Burgess, Rice, & Lulhere, 2001) and how often the event is thought of (e.g., Schartau, Dalgleish, & Dunn, 2009; Mellings & Alden, 2000). Individuals who are able to come up with alternative appraisals to their negative appraisals of

intrusive memories (i.e., through talking to a friend, reminding themselves that intrusive memories are common, etc.) may be better situated to decrease retrieval strength of the most distressing parts of the event and increase retrieval strength for broader, more conceptual, and less distressing aspects of the event. In brief, while encoding processes are thought to be implicated in the initial presence of intrusive memories, retrieval processes are more implicated in their pathological persistence over time.

Predictors of Intrusive Memories

In a systematic review of what predicts intrusive memories, there were few consistent predictors of intrusive memories of distressing events, despite over 100 studies exploring this very question (Marks et al., 2018). Pre-existing factors, factors at play during an event, and post-event factors may predict these memories. With respect to pre-existing factors, higher levels of pre-existing anxiety and depression and more negative appraisals prior to an event predicted more frequent intrusive memories. With regard to predictors of intrusive memories during an event, higher data-driven processing (i.e., heightened sensory-perceptual processing, often at the expense of more conceptual, meaningful processing) was the most consistent event-based factor with a sufficient number of studies to draw meaningful conclusions. A range of studies have examined biological arousal during exposure to analogue trauma exposure, but the indices of biological arousal were too varied to make meaningful conclusions. That said, one study with a clinical sample found increases in cortisol and salivary alpha amylase (sAA) together predicted frequency of intrusive memories of negative images in individuals with PTSD above and beyond either cortisol increases or sAA increases predicting higher intrusive memories on their own (Nicholson, Bryant, & Felmingham, 2013). Finally, regarding post-event processing, more negative appraisals of the event afterwards were also predictive of more frequent intrusive

memories. Perhaps most critical was the potential role of memory retrieval, where the event memory is reactivated from long-term memory; it is here where intrusive memory modification and/or reduction may be most likely to occur in a clinically meaningful way. That said, to date, very few studies examined retrieval processes, leaving this an unaddressed question. The review also very much highlighted the need for more studies with clinical samples in order to better understand the *persistence* rather than the *onset* of intrusive memories. Although translational research is clearly important, clinical translation and implications for intervention settings are tremendously by only studying healthy samples; of the 106 studies reviewed, only 14 were conducted with clinical samples. If analogue studies are unable to elicit the level of distress associated with intrusive memories seen in clinical samples and are unable to study the persistence of intrusive memories due to frequent floor effects, the understanding of analogue findings as they apply to clinical translation is severely limited. Examination of retrieval processes in non-clinical and then clinical samples, and how such processes affect the persistence of intrusive memories are key next steps for the intrusive memory field.

Memory Reconsolidation as an Opportunity for Adaptive Updating

Exposure-based therapies are thought to decrease intrusive memories through extinction processes (e.g., Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Norberg, Krystal, & Tolin, 2008). During extinction, a conditioned stimulus (CS), a previously neutral stimulus that becomes associated with a fear-eliciting stimulus (US) is presented repeatedly. The meaning of the CS is thought to become ambiguous through learning of a new inhibitory association, and will be interpreted differently depending on surrounding contextual information (e.g., Bouton, 1993; Bouton, 1994; Fanselow, 2010). In exposure-based treatment for PTSD, through repeated revisiting of the trauma memory and systematically approaching feared reminders of the trauma,

the meaning of their memory of the trauma becomes ambiguous and does not universally signal danger. Fear responses diminish as individuals learn these new inhibitory associations (e.g., Craske et al., 2008; Craske et al., 2014). For example, an assault survivor with PTSD may learn through repeated and prolonged exposure to different places that remind her of the assault that these places are actually safe. Similarly, she may learn that she can have non-threatening, and even pleasant, interactions with individuals who remind her of her perpetrator. This individual also learns that the high anxiety that arises in the presence of trauma-related stimuli is tolerable and decreases over time. Clinical trials data examining such interventions suggest that exposure-based interventions are robust, with treatment gains lasting 5 – 10 years after therapy ends (e.g., Resick, Williams, Suvak, Monson, & Gradus, 2012; Fava, Rafanelli, Grandi, & Conti, 2001). That said, some individuals experience a “return of fear” even after a course of successful exposure therapy. “Return of fear” is distinct from a resurgence of PTSD; “return of fear” may be characterized by a return of intrusive memories, a distressing nightmare, or becoming quickly startled, and can occur in situations where environmental cues very closely map onto those present during the actual traumatic experience (e.g., finding yourself in an elevator with the perpetrator). Recent work in the exposure therapy literature has emphasized various strategies through which this new learning may be enhanced in order to make exposure-based interventions increasingly robust and to be able to minimize such experiences where particular symptoms may temporarily or more persistently re-emerge (e.g., Craske et al., 2014).

One such theory to potentially enhance new learning and strengthen therapeutic outcomes to prevent relapse is memory reconsolidation. Memory reconsolidation is a process that is initiated when new learning relevant to a previously encoded memory occurs within a specific period of time following memory retrieval and is thought to enhance this new learning (e.g.,

Nader et al., 2000; Duvarci & Nader, 2004; Tronson & Taylor, 2007). The process of memory reconsolidation may be initiated when a previously consolidated memory is retrieved from long-term memory and reactivated by some type of retrieval cue. For example, the woman with PTSD walks into a restaurant that smelled like burnt grease similar to how the perpetrator smelled, thus reactivating memories of the assault. According to the reconsolidation hypothesis, there exists a window of time, approximately ten min to six hrs post-retrieval and termed the “reconsolidation window,” during which the retrieved memory is particularly malleable. Any new learning that occurs within this window is thought to be restored in long-term memory as a modified version of the originally retrieved memory (e.g., Walker, Brakefield, Hobson, & Stickgold, 2003; Duvarci & Nader, 2004; Nader, Schafe, & LeDoux, 2000). So, if this woman is able to enter the restaurant, meet up with a friend, and have an uneventful meal despite the smell, she may learn that the restaurant is actually safe and does not lead to being in danger. Importantly, this new learning is thought to be more durable and more robust than new learning that may occur outside of this particular time window of lability (i.e., immediately after memory retrieval or more than 6 hours after memory retrieval) and more robust than new learning that occurs without initial memory retrieval (e.g., having an uneventful meal at this restaurant without first thinking about the assault). If the woman had entered (e.g., trauma memory retrieved upon entering restaurant), immediately ordered takeout, and left 5 min later, memory reconsolidation would not generate new learning. This process of reconsolidation of memory updating is likely occurring in daily experiences without any awareness of the process, given the hypothesis that it functions to keep memories current and relevant (e.g., Lee, 2009; Nader & Hardt, 2009).

Memory reconsolidation is thought to be a protein synthesis-dependent process (e.g., Debiec, LeDoux, & Nader, 2002; Lee, Tronson & Taylor, 2007; Nader et al., 2000; Schafe &

LeDoux, 2000), during which *de novo* protein synthesis in the lateral and basal amygdala neurons must occur in order for the retrieved and modified memory to be restored to long-term memory as a more durable memory (e.g., Nader & Hardt, 2009). Much of the neurobiological evidence for fear memory reconsolidation comes from rodent studies that have used protein synthesis inhibitors in order to block various stages of the reconsolidation process. Post-retrieval administration of such drugs typically causes amnesia of the original memory (e.g., Sara, 2000; Nader et al., 2000), suggesting that reactivated memories retrieved from long-term memory are malleable and require reconsolidation in order to be restored to long-term memory. Importantly, this reconsolidation blockade only occurred for memories that had been reactivated (e.g., Lee, Milton, & Everitt, 2006; Nader et al., 2000). Further, this suggests that reactivation of a previously consolidated memory destabilizes the memory such that conditioned responding can still occur, but requires new protein synthesis in the synapses (e.g., Debiec et al., 2002; Nader, 2003; Nader & Hardt, 2009).

Glucocorticoids and noradrenergic activity, as expected based on their roles in memory consolidation, have also been linked to memory reconsolidation processes (e.g., Cai, Blundell, Han, Greene, & Powell, 2006; Debiec & LeDoux, 2006). There is substantial evidence that glucocorticoids (e.g., cortisol, corticosterone) and the noradrenergic system (e.g., epinephrine, norepinephrine [NE]) modulate the consolidation of emotional memory following their release from the adrenal medulla (epinephrine, norepinephrine) and cortex (glucocorticoids) (e.g., de Quervain, Schwabe, & Roozendaal, 2017; Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013; McGaugh, 2004; McGaugh & Roozendaal, 2009). The basolateral amygdala (BLA) appears critical in this modulation of memory consolidation. Infusions of β -adrenoreceptor agonists into the BLA block memory-enhancing effects of epinephrine (e.g., Liang, Juler, & McGaugh, 1986),

and glucocorticoid receptor agonists administered into the BLA enhance emotional memory in a dose- and time-dependent manner (e.g., Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). Critically, the memory-enhancing effects of glucocorticoids appear contingent on endogenous noradrenergic activity in the BLA (Roozendaal et al., 2006). More specifically, glucocorticoids bind to glucocorticoid receptors in noradrenergic neurons in the brainstem (e.g., Roozendaal, Barseghyan, & Lee, 2008; Roozendaal, Quirarte, & McGaugh, 2002). This then triggers NE release in the BLA and initiates a noradrenergic cascade thought to modulate the prefrontal cortex, hippocampus, and other brain regions involved in learning and memory, ultimately leading to enhanced memory of emotional information (e.g., McGaugh & Roozendaal, 2002; Quirarte, Roozendaal, & McGaugh, 1997). Importantly, the timing of glucocorticoid arousal and noradrenergic activity appears important, in that increases in cortisol levels must occur in tandem with release of noradrenaline (e.g., Joels, Guillen-Fernandez, & Roozendaal, 2011).

In humans, interactions between noradrenergic activity and glucocorticoids has also been observed; administration of propranolol, a non-selective noradrenergic antagonist, interfered with cortisol-dependent amygdala activation in response to emotional images (e.g., Cahill, Prins, Weber, & McGaugh, 1994; Maheu, Joaber, Beaulieu, & Lupien, 2004). Human studies have replicated the finding that increased noradrenergic activity is required in order for enhanced consolidation of emotional stimuli (e.g., Cahill & Alkire, 2003; Southwick et al., 2002). Elevated NE levels appear to enhance hippocampal response to emotional stimuli; when NE and cortisol levels are simultaneously elevated, the inhibitory effect of elevated cortisol on emotional fear memory encoding is reversed, suggesting that the effects of glucocorticoids on enhanced emotional memory consolidation are specifically contingent on noradrenergic activity (e.g., Kukolja, Klingmuller, Maier, Fink, & Hurlmann, 2011). Of key importance to this work, the

interaction effect of glucocorticoids and noradrenergic activity appears to hold in the setting of involuntary memory retrieval, namely intrusive memories (e.g., Bryant, McGrath, & Felmingham, 2013; Nicholson, Bryant, & Felmingham, 2014). The combination of increased glucocorticoid *and* increased noradrenergic activity influenced intrusive memories in both non-clinical (Bryant et al., 2013) and PTSD (Nicholson et al., 2014) samples, providing further evidence for this interaction effect as a specific neurobiological mechanism through stress or heightened emotion may enhance memory consolidation. Of note, in Bryant and colleagues' (2013) non-clinical sample, the interaction effect was specifically observed in men but not women. This finding is consistent with several studies examining gender differences, glucocorticoids, and memory consolidation (e.g., Andreano & Cahill, 2006; Buchanan & Tranel, 2008).

Though newer and less abundant, research focusing on the roles of glucocorticoid and noradrenergic activity in post-retrieval memory reconsolidation suggests similar neurobiological processes at play. Memory retrieval can result in synaptic destabilization; if the memory is modified or updated in some way within the reconsolidation window, synthesis of new proteins and synaptic plasticity are required in order to restore the newly modified memory back to long-term memory (e.g., Otis, Werner, & Mueller, 2015). More specifically, memory retrieval leads to immediate impairment in long-term potentiation (LTP), which is then enhanced about six hours post-retrieval (e.g., Nader & Hardt, 2009; Krawczyk et al., 2015). Reconsolidation is believed to be a process distinct from consolidation (e.g., Alberini, 2005), and fear extinction is a way in which retrieved fear memories can be modified within the reconsolidation window. With that said, a potentially important distinction is whether glucocorticoids and noradrenergic activity are affecting the extinction learning process or the reconsolidation of that now modified memory

to long-term memory (LTM) (e.g., de Quervain et al., 2017), as this distinction would affect development of novel interventions targeting glucocorticoids, as well as specific timing of such interventions. Thus far, evidence from animal studies suggests that post-reactivation administration of glucocorticoids affects extinction learning (e.g., Abrari, Rashidy-Pour, Semnani, & Fathollahi, 2008; Blundell, Blaiss, Lagace, Eisch, & Powell, 2011; Cai et al., 2006), whereas administration of protein synthesis inhibitors appears to block reconsolidation (e.g., Nader et al., 2000; Schafe & LeDoux, 2000). Inhibition of noradrenergic activity following memory retrieval appears to favorably disrupt memory reconsolidation processes (e.g., Debiec & LeDoux, 2006; Mueller, Porter, & Quirk, 2008; Otis et al., 2015; Przybylski, Roulet, & Sara, 1999). Cortisol has similarly been shown to enhance reconsolidation of fearful memories (i.e., enhancing the reactivated fear memory) in men (Drexler, Merz, Hamacher-Dang, Tegenthoff, & Wolf, 2015) but not women (Drexler, Merz, Hamacher-Dang, & Wolf, 2016). As would be expected based on fear memory consolidation literature, interaction effects of noradrenergic activity and glucocorticoids have also been evidenced, wherein a threshold level of noradrenergic activity is required in order for extinction-learning effects of glucocorticoids to occur (e.g., Pitman et al., 2011). That said, the vast majority of studies have examined either glucocorticoid or noradrenergic activity as they relate to memory reconsolidation, rather than the interaction effects of both systems together.

Although the above neurobiological findings suggest that neurobiological intervention within particular timeframes would be useful in decreasing the return of distressing memories following traumatic events in humans, a number of issues prevent direct translation to humans from a pharmacological standpoint. Propranolol is the only non-toxic drug that has been used in human studies, and clinically findings are far from robust. While a very small meta-analysis ($k =$

10) of effects of propranolol suggests that the drug is a promising form of intervention, only two of these studies examined reconsolidation blockade (Lonergan et al., 2013). Administration of cortisol has also been explored, both in healthy samples (e.g., Graebener, Michael, Holz, & Lass-Hennemann, 2017; Holz, Lass-Hennemann, Streb, Pfalz, & Michael, 2014) and samples with PTSD (e.g., Aerni et al., 2004; Ludascher et al., 2015), but overall effects are negligible. Critically, the majority of protein synthesis inhibitors, one of the most reliable agents to block reconsolidation of fear memories in rodents, are toxic to humans, limiting any translation of such pharmacological interventions to humans. In response to this limitation, Monfils and colleagues (2009) validated a retrieval-extinction paradigm in rats as a means to update a retrieved memory behaviorally (i.e., using a non-pharmacological alternative). Rather than inducing post-retrieval amnesia, fear extinction conducted within the reconsolidation window following fear acquisition memory retrieval via CS cue presentation served to update the memory with new learning. Rats who underwent fear extinction within the reconsolidation window showed no return of fear 24 hr and one month after extinction compared to rats who underwent extinction outside of the reconsolidation window. Schiller and colleagues (2010) conducted a similar study in a human sample, comparing extinction 10 min post-retrieval to extinction 6 hr post-retrieval to extinction in the absence of retrieval. Consistent with Monfils and colleagues (2009), findings suggest that post-retrieval extinction 10 min after CS presentation led to decreased return of fear 24 hr after extinction compared to the other conditions, and these differences held when participants returned one year after fear extinction to test the durability of post-retrieval extinction (Schiller et al., 2010). Of note, while studies of fear memory reconsolidation in rats using protein synthesis inhibitors are generally robust, overall effect sizes from studies with rats specifically examining post-retrieval fear extinction within the reconsolidation window are small ($g = 0.21$), and effect

sizes from reconsolidation studies with humans using post-retrieval fear extinction paradigms are small to moderate ($g = 0.40$; Kredlow, Unger, & Otto, 2016).

Importantly, this small to moderate effect of reconsolidation in human studies can be broken down further with regard to stimuli employed. When examining fear-relevant vs. fear-irrelevant stimuli in human post-retrieval extinction studies, reconsolidation appears to provide an advantage in strengthening extinction learning specifically when implemented with *fear-irrelevant* rather than fear-relevant stimuli (Kredlow et al., 2016). The majority of studies used fear-irrelevant stimuli such as combinations of different shapes and colors paired with and without an air puff or mild electrical shock as stimuli in fear acquisition and extinction paradigms, and physiological measures (e.g., startle response, skin conductance) as indices of fear (e.g., Schiller et al., 2010; Agren et al., 2012; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Oyarzun et al., 2012; Warren et al., 2014). In contrast, examples of fear-relevant stimuli include photos of snakes, spiders, and other innately fearful images, fearful human faces, etc. Quite consistently, studies that used fear-relevant stimuli have found no effect of reconsolidation on return of fear (e.g., Kindt & Soeter, 2013; Golkar, Bellander, Olsson, & Öhman, 2012; Soeter & Kindt, 2011; Meir Drexler et al., 2014). This is critical in considering translation of reconsolidation to clinical settings, where clients are facing fear-eliciting situations and memories through exposure exercises. If reconsolidation enhances post-retrieval learning related to fear-irrelevant stimuli but does not enhance post-retrieval learning related to fear-relevant stimuli, does it have a place in clinical translation?

Improving Ecological Validity of Translational Efforts

In initial work (Marks & Zoellner, 2014), a more ecologically valid paradigm for understanding how, and if, reconsolidation could enhance extinction learning was developed.

More specifically, the key question is whether post-retrieval learning can be enhanced via memory reconsolidation when complex and clinically relevant stimuli are utilized, a concern that was raised both in Kredlow and colleagues' (2016) reconsolidation meta-analytic findings, as well as by others in the field (e.g., Kindt & Soeter, 2013; Li et al., 2017; Drexler et al., 2014). The paradigm that was developed included more ecologically valid stimuli and also more ecologically valid indices of fear. When we think about the kinds of stimuli that elicit fear in the clients that we treat, such stimuli are complex and multisensory. Similarly, when we think about optimal ways of measuring fear responses in our clients, we consider not only an individual's objective physiological fear response but also one's subjective experience. When considering meaningful indices of memory-based psychopathology that commonly elicit fear and distress, intrusive memories are common, transdiagnostic experiences central to a range of psychological disorders (e.g., Brewin, 2014; Brewin et al., 2010). Thus, we developed a novel film fear learning paradigm meant to elicit intrusive memories. We merged the distressing film paradigm commonly used in experimental studies examining predictors of intrusive memories (see James et al., 2016, for trauma film paradigm review) with a fear acquisition and extinction paradigm like those used most frequently in fear memory reconsolidation studies. Fear acquisition consists of exposure to a brief, distressing 10 min film segment; fear extinction, conducted 48 hr after acquisition, consists of exposure to that same film clip repeatedly (30 min), gradually shifting to the most distressing 3 min segment. The extinction sequence is meant to mirror imaginal exposure over the course of prolonged exposure therapy (PE) for PTSD where clients gradually hone in on the most distressing moments of their traumatic memory. In PE, it is commonly more challenging for clients to approach these moments, and typically need more repetition and more time to emotionally process these parts. It would similarly be expected that in an analogue study,

participants may need more time to process the most upsetting part of a distressing film segment (Foa, Hembree, & Rothbaum, 2007).

In the initial study of the Film Fear Learning paradigm with undergraduate students ($N = 168$), memory reconsolidation was manipulated via different retrieval cue conditions prior to undergoing extinction. In the reconsolidation condition, participants viewed a retrieval cue 10 min prior to undergoing extinction. In the delayed condition, participants viewed a retrieval cue 10 min after undergoing extinction in order to compare extinction that *precedes* a memory retrieval cue. Finally, the control condition viewed a non-retrieval cue that mirrored color and intensity of the retrieval cue 10 min prior to extinction in order to compare retrieval vs. non-retrieval cues followed by within-window extinction. Contrary to the study hypothesis, participants in the reconsolidation condition reported *more* total intrusive memories 24 hr after extinction than participants in the non-retrieval cue condition; there was no difference in intrusive memory-related distress across conditions. When examining the pattern of distress during extinction, participants who viewed the retrieval cue 10 min prior to extinction were significantly more distressed throughout extinction compared to participants in control conditions. The retrieval cue presented was a graphic image from the most upsetting moment of the distressing film segment. It is possible that participants who saw this upsetting image and entered extinction more distressed consolidated the higher distress they experienced throughout extinction, thus leading to more rather than less intrusive memories in the 24 hr period following extinction. This explanation is consistent with some literature suggesting that increased stress may impair reconsolidation processes (e.g., Akirav & Maroun, 2013) and is consistent with the idea that all learning that takes place during extinction, rather than solely the end result, may be incorporated into the modified memory (Smits et al., 2013). Further, some evidence suggests

that presentation of a more negatively valenced conditioned stimulus cue may lead to higher fear following reinstatement (e.g., Zbozinek, Hermans, Prenoveau, Liao, & Craske, 2015), though this study was not a memory reconsolidation study. In sum, it appears that the reconsolidation did affect intrusive memory frequency following the extinction phase, though the precise mechanism driving this finding remains unclear. Retrieval cue valence appeared to affect distress during extinction, and thus may be related to how reconsolidation may or may not be advantageous when new learning occurs within the reconsolidation window.

Effects of Retrieval Cue Valence on Post-Retrieval Extinction and Subsequent Intrusive Memories.

Accordingly, a next critical step is to explore the role of retrieval cue valence on memory reconsolidation, specifically manipulating cue valence. In this study, we again employed the Film Fear Learning paradigm, this time with different cue conditions in order to better understand how cue valence may impact post-retrieval extinction and subsequent intrusive memories. All participants underwent the initial fear acquisition phase, followed by an assessment of intrusive memory frequency and distress 24 hr after acquisition. For extinction, participants were randomized into one of four extinction conditions. In the neutral reconsolidation condition, participants viewed a neutral retrieval image 10 min prior to viewing the extinction film segment, in order to assess effects of a neutral retrieval cue followed by within-window extinction on intrusive memories 24 hr after extinction. In the negative reconsolidation condition, the same retrieval cue from Marks and Zoellner (2014) was presented, followed by within-window extinction, which allowed for a direct comparison between neutral and negative retrieval cues and how they affect intrusive memories 24 hr after extinction. In the delayed condition, participants first viewed the film extinction segment, and then viewed the

same neutral retrieval cue used in the neutral reconsolidation condition, to examine effects of extinction occurring prior to retrieval cue presentation. Finally, in the control condition, participants viewed the same non-retrieval cue from Marks and Zoellner (2014) in order to examine any effects of directing attention toward something and then viewing the extinction film segment 10 min after cue presentation. Intrusive memories 24 hr after extinction were again assessed in order to determine whether there were differences between retrieval cue conditions in terms of either intrusive memory frequency or distress. In addition, glucocorticoid via salivary cortisol and noradrenergic activity via salivary alpha amylase were assessed as indices of physiological stress and arousal in order to understand how both glucocorticoid and noradrenergic systems may influence encoding, extinction, and intrusive memories during the film fear learning paradigm.

Based both on the exposure literature showing that all aspects of an exposure session are affected by enhancement of extinction (Smits et al., 2013) and also on findings from Marks and Zoellner (2014) specifically showing that participants in the reconsolidation condition were more distressed during extinction and reported more intrusive memories the day following, it was hypothesized that participants in the neutral CS condition would experience fewer and less distressing intrusive memories 24 hr after extinction compared to the participants in the delayed CS condition. Based on the prior finding that a negatively valenced cue presented prior to extinction led to more intrusive memories 24 hr after extinction (Marks & Zoellner, 2014), it was further hypothesized that participants in the neutral CS condition would experience fewer and less distressing intrusive memories 24 hr after extinction than those in the negative CS condition. Finally, based on findings suggesting that interactions of cortisol and sAA predict intrusive memories of an analogue stressor (Bryant et al., 2013; Nicholson et al., 2014), it was

hypothesized that higher levels of sAA and cortisol during acquisition would predict increased intrusive memories 24 hr after acquisition, whereas decreased levels of sAA and cortisol during extinction would predict fewer and less distressing intrusive memories 24 hr after extinction.

Method

Participants

One hundred and seventy-three undergraduate students (57.0% women, 43.0% men) enrolled in introductory-level psychology classes at a large metropolitan university completed this study. Participants were recruited via a web-based Psychology Subject Pool, where undergraduates needing to fill psychology course requirements through study participant signed up to participate. On this website, participants had the opportunity to read the study description that shared basic study procedures (e.g., “view a brief distressing film,” “give several saliva samples”), view participant inclusion and exclusion criteria. If interested, participants then enrolled online for time slots via a psychology subject pool website. Eligible participants were between the ages of 18 and 65 and were fluent in English. See Table 1 for participant demographics.

Design

Study design is both a between-subjects and within-subjects design. The between-subjects factor is extinction cue condition (4: Pre Neutral CS, Pre Negative CS, Pre Scrambled, Delayed Neutral CS). The within-subjects factor is time since acquisition (2: 24 hr, 72 hr). Primary dependent variables are intrusive memory frequency and distress 72 hr after acquisition. See Figure 1 for study flow diagram.

Materials

Film Fear Learning Paradigm. Footage from various parts of the feature film, *The Last King of Scotland*, was selected and merged into a 10-min segment. The segment includes graphic images of mutilation and death, and has been used in our previous work (Marks & Zoellner, 2014) as an effective way in which to elicit intrusive memories in a sample of healthy undergraduates.

For fear acquisition, the 10 min segment was shown one time. For fear extinction, the 10 min segment was shown in its entirety, followed by a 6 min shortened segment, followed by 5 repetitions of most graphic 3 min segment, for a total of 30 min of film viewing. The function of gradually honing in on the most graphic and salient film content was to mimic processes in exposure therapy for PTSD. Patients gradually shift to retelling the most distressing part of their trauma memory, called “hotspots,” during imaginal exposure as treatment progresses. The film was projected on a white wall (6 ft x 6 ft dimensions).

Day Three Conditioned Stimulus Cue Manipulations. Four different conditioned stimulus cue conditions were used during the fear extinction session: Pre Neutral CS, Pre Negative CS, Pre Scrambled, and Delayed Neutral CS. All images (all 6 ft x 6 ft projected onto white wall) and were presented for 8 seconds.

Pre Neutral CS condition. In this condition, participants viewed a neutral image of the female protagonist’s face 10 min prior to extinction film viewing. This image was taken directly from the acquisition film segment, and was meant to reactivate film-related memories (i.e., reconsolidation condition).

Pre Negative CS condition. In this condition, participants viewed a graphic image of the female protagonist’s mutilated body 10 min prior to extinction film viewing. This image was taken directly from the acquisition film segment, and was meant to reactivate film-related

memories before extinction (i.e., reconsolidation condition) and was also expected to elicit some degree of distress in participants. This was the same CS cue used in Marks and Zoellner (2014).

Pre Scrambled condition. In this condition, participants viewed a grey square 10 min prior to extinction film viewing. This cue was not intended to reactivate memories of the film in any way (i.e., non-reconsolidation condition). The grey square was derived from the negatively valenced image using MatLab programming, allowing us to control for any effect of saturation, hue, and brightness, as well as any effect of simply viewing an image prior to extinction.

Delayed Neutral CS condition. In this condition, participants viewed the neutral image of the female protagonist's face 10 min after extinction film viewing. This was the same cue used in the Pre Neutral CS condition, and was meant to reactivate film-related memories, but after extinction had already taken place (i.e., non-reconsolidation condition).

Visuospatial Distractor Task. Tetris, a visuospatial game played on the computer, was used as a stimulus offset technique (Pedreira et al., 2004) following CS retrieval cue presentation for the two conditions that were randomized to an extinction session. The goal of Tetris is to manipulate shapes as they fall in order to form as many horizontal lines as possible. Tetris is thought to compete with limited visuospatial cognitive resources believed to be necessary for intrusive memory formation. It is commonly used in intrusive memory research as well (e.g., Iyadurai et al., 2018; James et al., 2015; Marks & Zoellner, 2014; Holmes et al., 2010). Given that the purpose of Tetris is to shift participant attention away from any film-related memories retrieved due to CS cue presentation, the task's effectiveness was assessed with a single question: "How effective was the computer task in distracting you from your thoughts related to the film previously viewed?" Responses were rated on a 9-point scale from 0 (*not at all effective or no film-related thoughts*) to 8 (*extremely effective*).

Baseline Self-Report Measures

Posttraumatic Diagnostic Scale for DSM-5 (PDS-5; Foa et al., 2016). The PDS-5 is a 26-item self-report assessment of PTSD symptom severity. The first item assesses trauma exposure according to the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition; DSM-5; American Psychiatric Association, 2013) and the second item identifies the most traumatic experience in instances of multiple trauma exposures. Twenty items assess frequency and severity of each of the DSM-5 symptoms of PTSD. Each of the symptom-specific questions is rated on a scale from 0 (*not at all*) to 4 (*6 or more times per week / severe*), with a total score summing these 20 items. The next two items on this measure assess symptom-related distress and interference and are rated on the same 0 to 4 scale from the symptom questions. The final two questions assess symptom onset and duration; symptom onset is either less than 6 months or more than 6 months post-trauma exposure, and duration of symptoms is either less than 1 month or more than 1 month. The PDS-5 demonstrates good convergent validity with the PTSD Checklist ($r = .90$) and the PTSD Symptom Scale-Interview Version (PSSI-5; $r = .85$). The PDS-5 also shows good discriminant validity with the Beck Depression Inventory (BDI-II) and the State-Trait Anxiety Inventory-Trait scale (STAI-T), $Z_H > 3.05$, $p < .01$ for both.

Beck Depression Inventory- II (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II assesses presence and intensity of sleep, mood, appetite, worthlessness, suicidality, level of interest/engagement, and self-perception. Responses are symptom-specific and are rated on a 0 to 3 scale, with 0 representing the absence of that particular symptom and 3 representing high severity (e.g., 0 = *I don't criticize or blame myself more than usual*; 3 = *I blame myself for everything bad that happens*). Total BDI-II scores are calculated by summing the totals of all individual items, with higher scores representing higher severity of depression. The BDI-II has

demonstrated good concurrent validity with other self-report measures of depression and anxiety, including the State-Trait Anxiety Inventory (trait version) ($r = .77$; Storch, Roberti, & Roth, 2004), and the Hamilton Psychiatric Rating Scale for Depression ($r = .71$; Beck, Steer, & Brown, 1996).

Spontaneous Use of Imagery Scale (SUIS; Reisberg, Pearson, & Kosslyn, 2003).

This 12-item self-report measure is used to assess how individuals use mental imagery in their daily lives. This measure was included given the relationship between mental imagery and intrusive memories (e.g., Morina, Leibold, & Ehring, 2013). This measure focuses only on the use of visual imagery, and does not assess other spontaneous sensory experiences. Each item assesses how often a particular scenario fits an individual's typical experience, with responses rated on a 1 (*never appropriate*) to 5 (*always appropriate*) scale. For example, "When going to a new place, I prefer directions that include detailed descriptions of landmarks (such as the size, shape, and color of a gas station) in addition to their names." Total score is calculated by summing all items, with higher scores indicating those with higher image vividness. The SUIS is reported to have good internal consistency ($\alpha = .83$; McCarthy-Jones, Knowles, & Rowse, 2012). Additional psychometrics have not been reported at present (Nelis, Holmes, Griffith, & Raes, 2014).

Demographics. Demographics questions included questions regarding age, race, ethnicity, education level, sex, and gender.

Health & Medication Questionnaire. This questionnaire assessed a range of factors known to influence cortisol and sAA levels, specifically sleep, teeth brushing, food consumption, cigarette smoking, caffeine intake, menstrual period, stress level, and current medications.

Additional Post-Film Questions. Four additional questions relevant to film viewing experience were asked after acquisition in order to assess for predisposing factors that may make someone more or less prone to developing intrusive memories from a graphic film segment.

These questions were: 1) “How enjoyable do you find violent, graphic movies?” with responses rated on a 0 (*not at all*) to 6 (*very enjoyable*) Likert scale. 2) “How often do you seek out violent, graphic movies to watch?” also rated on a 0 (*never*) to 6 (*often*) scale. 3) “Did you pay attention during the movie?” with yes/no responses. 4) “Did you turn your head or look away at any point during the movie?” with yes/no responses, followed up with “If yes, how many times?”

State Self-Report Measures

State-Trait Anxiety Inventory (STAI; Spielberger, Gorusch, Lushene, Vagg, & Jacobs, 1983). The measure is a self-report measure of both state anxiety and trait anxiety via two separate subscales (STAI-S and STAI-T, respectively). The STAI-T allows for assessment of overall baseline anxiety, whereas the STAI-S allows for a more concise assessment of anxiety in that given moment. The measure includes 40 total items that assess feelings of anxiety, contentedness, tension, etc. The STAI-T was administered once prior to acquisition; the STAI-S was administered prior to acquisition and extinction sessions as a measure of state anxiety coming into sessions. All items are rated on a scale from 0 (*not at all*) to 4 (*very much so*). Examples of items from the STAI-T include “I wish I could be as happy as others seem to be,” “I feel secure,” and “I worry too much over something that does not really matter.” Sample questions from the STAI-S include “I feel calm,” “I feel tense,” and “I feel frightened.” The two subscales are scored separately; subscale scores are calculated by summing the 20 corresponding items, with reverse scoring where indicated. Higher total scores are indicative of higher anxiety.

The STAI-T demonstrates good test-retest reliability ($r = .73 - .86$; Spielberger et al., 1983) and correlates well with other measures of trait anxiety ($r = .52 - .80$; Spielberger et al., 1983).

Subjective Units of Distress (SUDs; Wolpe, 1969). This self-report measure of subjective state distress is a single question (i.e., “What is your SUDs level?”) and responses are on a 0 to 100 scale. The SUDs scale allows for repeated assessment of participants’ distress in response to film content, and also in response to retrieval cue material. This rating is additionally used as a subjective rating in conjunction with participants’ cortisol/sAA data. Zero represents a completely calm and relaxed state, and 100 represents the most distress an individual has ever felt or could imagine feeling. Participants were asked to give SUDs ratings each time they give a saliva sample, and every 2 min during the film acquisition segment. In addition, participants randomized to an extinction condition gave SUDs ratings in response to the retrieval cue, and every 5 min during the 30 min extinction segment. Peak SUDs during acquisition and extinction phases were defined as the highest SUDs rating reported during each segment. This measure of distress is associated with objective measures of physiological arousal (heart rate, $r = .39$; peripheral vasoconstriction, $r = .84$; Thyer, Papsdorf, Davis, & Vallecorsa, 1984).

Thoughts and Feelings Questionnaire (TFQ; Ehlers, 1998). This questionnaire captures conceptual and data-driven processing in response to emotional stimuli. Individuals are asked about the way in which they processed the film segment, including how well they tracked what was happening, how absorbed they were in the sensory material rather than the chronology, etc. This measure is important given that individuals who process stimuli in a primarily data-driven way (i.e., primarily focused on sensory images, emotions, etc.) may be more likely to experience intrusive memories of the content. The measure includes 14 total items, 8 of which correspond to the data-driven subscale and 6 of which correspond to the conceptual subscale.

The two subscales are scored separately, summing all items. Items are answered on a 0 (*not at all*) to 4 (*very strongly*) scale. An example of a data-driven item is, “My mind was full of impressions and my reactions to them,” whereas an example of a conceptual item is, “I tried to figure out what would happen next.” The TFQ shows good internal consistency ($\alpha = .70$; Ehlers, 1998). No other psychometrics have been published to date.

Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988).

The PANAS is a 20-item self-report measure that captures both positive (PA) and negative (NA) affective experiences. The PANAS allows for assessment of an individual’s state affect in a given moment, and was administered immediately after participants viewed the acquisition film segment, and again immediately following extinction content for those randomized to an extinction condition. The positive subscale assesses the extent to which an individual experiences desirable mood states, such as interest, enthusiasm, and excitement; the negative subscale assesses the extent to which one experiences undesirable mood states, such as shame, irritability, and fear. Items responses are rated on a scale from a 5-point Likert scale from 1 (*slightly or not at all*) to 5 (*extremely*). The two subscales demonstrate good convergent validity with the BDI (NA: $r = .58$; PA: $r = -.36$) and with the Hopkins Symptom Checklist (NA: $r = .74$; PA: $r = -.19$).

Salivary alpha amylase (sAA) and cortisol. Saliva samples were collected using the SalivaBio swab (as opposed to passive drool) method. Approximately 50 μL were collected using standard salivette sampling devices (Sarstedt, Numberg, Germany). Participants were explicitly instructed to place the salivette between their gum and their cheek, and leave it in place for two min. Research assistants instructed participants to spit the salivette back into the storage tube at the end of the two-min period. Immediately after all session samples were completed,

samples were stored in a -20 C freezer until all data collection was completed. Samples were then shipped to Dresden Lab Service in Dresden, Germany, where they were thawed and centrifuged at 2000 x g for 5 min. Concentrations of cortisol in each sample were determined by interpolation from a standard curve, which is created by mapping standard cortisol concentrations against an optical density ratio (e.g., Felmingham, Tran, Fong, & Bryant, 2012). For sAA, an enzyme kinetic method was used. Briefly, a series of dilutions and incubations were conducted, with linear regression used to translate increases in absorbance to sAA concentrations (Segal & Cahill, 2009; Granger et al, 2007).

Intrusive Memory Assessment

Intrusive memory frequency and distress 72 hr after acquisition were the main dependent variables of interest. Intrusive memories were assessed via telephone. A definition of intrusive measures was provided: “An intrusive memory is a memory of an event that pops into your mind spontaneously, out of the blue, without any obvious cue or trigger. These memories are usually intense and very vivid, like brief snapshot images of a particular moment.” Four different types of intrusive memories are captured: sensory-based cued, sensory-based uncued, conceptual cued, and conceptual uncued. Examples of both cued (e.g., watching a news story about a child who drowned, and having an intrusive image pop into your head as you walk across a bridge) and uncued intrusive memories (e.g. an image of a wounded child popping into your head as you make breakfast in the morning), and examples of both sensory-based intrusive memories (intense, vivid, snapshot-like) and conceptual intrusive memories (e.g., recalling what it was like to view the film) are provided. Frequency and distress of intrusive memories were assessed separately. Distress responses were rated on a 0 (*not at all distressing*) to 8 (*extremely distressing*). In cases where participants reported having experienced more than one intrusive

memory in a given category, distress ratings were based on the *most* distressing intrusive memory. Overall total number of intrusive memories were calculated, as well as subtotals for sensory-based and conceptual intrusive memories. Cued and uncued were totaled together to create a sum total of intrusive memories. Two different distress ratings were calculated: maximum distress rating (i.e., single highest distress rating), and average distress rating across all categories (i.e., accounting for distress level for all intrusive memories).

Procedure

This study was conducted in groups, with each group ranging from 6 to 9 participants. Upon arrival to the computer lab, informed consent was obtained. Study-related questions were answered first in the group setting, after which participants were then given the opportunity to ask any questions individually with a research assistant. All interested participants then transitioned immediately into the acquisition phase.

Acquisition (Day 1). Prior to beginning study procedures, research assistants explained to participants what SUDs levels were, and participants were instructed how to rate their SUDs when prompted throughout the study. They were then asked to rate their SUDs levels, and provided a saliva sample (“Saliva 1”). Next, they completed baseline questionnaires, which included the demographics questionnaire, the health and medication questionnaire, PDS-5, BDI-II, STAI-T & S, and SUIS. A second SUDs level and saliva sample (“Saliva 2”) were collected following completion of baseline questionnaires, approximately 20 – 30 min after beginning questionnaires. Time of saliva samples were tracked. Participants were told that they would view a brief film, and were asked to pay attention closely to the film. They were asked to rate their SUDs immediately prior to film viewing (pre-viewing SUDs), and were oriented that SUDs ratings would be prompted throughout the film. Every 2 min throughout the 10 min acquisition

clip, a research assistant then asked participants to rate their SUDs levels. A final SUDs rating was collected immediately after the film viewing. Participants then received an explanation about phone assessment scheduling and were given a brief overview of the extinction phase of the study. Participants then gave a final saliva sample and SUDs rating (“Saliva 3”), and completed two post-film questionnaires (PANAS, TFQ), and answered the additional post-film questions. They then scheduled their acquisition phone assessment with a research assistant.

Acquisition phone assessment (Day 2). A research assistant phoned each participant approximately 24 hr after acquisition and the participant completed the intrusive memory assessment. Participants were reminded of their extinction session the following day.

Extinction (Day 3). Forty-eight hrs after acquisition, participants returned in their same groups for extinction. Participants were block-randomized as a group to one of four cue conditions: Pre Neutral CS, Pre Negative CS, Scrambled, or Delayed Neutral CS. A computerized randomization program counterbalanced based on number of participants in the group. Participants in all groups, regardless of cue condition randomization, provided an initial SUDs rating, gave their first saliva sample (“Saliva 4”), and completed the STAI-S upon arrival to the lab.

Pre conditions (Pre Neutral, Pre Negative, and Scrambled). After completing the STAI-S, participants viewed their designated cue for 8 s and were instructed to focus on the image until it disappeared. Participants were asked to rate their SUDs immediately following the cue presentation (Cue SUDS), in order to capture differences in subjective distress between cue conditions. After SUDs rating, participants were instructed to engage in the visuospatial distractor task on their individual computers for 10 min. Participants then rated how effective Tetris was at reducing any film-related images and thoughts that may have been elicited by the

cue presentation. The second saliva sample and SUDs rating were then collected (“Saliva 5”). Participants were then instructed, “*You will now watch a 30 min film clip that will be projected onto the wall at the front of the room. Please pay careful attention to what is happening once the film begins.*” Participants rated their pre-viewing SUDs, SUDs every 5 min throughout the film, and post-viewing SUDs levels. After film viewing, participants provided a final saliva sample (“Saliva 6”), and received instructions regarding the final phone assessment. Finally, participants completed the PANAS and TFQ and scheduled their phone assessments.

Delayed condition. In this condition, participants viewed the extinction film clip after completing the STAI-S. Participants provided pre-viewing SUDs, SUDs every 5 min throughout, and post-viewing SUDs. After the film, participants provided another saliva sample (“Saliva 5”), and completed the PANAS and TFQ. About 10 min after the extinction clip, participants were instructed to direct their attention to an image, and the neutral CS image was shown for 8 sec. Participants then played Tetris for 10 min and answered the Tetris effectiveness question. The final saliva sample and SUDs rating (“Saliva 6”) was collected after Tetris procedures.

Extinction phone assessment (Day 4). A research assistant again phoned each participant at 72 hr after acquisition to administer their final intrusive memory assessment. The research assistant provided a comprehensive debriefing on study procedures, and answered any questions. All participants received course credit upon study completion.

Data Analysis

Data reduction. Data were screened prior to analyses to check for missing data and outliers. A means test was done looking for differences between cases missing data and cases without. Data from participants who do not complete all study procedures were excluded from analyses. Missing data were tested for randomness using dummy coding (Tabachnick & Fidell,

2007). Initial group and condition differences were also assessed. Normality, homoscedasticity, and linearity assumptions were tested, and transformations were conducted for any violated assumptions.

Data analytic strategy. A planned contrast strategy, based on specific directional *a priori* hypotheses, was used to increase power and allow for more precision (Rosenthal & Rosnow, 1991). Planned contrasts were conducted at 72 hr after acquisition to test whether participants in the Pre Neutral CS condition reported fewer and less distressing intrusive memories 72 hr after acquisition compared to Delayed Neutral CS condition, and to examine whether participants in the Pre Neutral condition reported fewer and less distressing intrusive memories 72 after acquisition than participants in the Delayed Neutral CS condition. We then conducted univariate ANCOVAs by condition (4: Pre Neutral, Pre Negative, Pre Scrambled, Delayed Neutral). Intrusive memory frequency 24 hr after acquisition was entered as a covariate, given unexpected differences between conditions on intrusive memories after acquisition. Intrusive memory frequency and maximum intrusive memory-related distress 72 hr after acquisition were primary dependent variables.

In order to examine whether cortisol and sAA levels during extinction predicted lower intrusive memories after extinction, both the total output of cortisol and sAA (AUC_g) as well as amount of increase in cortisol and sAA during a given session relative to initial level (AUC_i) were examined (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). We examined correlations between demographic factors to control for factors known to influence glucocorticoid and noradrenergic activity (e.g., Granger et al., 2007), and ran regressions with and without any factors that were significantly related to cortisol and sAA values in order to determine whether inclusion of related factors changed regression models. Predictor variables

were sex, cortisol (AUC_g or AUC_i), sAA (AUC_g or AUC_i), two-way interactions between sex and cortisol, sex and sAA, and cortisol and sAA, and a three-way interaction between sex, cortisol, and sAA. Dependent variables were intrusive memory frequency and distress 24 or 72 hrs after acquisition. All variables were entered simultaneously into the regression model, as this is the most conservative statistical approach (Tabachnick & Fidell, 2007) and there were no strong *a priori* hypotheses regarding differential effects of these predictors.

To examine demographic, psychopathology, and state predictors of intrusive memories, separate linear regressions were conducted. Demographic variables included age, sex (-1 = females, 1 = males), race (dummy coded, with separate variables for Caucasian, Asian, Black/African American, Native Hawaiian/Pacific Islander, American Indian, and Mixed Race/Other), and criterion A status (-1 = no, 1 = yes). Baseline psychopathology variables included were PTSD severity (PDS-5), depression (BDI-II), and trait anxiety (STAI-T). Regressions predicting intrusive memory frequency and maximum distress 72 hr after acquisition were run separately. State factors that were assessed either immediately preceding or succeeding acquisition film exposure included state anxiety (STAI-S), negative and positive affect (PANAS), and data-driven and conceptual processing (TFQ). Variables were entered simultaneously into the regression once again given lack of *a priori* hypotheses regarding differential effects of these predictors.

Results

Manipulation Checks

Acquisition phase. The 10 min acquisition film was effective, eliciting an increase in subjective distress over the course of the film (pre-viewing SUDs: $M = 13.35$, $SD = 14.23$; post-viewing SUDs: $M = 40.29$, $SD = 22.32$, $t(172) = -18.65$, $p < .001$, $d = 1.37$).

With respect to intrusive film-related memories 24 hr after acquisition, with the majority of participants (81.50%; $n = 141$) reporting at least one intrusive memory 24 hr after acquisition. On average, participants reported 3.19 intrusive memories after acquisition ($SD = 2.85$). Of those who reported at least one intrusive memory, 90.91% reported at least some intrusive memory-related distress. Average maximum intrusive memory-related distress reported after acquisition averaged 2.49 on the 0 – 6 distress scale ($SD = 1.39$). Prior to randomization, there were unexpected differences in cue condition, with participants in the pre neutral CS condition reporting significantly more intrusive memories 24 hr after acquisition ($M = 3.53$, $SD = 3.18$) compared to participants in the pre negative CS condition ($M = 2.37$, $SD = 2.35$), $t(160) = 2.02$, $p = .045$, $d = 0.40$. There were no differences in intrusive memory-related distress after acquisition across the four cue conditions. In addition, there were no differences across conditions in subjective distress (SUDs) reported before and after acquisition. Intrusive memory frequency 24 hr after acquisition was used as a covariate for subsequent analyses.

Cue valence distress. As expected, participants differed by condition on CS cue SUDs ratings, $F(3, 165) = 8.26$, $p < .001$. Participants who viewed the negative cue were significantly more distressed by the cue presentation ($M = 23.61$, $SD = 20.31$) than the pre neutral ($M = 12.36$, $SD = 12.91$), the pre scrambled ($M = 7.43$, $SD = 7.80$) and the delayed neutral ($M = 15.50$, $SD = 13.77$) cue conditions combined ($M = 12.36$, $SD = 12.91$), $t(162) = -4.45$, $p < .001$, $d = 0.76$.

Visuospatial distractor task. Playing Tetris for 10 min after cue presentation appeared to be effective; on average, participants rated the task as quite effective at stopping film-related intrusive memories that may have occurred following cue presentation on the 0 to 8 single-item scale ($M = 6.18$, $SD = 2.46$). There were no differences across conditions in terms of task effectiveness.

Effect of Cue Condition on Intrusive Memories 72 hr After Acquisition

Planned contrasts were conducted based on the *a priori* hypotheses specifically comparing neutral vs. negatively valenced cue conditions and cue timing comparing pre neutral vs. pre delayed cue conditions. Following planned contrasts, analyses of covariance, controlling for intrusive memories 24 hrs after acquisition, were run separately for frequency and distress.

Effects of cue condition on intrusive memory frequency and distress. Means and standard deviations of primary dependent variables by condition can be seen in Table 2. When examining cue valence, there were no differences in intrusive memories 72 hr after acquisition between participants in the pre neutral cue condition ($M_{adj} = 0.95, SE = .21$) and those in the pre negative cue condition ($M_{adj} = 1.32, SE = .25$). See Figure 2. As shown in Figure 2, in regard to cue timing, there were no differences in intrusive memory frequency between the pre neutral CS cue ($M_{adj} = 0.98, SE = .20$) and the delayed neutral CS cue ($M_{adj} = 0.94, SE = .48$); inconsistent with the hypothesis that the neutral cue presented 10 min prior to extinction would lead to fewer intrusive memories 24 hr after extinction. When examining the overall ANCOVA across cue condition (pre neutral CS, pre negative CS, pre scrambled, delayed neutral CS) on intrusive memory frequency 72 hr after acquisition, controlling for initial intrusion frequency, there was no difference across cue condition, $F(3, 158) = 1.09, p = .35$.

When examining intrusive memory distress, for the *a priori* hypotheses via planned contrasts, the pre neutral CS cue condition ($M_{adj} = 2.09, SE = .24$) did not differ from the pre negative cue condition ($M_{adj} = 1.93, SE = .25$), both contrary to hypotheses. Further, in regard to cue timing, participants in the pre neutral CS cue condition ($M_{adj} = 2.18, SE = .23$) did not differ compared to the delayed neutral CS condition ($M_{adj} = 1.74, SE = .26$). See Figure 3. Using a one-way ANCOVA to examine maximum intrusive memory distress 72 hr after acquisition,

controlling for intrusive memory frequency 24 hr after acquisition, there were no significant differences across conditions on self-reported maximum intrusive memory distress, $F(3, 111) = 0.26, p = .86$.

Cortisol and sAA levels Predicting Intrusive Memories

Cortisol and sAA levels during acquisition session predicting intrusive memories 24 hr post-acquisition. To examine whether increased glucocorticoid and noradrenergic activity predicted enhanced consolidation of emotional memory, cortisol and sAA levels during acquisition were first examined as possible predictors of intrusive memories 24 hr after acquisition. For number of intrusive memories 24 hrs after acquisition, the overall model using examining total output (AUCg) was not significant, $F(7, 130) = 0.81, p = .58$. When examining maximum intrusive memory-related distress 24 hrs after acquisition as the dependent variable and total cortisol and sAA output (AUCg), the overall model was significant, $R^2 = .16, F(7, 113) = 3.22, p = .004$. Specifically, sex predicted maximum intrusive memory-related distress, $b = -.30, t(112) = -3.41, p = .001$, such that women report higher intrusive memory distress than men. See Table 3 and Figure 4.

When examining magnitude of change during acquisition solely with respect increases in cortisol and sAA values (AUCi), the overall model predicting intrusive memory frequency was not significant, $R^2 = .07, F(7, 137) = 1.35, p = .23$. Similar to above, when predicting intrusive memory-related distress 24 hrs after acquisition, the overall model fit well, $R^2 = .15, F(7, 113) = 2.65, p = .02$. This was predominantly driven by sex, such that once again, women report higher intrusive memory-related distress compared to men, $b = -.31, t(114) = -3.24, p = .002$. See Table 4 and Figure 5.

In brief, though regression models using both acquisition magnitude of cortisol and sAA change (AUCi) as well as total output (AUCg) predicted intrusive memory distress 24 hr after acquisition, in both cases the findings were predominantly driven by sex differences rather than cortisol and/or sAA levels or changes. In general, women reported higher distress related to intrusive memories compared to men 24 hr after acquisition.

Cortisol and sAA levels during acquisition session predicting intrusive memories 72 hr post-acquisition. To examine the role of increased glucocorticoid and noradrenergic activity predicted enhanced consolidation in intrusive memory persistence, cortisol and sAA levels and changes during acquisition were examined as predictors of intrusive memory frequency and distress 72 hr after acquisition. For number of intrusive memories 72 hr after acquisition with total output cortisol and sAA values (AUCg) as predictors, the overall model was not significant, $R^2 = .05$, $F(7, 135) = 0.92$, $p = .49$. The regression model with maximum intrusive memory distress 72 hr after acquisition was also not significant, $R^2 = .06$, $F(7, 101) = .82$, $p = .57$. When exploring magnitude of change (AUCi) to predict intrusive memories 72 hr after acquisition, the overall model was significant, $R^2 = .11$, $F(7, 135) = 2.34$, $p = .03$. There was an effect of sAA, $b = .23$, $t(134) = 2.67$, $p = .01$, and a sAA by cortisol interaction, $b = .25$, $t(134) = 2.62$, $p = .01$, predicting the number of intrusive memories 72 hr after acquisition. See Table 5 and Figure 6. Finally, the regression model incorporating acquisition AUCi values predicting maximum intrusive memory distress 72 hr after acquisition was also not significant, $R^2 = .08$, $F(7, 101) = 1.09$, $p = .38$.

Overall, greater increase in sAA and greater increases in cortisol and sAA together over the course of acquisition predict frequency of intrusive memories 72 hr after acquisition, but

neither cortisol nor sAA output or magnitude of change predict intrusive memory-related distress 72 hr after acquisition.

Cortisol and sAA levels during extinction session predicting intrusive memories 72 hr post-acquisition. Here, cortisol and sAA during extinction were examined to see whether output and magnitude of change during extinction affected intrusive memories and whether cortisol and sAA may interact with reconsolidation processes. The regression model for total output (AUCg), examining number of intrusive memories 72 hr after acquisition was not significant, $R^2 = .07$, $F(7, 135) = 1.42$, $p = .20$. The regression model predicting maximum intrusive memory distress 72 hr after acquisition was also not significant, $R^2 = .07$, $F(7, 96) = 0.91$, $p = .50$.

When examining increases in cortisol and sAA (AUCi), the model predicting number of intrusive memories 72 hr after acquisition was significant, $R^2 = .16$, $F(7, 141) = 3.62$, $p = .001$. This finding was predominantly driven by an increase in cortisol during extinction (AUCi) predicting higher intrusive memories, $b = .28$, $t(134) = 2.88$, $p = .01$, and an increase in sAA during extinction (AUCi) predicting higher intrusive memories, $b = .25$, $t(141) = 2.98$, $p = .003$. See Table 6 and Figure 7. Finally, when predicting intrusive memory distress 72 hr after acquisition, the overall model was also significant, $R^2 = .15$, $F(7, 96) = 2.19$, $p = .04$. This was primarily driven by an increase in sAA during extinction predicting higher intrusive memory distress, $b = .27$, $t(102) = 2.63$, $p = .01$. See Table 7 and Figure 8.

In brief, the overall output of cortisol and sAA during extinction (AUCg) did not predict intrusive memories 72 hr post-acquisition. However, the magnitude of increase of cortisol and sAA during extinction (AUCi) predicted later intrusive memories, such that an increase in cortisol independently predicted higher intrusive memories 72 hr post-acquisition, and an

increase in sAA over the course of extinction predicted higher intrusive memory distress 72 hr post-acquisition.

Distress Levels during Extinction by Cue Condition

To examine the pattern of distress (SUDs) over the course of extinction, a repeated measures mixed ANCOVA, with a between-subjects factor of condition (4: pre neutral CS, pre negative CS, pre scrambled, delayed neutral CS) and within-subjects factor of time (7: pre, every 5 min during, post) was conducted, controlling for intrusive memory frequency at 24 hrs after acquisition. There was a significant change in distress over the course of extinction, $F(6, 966) = 32.09, p < .001$, as well as a significant condition by time interaction, $F(18, 966) = 2.27, p = .002$. When further breaking down this interaction, only the pre scrambled and delayed neutral condition interaction over time was significant, $F(6, 468) = 5.10, p < .001$. At 20 min, the participants in the pre scrambled condition reported higher distress, $M_{adj} = 30.57, SE = 3.45$, than the delayed neutral condition, $M_{adj} = 20.22, SE = 3.01, F(1, 78) = 5.07, p = .03, d = 0.51$. This effect continues at 25 min into extinction, again with the pre scrambled condition reporting higher distress $M_{adj} = 27.95, SE = 3.36$ than the delayed neutral condition, $M_{adj} = 18.30, SE = 2.93, F(1, 78) = 4.65, p = .03, d = 0.50$. At the post-viewing time point just after extinction film clip ended, the difference in distress between these conditions was no longer significant. See Figure 9 for a visual depiction of distress during extinction by cue condition. In brief, there were differences in distress levels over the course of extinction, driven primarily by participants in the scrambled cue condition reporting higher distress during the second half of extinction compared to participants in the delayed neutral cue condition.

Baseline Demographic, Psychopathology, and State Factors Predicting Intrusive Memories 72 hr Post-Acquisition

To examine whether demographic factors, baseline psychopathology (e.g., trait anxiety, depression), and state factors (e.g., data-driven processing, negative affect) assessed directly before and after exposure to the acquisition film segment predicted intrusive memories, we examined relationships between demographic, baseline psychopathology, and state factors and intrusive memories 72 hr after acquisition. See Table 8 for demographic and baseline psychopathology and Table 9 for peri-film and post-film state factors for bivariate correlations between predictors and intrusive memory frequency and distress.

The demographic regression (sex, age, race, criterion A exposure) did not predict intrusive memory frequency 72 hr after acquisition. Baseline psychopathology factors (PTSD, depression, trait anxiety) did not predict intrusive memory frequency 72 hr after acquisition. However, demographic factors did predict maximum intrusive memory distress, $R^2 = .15$, $F(6, 108) = 3.13$, $p = .01$. The model fit is primarily driven by race, where Asians reported higher intrusive memory distress 72 hr after acquisition than other racial groups, $b = .39$, $t(113) = 3.79$, $p < .001$. The baseline psychopathology model did not predict intrusive memory distress 72 hr after acquisition, $R^2 = .06$, $F(3, 111) = 2.29$, $p = .07$.

State factors (state anxiety [STAI-S], negative affect [PANAS], positive affect [PANAS], data driven processing [TFQ], conceptual processing [TFQ]) during acquisition predicted intrusive memory frequency 72 hrs post-acquisition, $R^2 = .11$, $F(5, 156) = 3.65$, $p = .004$. Model fit here was almost solely driven by negative affect (PANAS), $b = .35$, $t(161) = 4.05$, $p < .001$, where higher negative affect during acquisition predicted a higher number of intrusive memories reported 72 hrs after acquisition. The model including state factors during acquisition also predicted maximum intrusive memory distress 72 hr after acquisition, $R^2 = .26$, $F(5, 112) = 9.18$,

$p < .001$. Once again, higher negative affect during acquisition predicted of higher intrusive memory distress 72 hrs after acquisition, $b = .44$, $t(117) = 4.70$, $p < .001$.

In brief, negative affect that participants report following exposure to the acquisition film segment was a strong predictor of more intrusive memories experienced 72 hr after acquisition and higher distressing these intrusive memories. Demographic and psychopathology predictors were weaker.

Discussion

Given that intrusive memories are transdiagnostic, distressing, and debilitating when they persist over time, an opportunity to more effectively decrease their intensity is needed. Memory reconsolidation is a harmless and potentially easy way in which memories may be modifiable following retrieval, yet the translational research on how advantageous memory reconsolidation processes may be in real-world and clinical settings is unclear. In this study, the role of retrieval cue valence in opening the reconsolidation window was examined, in order to better reduce intrusive memories. Contrary to expected hypotheses, the valence of retrieval cue presented prior to extinction did not predict the number of intrusive memories nor intrusive memory distress after extinction. This suggests that the level of distress elicited by a retrieval cue does not differentially affect what is learned during extinction; no other studies to date have examined the role of retrieval cue valence specifically, though Marks and Zoellner (2014) found higher distress trajectories during extinction and more intrusive memories related to presentation of a negative cue before vs. after extinction.

This study also examined reconsolidation as a way of enhancing fear learning, comparing within-window vs. out-of-window extinction. Here again, there were no differences between in how many intrusive memories participants experienced, nor in how distressing they reported

these memories to be between within-window and out-of-window extinction. These findings are consistent with other studies that used fear-relevant stimuli and found no effects of reconsolidation on enhancing extinction learning (e.g., Golkar et al., 2012; Fricchione et al., 2016; Kindt & Soeter, 2013; Drexler et al., 2014; Soeter & Kindt, 2011). These findings indicate that boundary conditions of reconsolidation, particularly within nuanced translational paradigms that more closely mirror clinical interventions, remain unclear. As paradigms increase in complexity, numerous factors are at play that could predict outcome and/or explain findings. Here, insufficient new learning, stimulus characteristics, and idiographic factors such as intensity of emotions elicited are several specific factors to consider. Some of these potential drivers may be more powerful than the experimental manipulation of reconsolidation, particularly in light of uncertainty as to whether reconsolidation when applied to fear-relevant stimuli can indeed have an enhancing effect on extinction learning (e.g., Elsey & Kindt, 2017; Golkar et al., 2012; Kredlow et al., 2016).

With this, it is challenging to localize determinants of causality. That said, there are a number of plausible explanations in regard to why there was no strong reconsolidation effect. It is possible that the reconsolidation window opening was indeed initiated but that participants did not incorporate sufficient new learning during the extinction film (i.e., within the reconsolidation window) to lead to the film memory being restored as a less fearful or less distressing memory. Memory reconsolidation is only thought to be an adaptive mechanism through which return of fear may be reduced if the memory is modified in some way upon retrieval (e.g., Exton-McGuinness, Lee, & Reichelt, 2015; Tronson & Taylor, 2007; Forcato, Argibay, Pedreira, & Maldonado, 2009; Pedreira, Perez-Cuesta, & Maldonado, 2004). In the extinction film presented, there was no clear-cut CS presentation in the absence of the US as is typical in

extinction paradigms (Pavlov, 1927). Prediction error is thought to be critical in initiating reconsolidation processes once a memory is reactivated (e.g., Fernandez, Boccia, & Pedreira, 2017; Beckers & Kindt, 2017; Kindt & Soeter, 2013). Importantly, as translational research moves from basic to more complex experimental designs and stimuli, a certain degree of experimental control is lost. With the film fear learning paradigm, some participants may have desensitized to the film material over the course of the 30 min extinction period, which would likely be a form of prediction error. For others, repeated exposure to distressing content may have functioned more as a prolonged fear acquisition, where with each repeated exposure participants became more and more distressed. When examining trajectories of general distress during fear extinction as seen in Figure 8, participants appeared to start extinction fairly low in distress, increased in distress over the 30 min extinction period, and did not return to pre-viewing levels of distress by the end of extinction. Participants who viewed the scrambled cue prior to extinction demonstrate a distress trajectory more suggestive of prolonged acquisition; whereas, participants who viewed the cue of the woman's face after extinction decreased more in distress in the last ten minutes of extinction. The "prolonged acquisition" pattern would likely be inconsistent with prediction error, given that during acquisition participants experienced a substantial increase in distress from pre- to post-viewing and seem to be similarly distressed by extinction. Given that this paradigm is working to better mimic exposure therapy, it is possible that this kind of extinction paradigm requires multiple extinction trials, rather than a single trial. This fits with literature suggesting that it is not within-session but rather between-session habituation that predicts better outcomes in exposure-based interventions (e.g., Sripada & Rauch, 2015; Craske et al., 2008).

Kunze, Arntz, and Kindt (2015) recently sought to combine distressing film and fear learning paradigms, emphasizing the importance of more ecologically valid stimuli and increasing understanding of how fear acquisition and extinction apply to complex associative memories. In brief, the paradigm used images, film clips, and sounds, yet extinction was still a clear learning session, where the image of a girl previously paired with the sound of her scream were no longer presented together. In addition, participants were told when returning for the extinction training that they would be presented with the same stimuli as the day prior during acquisition, which may have better elicited prediction error since the image was no longer paired with the scream. In contrast, in the current film fear learning paradigm, the lack of clear new CS-learning and not knowing whether prediction error would occur may have mitigated reconsolidation effects, given that these conditions are thought to be important in initiating reconsolidation processes (e.g., Alfei, Monti, Molina, Bueno, & Urcelay, 2015; Exton-McGuinness & Lee, 2015; Sevenster et al., 2013).

Certain stimuli that are innately threatening and fear-relevant have been shown to be more resistant to extinction (e.g., Lovibond, Siddle, & Bond, 1993; McNally, 1987), which may well affect return of fear and the potential role of reconsolidation. The present study, Kindt and Soeter (2013), and others (e.g., Golkar et al., 2012; Drexler et al., 2014; Oyarzun et al., 2012) that have used fear-relevant stimuli of various kinds by and large fail to find enhanced effects of extinction learning that occurred within the reconsolidation window. This may be due to fear-relevant and negatively-valenced stimuli simply being more resistant to extinction (e.g., Mineka & Ohman, 2002; Ohman & Soares, 1993; Lovibond, Siddle, & Bond, 1993). Alternatively, perhaps it is the complexity of stimuli used here rather than solely the fear-relevance of the stimuli that may lead to more resistance during extinction. The film segment served as a

multisensory acquisition and extinction experience, and the acquisition segment has been shown to elicit multiple emotions including anxiety, disgust, and fear in addition to general distress (Marks & Zoellner, 2014). Some prior research shows that extinction of complex stimuli (e.g., tone plus light with rats) can still be enhanced within the reconsolidation window, but each individual component must be extinguished separately (e.g., Jones, Ringuelet, & Monfils, 2013). In humans, extinction learning appears to be impaired when compound stimuli are used in acquisition and extinction (Lovibond, Davis, & O’Flaherty, 2000; Vervliet, Vansteenwegen, Hermans, & Eelen, 2007). In both studies, each stimulus needed to undergo extinction separately in order to prevent the return of fear, which has important implications as studies, including this study, transition to increasingly complex stimuli. In this study, while the film segment was certainly complex in that many different stimuli were viewed during acquisition and extinction, it is unclear what “separate” extinction might look like. The image of the mutilated body was without a doubt the most graphic and distressing moment in the film, and the goal of extinction was to learn that the film was just a film and there was no imminent danger present. At the same time, it is clear that the film segment was not a “simple” stimulus; it consists of multiple memory traces, multiple emotional responses, etc. In brief, further research is needed using more ecologically valid and complex stimuli to determine whether a clear-cut weakening of associations between a specific CS and US is a boundary condition of reconsolidation, or whether extinction learning that generalizes, if conducted after a retrieval cue, can also initiate reconsolidation processes.

The film fear learning paradigm utilized here is novel in its transition into the world of more ecologically valid stimuli with extinction attempting to mirror exposure therapy. With this comes a lesser degree of experimental control but also a clearer sense of whether memory

reconsolidation could be of real clinical utility. Memory reconsolidation is thought to be a process that keeps memories current and relevant in dynamic environment (e.g., Dudai, 2004; Lee, 2009; Nader & Hardt, 2009). As is highlighted in a recently proposed model of how intrusive memories may develop and persist, factors such as personal relevance, pre-existing psychopathology, frequency of memory retrieval leading to changes in retrieval strength, etc. affect how an intrusive memory may persist or diminish (Marks et al., 2018). Factors such as these likely may be more powerful and more robust predictors of intrusive memories than manipulations of extinction or reconsolidation. Indeed, one particularly strong predictor in the present study emerged, negative affect immediately after acquisition predicted both frequency and distress of film-related intrusive memories several days after acquisition. This finding is in line with much of the memory consolidation research pointing to enhanced consolidation of emotional memories (e.g., McGaugh, 2004; LaBar & Cabeza, 2006).

There were no differences in intrusive memories between participants who viewed a neutral image of a woman's face prior to extinction and participants who viewed the graphic image of the mutilated woman prior to extinction. Distress ratings specific to the cue were indeed different as would be expected, where participants reported higher distress related to the graphic image than to the neutral face. This suggests that even with higher distress elicited shortly before extinction did not effect extinction processes as had been hypothesized based on prior work (Marks & Zoellner, 2014). There is limited reconsolidation-specific literature that examines retrieval cue valence, as retrieval alone is not thought sufficient to initiate reconsolidation processes (e.g., Sevenster et al., 2012; Forcato et al., 2010). These findings add to this limited literature, in that cue valence did not predict whether reconsolidation occurs, and that memory retrieval accompanied by distress does not predict an altered course of distress

during extinction. In fact, activating fear networks and ensuring emotional engagement during exposure-based interventions are considered cruxes of how exposure treatment is thought to work (e.g., Foa & Kozak, 1986; Jaycox, Foa, & Morral, 1998), and the initial cue presentation may be viewed as an initial, albeit brief, activation of one's fear network. That said, the degree to which fear is activated in the form of a retrieval cue appears unrelated to how participants fare over extinction and also unrelated to later intrusive memory frequency and distress.

In addition to subjective reports of distress, intrusive memory frequency, and related distress, this study explored cortisol and noradrenergic activity as they relate to emotional memory formation, extinction, and reconsolidation. These systems are fairly well-established as they relate to memory consolidation, but how the two systems may affect memory reconsolidation and intrusive memories is less clear as of now. Only sex, not cortisol or noradrenergic activity, predicted intrusive memory frequency and distress 24 hr after acquisition. Women reported more frequent and more distressing film-related intrusive memories the day following acquisition. These findings are consistent with some intrusive memory literature showing that women may have enhanced consolidation of emotional material (e.g., Andreano & Cahill, 2006; Felmingham et al., 2013) and certainly fit with higher prevalence rates of PTSD among women compared to men (e.g., Breslau, Davis, Andreski, Peterson, & Schultz, 1997). However, Bryant and colleagues (2013) found that gender interacts with glucocorticoids to predict intrusive memories, which was not evidenced in this data.

The role of the glucocorticoid and noradrenergic activity during acquisition was more relevant to the persistence of intrusive memories 72 hr after acquisition took place. The amount of increase during acquisition in sAA alone, and also the amount that sAA and cortisol together both predicted intrusive memory frequency. These findings are consistent with a strong body of

research suggesting higher glucocorticoid and noradrenergic levels are indicative of enhanced consolidation of emotional memories (e.g., McGaugh, 2004; McGaugh, 2018; Roozendaal et al., 2006). More specifically, the interaction of cortisol and sAA increases predicting intrusive memories fits with research suggesting that effects of glucocorticoids depend on noradrenergic system involvement (Kukolja et al, 2011). It is interesting that this interaction between the systems emerges as a predictor of intrusive memories when looking from acquisition beyond extinction (i.e., 72 hr after acquisition occurs), but not when examining how the systems during acquisition predict more immediate intrusive memories (i.e., 24 hr after acquisition occurs). This may be partially explained by the length of the acquisition film clip and length of experimental session. The acquisition film segment was short (6 min), and only one of the three saliva samples collected during this session was collected *after* acquisition. Though changes in sAA in response to threat and stress are detectable immediately (Nater et al., 2005; Nater & Rohleder, 2009), changes in cortisol levels are detectable about every 15 min (Kirschbaum & Hellhammer, 1989; Kirschbaum & Hellhammer, 1994). There are also vast inter-individual differences related to cortisol (Kirschbaum & Hellhammer, 1994) and sAA (Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004) levels both in terms of amount of output and also how much and at what rate output increases in response to stress. In the acquisition procedure, saliva samples collected shortly after the acquisition film clip; for participants who may have been slower to react physiologically this assessment may not have captured changes in cortisol and sAA resulting from film exposure.

In addition to understanding how changes in stress and noradrenergic activity during acquisition predict intrusive memories 72 hr after acquisition, we additionally looked at how changes over the course of extinction affect intrusive memories. The amount that stress and

noradrenergic markers increased over the course of extinction predicted intrusive memory frequency and distress the next day. More specifically, the amount of increase (i.e., increase in levels relative to initial levels at the start of extinction) as measured by increases in cortisol and sAA during extinction were related to both intrusive memory frequency and distress.

Interestingly, cortisol and sAA increases separately predicted intrusive memory frequency, and the amount that sAA levels increased during extinction independently predicted intrusive memory distress the day after extinction. These findings are inconsistent with the glucocorticoid and noradrenergic activity literature related to facilitation of extinction learning and exposure therapy (e.g., de Quervain et al., 2011; Janak & Corbit, 2010; Mueller et al., 2008; Yang, Chao, & Lu, 2006), where increased levels of cortisol and norepinephrine enhanced fear extinction learning; if this were the case, in the present study higher cortisol would have predicted fewer and less distressing intrusive memories.

Importantly, research in intrusive memories, glucocorticoid, and noradrenergic systems is an emerging area; findings here regarding acquisition changes in cortisol and sAA together predicting intrusive memories two days later fits well with Bryant and colleagues (2013) and Nicholson and colleagues (2014). In all three studies, intrusive memories were measured several days following initial stress exposure, and in all three studies the increased levels of both cortisol and sAA together (rather than separately) predicted later intrusive memory frequency. In this study, the interaction of the two systems during acquisition did not predict intrusive memory-related distress after extinction. Nicholson and colleagues (2014) only included intrusive memory frequency but not distress, and Bryant and colleagues (2013) used a measure subscale that incorporated both frequency and distress ratings, so it is unclear how stress and noradrenergic activity relate to intrusive memory distress.

Few predictors of intrusive memories emerged when demographic, psychopathology, and state factors were examined. Race and negative affect immediately following acquisition were the two predictors that did emerge. Though no studies to date have specifically examined race as a predictor of intrusive memories, broader mental health research related to racial differences suggests that college students of Asian descent score higher on measures of anxiety and emotional distress (e.g., Chang, 2002; Cheng, Leong, & Geist, 1993; Okazaki, 1997). The findings regarding heightened negative affect after acquisition fit well with some prior intrusive memory research (e.g., Hall & Bernstein, 2008). Further, these findings are consistent with the above findings related to higher cortisol and sAA levels during acquisition predicting intrusive memories after extinction, in that subjective experience of heightened negative emotions immediately following acquisition maps onto heightened cortisol and sAA changes during acquisition predicting later intrusive memories (Bryant et al., 2013; Nicholson et al., 2014). Nonspecific or general distress, synonymous with a negative affective state, is theorized to be an shared factor across anxiety and depressive disorders, and is related to one's self-reported symptoms of psychopathology (Clark & Watson, 1991). Consistent with this, in the present study, negative affect after acquisition was a fairly robust individual difference predictor of later intrusive memories, which serves as an important reminder that there are many different contributing factors to intrusive memories. As is evidenced in a recent review of predictors of intrusive memories, pre-existing psychopathology, negative appraisals both before and after an event, higher data-driven processing during an event, and conceptual processing after an event all appear to predict intrusive memories (Marks et al., 2018). With that, as studies move toward clinical samples with more complex stimuli and designs, it is important to continue examining

predictors of intrusive memories, as experimental manipulations may be overpowered by more prominent predictors.

Several limitations of the present study should be noted. First, there was a general floor effect with intrusive memory, most notably in intrusive memory frequency 72 hr after acquisition, but also in intrusive memory distress ratings as well. The majority (74%) of participants report either zero or one intrusive memory at that time. Although, on the one hand, this may be expected given that the goal of the extinction paradigm is to effectively reduce both frequency and associated distress of film-related intrusive memories, it simultaneously impaired the ability to identify any added effect of particular cue conditions on reductions of intrusive memories. When assessing return of fear via more objective measures such as skin conductance, fear potentiated startle, etc., one advantage is substantially more heterogeneity in the measurement. Furthermore, and related to the floor effect seen with the final intrusive memory assessment, it is unclear how the extinction paradigm compares to no intervention at all. Given that the intrusive memories reported were generally only low to moderate distress and diminished over the several day monitoring period, one might expect that these are intrusive memories that would dissipate naturally. It is important to be able to differentiate between intrusive memories that would naturally diminish if left alone and those that would persist; as it is the latter, persistent type of intrusive memories that best map onto clinical psychopathology and that would be targeted via modification within the reconsolidation window. Of note, there was more variability across distress ratings than for intrusive memory frequency, but the power for these analyses was reduced given that participants who deny intrusive memories following extinction could not provide distress rating. However, though the vast majority of studies employing distressing film paradigms assess intrusive memories over the course of a week rather

than 24 hr (James et al., 2016), this paradigm appears to elicit comparable (or perhaps more) intrusive memories when taking into account timeframe of intrusive memory assessment.

A second limitation was the inability to control film memory retrieval between the acquisition and extinction/reconsolidation sessions. Importantly, individuals likely retrieved film-related memories in a variety of different contexts, including once they re-entered the laboratory space upon arrival for the second session. Indeed, mental retrieval even without clear external retrieval can induce memory lability (e.g., Mystkowski, Craske, Echeverri, & Labus, 2006; Hupbach, Gomez, Hardt, & Nadel, 2007). For some of the participants, entering the physical space may have served as the initial retrieval cue necessary to open the reconsolidation window. Retrieval cue offset is a boundary condition required in order for reconsolidation to occur (e.g., Pedreira et al., 2004), but retrieval cue offset could have occurred via simple distraction by completing questionnaires. It is thus possible that the cue manipulation prior to extinction was not the only way in which reconsolidation may have occurred in this study; however, it would be virtually impossible to control all the ways in which a memory is retrieved for each participant.

A third limitation that related to assessment of cortisol and sAA was the varying of timing of final saliva samples during acquisition and extinction. It is possible that the final saliva samples on each day was not delayed long enough to capture changes in cortisol that occurred due to film exposure. While sAA is immediately responsive to threat (Nater & Rohleder, 2009), cortisol can take up to 20 min post-stressor to peak (Kirschbaum & Hellhammer, 1994). Though samples were spaced 15 min apart in order to ensure that changes overall were being captured in each session, it may be more important to space the final sample further out from the end of film exposure to specifically capture film-related changes in cortisol levels. That said, the reaction to

the film clip is certainly not the only time point that is of interest; overall levels of stress as participants enter the study and participants' changes in cortisol and sAA levels over the course of the session (e.g., completing questionnaires about psychopathology), are also likely to affect later intrusive memories and how strongly the film clip is encoded.

Future research should continue to work on translation efforts of fear memory reconsolidation in a number of ways. Incorporating an assessment-only condition as a comparison condition would be important, as this helps to better understand whether findings are simply natural decreases in intrusive memory frequency and associated distress. Most fear learning studies examining reconsolidation do not include a no-extinction control condition (e.g., Golkar et al., 2012; Kindt & Soeter, 2013; Schiller et al., 2010). This is important, because if the intrusive memories being targeted via reconsolidation and extinction are ones that would decrease naturally, the interventions are no longer targeting persistent or pathological intrusive memories. Furthermore, it is imperative to include individuals already experiencing trauma-related intrusive memories in extinction/reconsolidation studies, given the goal of clinical application of reconsolidation and knowing that learning and memory processes in individuals with ongoing psychopathology are distinct from those in healthy individuals. Particularly given the complexity of stimuli used here compared to prior studies and the wide range of factors that predict intrusive memories beyond an experimental procedure (e.g., Marks et al., 2018), it is critical to be able to ensure that new learning is indeed occurring. Alternative extinction paradigms that still incorporate the complex stimuli but more clearly disentangle the CS-US association from acquisition may be warranted.

Reconsolidation processes continue to have promising future clinical applications. However, researchers continue to attempt to define boundary conditions necessary in order for

distressing memories to undergo enhanced modification, which has proven to be a challenging process with many nuances, particularly with translational efforts toward more clinically relevant stimuli and procedures. As Lee and colleagues (2017) very aptly point out, it is essential to continue to identify whether failures of reconsolidation occur due to failures in memory destabilization (i.e., retrieval from long-term memory back to working memory), failures in updating the memory once it is destabilized (i.e., lack of new learning occurring during extinction), or both. It is critical to continue improving the understanding of null findings while simultaneously working to translate reconsolidation paradigms to more real-world, clinically relevant settings. Perhaps the benefit of reconsolidation will be in making existing interventions more efficient, or perhaps reconsolidation will lead to the development of a novel intervention of some kind. In any case, the current state of research calls for further translational studies to better understand reconsolidation boundary conditions in order to take advantage of reconsolidation in clinical settings, if evidence indeed suggests enhancing therapeutic effects.

Study Two: Investigation of Persistent Intrusive Memories and Reconsolidation in Individuals With and Without Current Re-experiencing

In fear memory reconsolidation research, there seem to two key questions that are sources of ongoing research and debate. First, what are the “boundary conditions” under which reconsolidation will occur? Second, will reconsolidation be helpful in clinical settings as a mechanism through which in-session adaptive learning during exposure-based interventions can be enhanced?

The first of these two questions has been quite extensively studied, and a number of different boundary conditions have been consistently identified. First and perhaps most obvious but also most critical, new post-retrieval learning must occur in order for reconsolidation

processes to restore the memory as an enhanced, modified memory (e.g., Lee, 2009; Walker, Brakefield, Hobson, & Stickgold, 2003). A working hypothesis is that this retrieval-induced plasticity essentially serves to ensure that memories are kept relevant in dynamic, consistently changing environments (e.g., Nader & Hardt, 2009; Hardt, Einarsson, & Nader, 2010; Dudai, 2004; Lee et al., 2017; Alberini & LeDoux, 2013). Even when memories are retrieved but not updated, retrieval strength of that memory increases as a result (e.g., Anderson, Bjork, & Bjork, 2000). For example, imagine that you get attacked by a bear while hiking in the North Cascades. You then go on a trip to Africa and go trekking through the desert. You may recall that the last time you went on a big outdoor expedition you were attacked. However, you also look at your surroundings and recognize that in this setting there are no bears. Your memory adjusts to your current context, and you are able to relax and enjoy your desert trek. One can quickly see how adaptive it is to incorporate the new information prior to the memory being reconsolidated in order to change not only the memory but also subsequent behavior that results from the newly modified memory.

From a basic fear conditioning and extinction perspective, individuals initially learn to associate a particular shape (conditioned stimulus; CS) with an electric shock, air puff to the throat, or aversive auditory stimulus (unconditioned stimulus; US); and then, during the extinction phase, individuals learn that that same shape is no longer followed by an aversive stimulus. In this case, there is clear new learning that occurs during extinction; the CS is no longer paired with the US. In post-retrieval cue extinction paradigms, memory modification occurs within the reconsolidation timeframe parameters and activates reconsolidation processes because new learning occurs (e.g., Schiller et al., 2010; Golkar et al., 2012; Oyarzun et al., 2012). Even with more ecologically valid stimuli in basic fear conditioning paradigms, the

learning that takes place during post-retrieval extinction is still clear cut. Fear-relevant images (e.g., spiders, fearful faces, snakes, guns) are paired with an aversive unconditioned stimulus (electric shock) during fear acquisition; and during extinction, the fear-relevant images are presented in the absence of the shock (e.g., Drexler et al., 2014; Kindt & Soeter, 2013; Golkar et al., 2012; Soeter & Kindt, 2011). Importantly, no study to date that has used fear-relevant stimuli has found an enhanced effect of post-retrieval extinction compared to standard extinction or out-of-window reconsolidation cue extinction, despite participants clearly exhibiting new learning during extinction (e.g., Golkar et al., 2012; Kindt & Soeter, 2011; Drexler et al., 2014; Soeter & Kindt, 2011).

This calls into question other boundary conditions that may dictate whether reconsolidation processes are initiated when fearful memories are retrieved. There are a number of different boundary conditions that continue to be debated and studied; the most common conditions are strength of memory, personal or evolutionary relevance of stimuli, duration and specificity of the retrieval cue, and context shifts between acquisition and retrieval or extinction (e.g., Treanor et al., 2017). With respect to duration of the reminder cue, the literature suggests that between a few seconds and a few minutes is the optimal length of time for which to present a retrieval cue, though there is some variability depending on type of paradigm in use (e.g., Power, Berlau, McGaugh, & Steward, 2006; Soeter & Kindt, 2011). If presented for too long, a retrieval cue can initiate extinction rather than reconsolidation processes; it appears that retrieval cue presentation length is also dependent on length of exposure to the CS during acquisition (e.g., Treanor et al., 2017). With regard to cue specificity, few studies have systematically examined effects of cue characteristics on initiating memory destabilization and reconsolidation. One study found that first-order (e.g., exact same CS that was used during fear acquisition) but

not second-order CS presentations prior to extinction (e.g., a second CS that was paired with the first CS once the first CS was effectively paired with the US) initiated reconsolidation (e.g., Debiec, Doyere, Nader, & LeDoux, 2006). Other research suggests that when two CSs are conditioned separately to be associated with the same US, the presentation of one specific CS does not initiate reconsolidation-facilitated extinction for the second CS (e.g., Schiller et al., 2009; Doyere, Debiec, Monfils, Schafe, & LeDoux, 2007; Soeter & Kindt, 2011). Perhaps most relevant to this work with more ecologically valid stimuli is when presentation of one component of a compound CS is presented as a retrieval cue. When conditioned to compound stimuli (e.g., tone-light combination paired with shock) and then treated pharmacologically to disrupt reconsolidation of the fear memory, both tone and light fear responses decreased when only one CS (i.e., tone or light) was presented as the retrieval cue (Debiec, Diaz-Mataix, Bush, Doyere, & LeDoux, 2013).

Stronger memories are thought to be less susceptible to modification via reconsolidation compared to weaker memories (e.g., Suzuki et al., 2004). “Strong” memories typically refer to memories that have undergone more extensive training compared to “weaker” memories. For example, fear memory encoded as a result of an acquisition phase wherein participants are presented with 40 shape-shock pairings would be considered a stronger fear memory than a memory from 20 shape-shock pairings. Under certain conditions, however, it appears that even strong memories are susceptible to destabilization and modification. These conditions include a longer period of time between training and reactivation phases (Robinson & Franklin, 2010) and increased length of reminder trial to initiate the reactivation phase (Suzuki et al., 2004). Increasing the length of reminder trial can be risky, however, as extinction rather than reconsolidation can be initiated if the reminder trial duration is too long.

Context is another boundary condition thought to be important in whether or not reconsolidation processes are initiated. In paradigms where extinction learning occurs in a different context from acquisition and return-of-fear testing (i.e., ABA designs), retrieval plus extinction does not appear to lead to disruptions in reconsolidation of the fear memory (e.g., Chan et al., 2010), whereas there is favorable disruption in reconsolidation when contexts remain the same (e.g., Monfils et al., 2009; Winocur, Frankland, Sekeres, Fogel, & Moscovitch, 2009). That is, a low degree of similarity between acquisition and retrieval phases may prompt new learning (i.e., consolidation of extinction learning), whereas a high degree of similarity between acquisition and retrieval phases may prompt memory updating (i.e., destabilization followed by reconsolidation, with extinction learning incorporated into the original memory trace) (Besnard, 2012). Importantly, this contextual boundary condition appears specific to behavioral means of memory updating rather than pharmacological means of memory updating (e.g., Duvarci & Nader, 2004; Chan et al., 2010).

Finally, the nature of the CS and US employed in different paradigms is of particular importance when investigating whether reconsolidation may be taken advantage of in clinical settings. As previously mentioned, no studies to date that have employed more “fear-relevant” stimuli in their paradigms have demonstrated that extinction within the reconsolidation window leads to a more robust decrease in fear when tested after extinction than extinction without prior memory retrieval. This perhaps speaks to the fear-relevant nature of stimuli causing reconsolidation processes to be irrelevant, as authors of these studies point out (e.g., Kindt & Soeter, 2011; Soeter & Kindt, 2011; Golkar et al., 2012). This may in part be related to innately fearful stimuli such as those used in these paradigms being more resistant to extinction (e.g., Mineka & Ohman, 2002; Ohman & Soares, 1993; Lovibond, Siddle, & Bond, 1993). One’s fear

response to initial exposure may lead to stronger encoding of these fear-relevant memories (e.g., Cahill, 2004; LaBar & Cabeza, 2006) and resistance to extinction (e.g., Suzuki et al., 2004). Even if extinction is effective and generalizable (e.g., Vervliet et al., 2004; Vervliet et al., 2005), these strongly encoded memories may be more prone to involuntary retrieval.

The above boundary conditions are crucial when considering whether reconsolidation presents an opportunity for improving existing exposure-based interventions for psychiatric disorders and for developing novel interventions. The appeal of capitalizing on the reconsolidation window in order to more effectively reduce the return of fear is clear. It is in theory a simple and noninvasive augmentation to already existing therapies that are based in extinction learning. If, for example, an imaginal exposure therapy session for a client with PTSD could take place following memory reactivation and destabilization, perhaps beyond extinction learning, the learning that occurs in session could be restored to long-term memory as a more durable and stable memory (i.e., fewer intrusive memories, avoidance, hyperarousal, etc.). However, there has been little success thus far in translational efforts harnessing reconsolidation processes specific to fearful memories. The challenges in translation are directly related to the various boundary conditions at play during reconsolidation. For the vast majority of studies that find particular parameters to be required of a given boundary condition, there exist other studies suggesting alternative parameters for that same boundary condition (Treanor et al., 2017).

Psychopathology is complex and multifaceted; for example, individuals with PTSD typically present for treatment years after trauma exposure and with overgeneralized fear related to a wide range of different situations and stimuli. Some studies have examined reconsolidation in subclinical and clinical samples, specifically in individuals with spider fears (Soeter & Kindt, 2015), spider and snake fears (Telch, York, Lancaster, & Monfils, 2017), and PTSD (Brunet et

al., 2011). Soeter and Kindt found that a single dose of propranolol decreased fear responses to spiders up to 1 year after exposure, only in individuals who received the propranolol dose after memory retrieval. Telch and colleagues (2017) received a single session of *in vivo* exposure, with a memory retrieval cue presented either 30 min before or after exposure. Participants who viewed the cue prior to exposure showed decreased fear 1 month after the exposure session, and also showed a more rapid decrease in fear during exposure. Brunet and colleagues (2011) engaged participants with PTSD in a script-driven imagery task, where participants received either propranolol or placebo after describing their traumatic experience. Findings suggest that one week later, participants who had received propranolol showed lower physiological arousal during a trauma-related mental imagery task compared to those who received placebo. Though findings from all three studies are consistent with the memory reconsolidation hypothesis, only one applied exposure therapy (Telch et al., 2017), and this study did not include individuals with clinical levels of phobic responding.

Even if there were clear evidence delineating exact parameters required, translation would be extremely challenging. Rather than repetitively conducting studies examining each individual boundary condition in isolation, it is important to better understand reconsolidation from a clinical perspective. If extinction mirrors exposure therapy rather than basic extinction, particularly given that these are two related but distinct interventions, can reconsolidation still enhance new learning that may occur? Another key question related to translation of this research to clinical settings is whether our indices of fear and distress parallel the persistent fear and distress seen in individuals with psychopathology. Though analogue research by definition does not elicit comparable levels of emotion as seen clinically, it is problematic that comparisons of extinction vs. no extinction are typically not included in studies. Inclusion of a clinical

sample, more clinically relevant extinction sessions, and comparison of extinction to no post-acquisition intervention are critical next steps to advance translational reconsolidation research toward potential clinical applications.

In clinical translation, effectiveness of reconsolidation ought to alter more than physiological responding, altering subjective (e.g., distress) and behavioral responding (e.g., intrusive memories) as well. The previous study, incorporating all three of these indices, found no difference between negative and neutral retrieval cue presented prior to extinction. Given this, one possibility was that other boundary conditions were violated in this study. One of the most obvious potential candidates and a key question across the reconsolidation literature is whether new learning is actually occurring; the above extinction paradigm was less clear-cut as to what the new learning is, and prediction error and expectancy violation are consistently discussed as necessary boundary conditions. Given that intrusive memory frequency and distress are the primary outcome variables of interest, it is also worth noting that many factors likely influence the both the presence and persistence of intrusive memories, particularly when related to stimuli that is moderately distressing at best for most individuals.

The purpose of this study was to extend the film fear learning paradigm to a trauma-exposed, clinical sample, to systematically explore what kind of new learning needs to occur post-retrieval to harness reconsolidation advantages by adding a new extinction condition and natural recovery control condition, and to understand factors related to the persistence intrusive memories. Given that intrusive memories are transdiagnostic phenomena and commonly occur not only for individuals with PTSD but also individuals with MDD (e.g., Reynolds & Brewin, 1998; Starr & Moulds, 2006), individuals who met criteria for PTSD, MDD, or both were included who were already experiencing intrusive memories. For a comparison control

condition, individuals were selected who had trauma exposure but no current PTSD or MDD, not experiencing any form of re-experiencing symptoms from their trauma. This allowed for interpretation of any between-group differences as related to current psychopathology, rather than effects of trauma exposure.

Further, this study systematically investigated whether a clearer separation of the CS and US association during extinction allowed for enhancement of extinction within the reconsolidation window, given that reconsolidation effects have yet to emerge in previous studies using the film fear learning paradigm and that gauging what participants learn from repeated exposure to a film becomes more challenging. To explore effects of more concrete CS-US learning, an additional extinction condition was added to better mirror laboratory extinction paradigms, where during extinction a very brief segment of the acquisition clip (CS-) was repeatedly viewed, interspersed with neutral images of nature. The video of the mutilated body was not presented during extinction. Finally, an assessment-only condition, was added in order to assess natural decreases in film-related intrusive memories that likely occur in experimental paradigms with analogue trauma exposure.

First, it was hypothesized that participants with PTSD/MDD (i.e., participants already with re-experiencing symptoms) in the extinction conditions would experience decreased intrusive memories 72 hr after acquisition compared to trauma-exposed individuals with PTSD/MDD in the assessment-only condition 24 hr after extinction. Despite the lack of research on fear extinction using intrusive memories as an outcome measure, fear extinction generally is superior to it would be expected that extinction is more effective than no intervention. Further, it was predicted that participants with PTSD/MDD in either of the extinction conditions would report higher intrusive memories 24 and 72 hr after acquisition than the trauma exposed control

group, given that pre-existing psychopathology has been found to predict more intrusive memories (e.g., Laposa & Alden, 2008; Logan & O’Kearney, 2012). It is also expected that the image extinction condition would predict fewer and less distressing intrusive memories 72 hr after extinction compared to the film extinction condition, as prediction error is more likely with image extinction and prediction error is critical in fear extinction (e.g., Craske et al., 2014) and is posited as a key boundary condition of reconsolidation (e.g., Exton-McGuinness et al., 2015).

Second, it was hypothesized that higher noradrenergic activity and higher cortisol during acquisition would predict increased intrusive memories and higher intrusive memory distress at both 24 and 72 hr post-acquisition. More specifically, there would be interaction between these two systems, such that increases in cortisol and sAA combined would predict intrusive memory frequency and distress. This hypothesis was based on the literature examining noradrenergic and glucocorticoid involvement in the development of intrusive memories (e.g., Bryant et al., 2013) and literature suggesting that these systems are dependent on one another in predicting enhanced consolidation of emotional memory more generally (e.g., Andreano & Cahill, 2006; Kukulja et al., 2011).

Finally, demographic factors, pre-existing psychopathology such as PTSD, depression, and anxiety, and film-related processing factors such as state anxiety, negative affect, and data-driven processing, were explored as predictor of intrusive memories 24 hr after acquisition and 72 hr after acquisition. Specifically, it was hypothesized that higher levels of pre-existing psychopathology, data-driven processing, and negative affect would predict more frequent and distressing intrusive memories 24 hr after acquisition and extinction, in line with research suggesting that these pre-existing psychopathology vulnerabilities (e.g., Laposa & Alden, 2008; Logan & O’Kearney, 2012), emotional arousal (e.g., Hall & Bernsten, 2008), and data-driven

processing factors (Bourne et al., 2010; Holmes et al., 2004) would predict increased intrusive memories.

Method

Participants

Sixteen participants (57.1% men, and 42.9% women), with 5 individuals in the film extinction condition, 5 individuals in the image extinction condition, and 4 in the control condition. Participants were recruited primarily through flyers in the community and through a Craigslist advertisement. For the PTSD/MDD group, inclusion criteria were: exposure to DSM-5 traumatic event in their lifetime, a minimum score of 5 on the re-experiencing subscale of the assessor-administered Posttraumatic Symptom Scale-Interview for DSM-5 (PSSI-5; Foa et al., 2016), and a current diagnosis of PTSD, major depressive disorder (MDD), or both based on the PSSI-5, the Quick Inventory of Depressive Symptomatology-Self-Report version (QIDS-SR-16; Rush et al., 2003), and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Exclusion criteria for the PTSD/MDD group included a lifetime diagnosis of OCD, psychotic disorders, and/or bipolar disorders, depression severe enough to require immediate psychiatric treatment (i.e., actively suicidal), less than three months stable on a psychotropic medication (e.g., SSRI, SNRI), and current use of beta-blockers or benzodiazepines. Inclusion criteria for the control group were lifetime exposure to a traumatic event as defined by DSM-5, and a score of zero on the re-experiencing subscale of the PSSI-5. Exclusion criteria were the same as for the control group, with the addition of any DSM-5 Axis I diagnosis in the past six months. See Table 10 for demographic information; see Table 11 for baseline psychopathology in PTSD/MDD sample.

Design

Study design was both a between-subjects and within-subjects design. The between-subjects factors were group (2: PTSD/MDD, control) and Day 3 condition (3: film extinction, image extinction, assessment only). The within-subjects factor was time since acquisition (2: 24 hr, 72 hr). Primary dependent variables were intrusive memory frequency and distress 72 hr after acquisition. See Figure 10 for study flow diagram.

Film Fear Learning Paradigm

Footage from various parts of the feature film, *The Last King of Scotland*, was selected and merged into a 6-min segment. The segment included graphic images of mutilation and death and has been used in previous work (Marks & Zoellner, 2014) as an effective way in which to elicit intrusive memories in a sample of healthy undergraduates. For all study phases, the film was projected on a white wall; with a dimension of 6' x 6'.

Acquisition. For fear acquisition, a 6 min segment was shown one time. This segment included adequate lead-in information about the plot, anticipatory anxiety prior to the analogue traumatic scene, and the traumatic scene where the protagonist discovers that his lover has been mutilated and killed. The acquisition segment ends shortly after the mutilated body is discovered, with a child peering out from behind his mother's legs to view the body.

Day Three Manipulation Conditions. Participants were randomized to one of three conditions for Day 3: film extinction, image extinction, or assessment only.

Film extinction condition. In the film extinction condition, the 6 min segment was shown in its entirety two times, followed by six repetitions of most graphic 3 min segment, for a total of 30 min of film viewing. The function of gradually honing in on the most graphic and salient film content was to mirror clinical processes in imaginal exposure to the traumatic memory for PTSD (e.g., Foa et al., 2005; Rothbaum, Astin, & Marsteller, 2005; Tarrier et al., 1999). Patients

gradually shift to revisiting the most distressing part of their trauma memory, called “hotspots,” during imaginal exposure as treatment progresses (Foa, Hembree, & Rothbaum, 2007)

Nature image extinction condition. In the nature image extinction condition, the length of content was the same as the film extinction condition (30 min) but consisted of a combination of very brief (20 s) film clips interspersed with images of nature. The film clip was the 20 s of footage from the acquisition clip that directly preceded the discovery of the mutilated body. The footage was stopped right before the body is discovered, as a way of presenting conditioned stimuli without presenting the unconditioned stimulus (mutilated body), mirroring laboratory extinction procedures (e.g. Lissek et al., 2005). The nature images were interspersed between the film clip, with intertrial variability ranging from 90 s to 150 s.

Assessment only condition. In this condition, no Day 3 procedures occurred. Once acquisition was completed, they simply completed the first intrusive memory phone assessment 24 hr after extinction, and then completed their second phone assessment 48 hr after the first phone assessment. The purpose of this condition was to serve as a control for changes in intrusive memories following acquisition without any intervention, as intrusions often decrease spontaneously over time (McFarlane, 1988; Shalev, 1992).

Reconsolidation Conditioned Stimulus Cue

The conditioned stimulus (CS) cue used as a film memory retrieval cue for participants assigned to the film extinction and nature image extinction conditions was a neutral headshot of the female protagonist’s face. This was the same “Neutral CS” image used in our previous study. The image was 6’ x 6’, projected onto a white wall, for 8 s before participants received instructions regarding the visuospatial distraction task.

Visuospatial Distraction Task

Tetris, a visuospatial game played on the computer, was used as a stimulus offset technique (Pedreira et al., 2004) following CS retrieval cue presentation for the two conditions that were randomized to an extinction session. The goal of Tetris is to manipulate shapes as they fall in order to form as many horizontal lines as possible. Tetris is thought to compete with limited visuospatial cognitive resources believed to be necessary for intrusive memory formation. It is commonly used in intrusive memory research as well (e.g., Iyadurai et al., 2018; James et al., 2015; Marks & Zoellner, 2014; Holmes et al., 2010). Given that the purpose of Tetris is to shift participant attention away from any film-related memories retrieved due to CS cue presentation, the task's effectiveness was assessed with a single question: "How effective was the computer task in distracting you from your thoughts related to the film previously viewed?" Responses were rated on a 9-point scale from 0 (*not at all effective or no film-related thoughts*) to 8 (*extremely effective*).

Interview Measures

Given that groups for this study were determined by diagnostic and symptom severity thresholds, relevant interview measures assessing PTSD, depression, and exclusionary diagnoses were included and administered by trained independent evaluators.

Posttraumatic Stress Disorder Symptom Scale Interview (PSSI-5; Foa et al., 2016). The PSSI-5 is a 24-item clinician-administered assessment of PTSD symptom severity. Twenty items assess frequency and severity of each of the DSM-5 symptoms of PTSD, ordered according to symptom cluster (re-experiencing, avoidance, negative mood and cognition, and increased arousal and reactivity). Each of the symptom-specific questions is rated on a scale from 0 (*not at all*) to 4 (*6 or more times per week / severe*), with a total score from summing these 20 items. The PSSI-5 demonstrates good internal consistency ($\alpha = .89$), test-retest

reliability ($r = .87$), and interrater agreement for PTSD diagnosis ($k = .84$; Foa et al., 2016). The measure shows good convergent validity with other measures of PTSD (Clinician-Administered PTSD Scale for DSM-5, Posttraumatic Diagnostic Scale for DSM-5, and PTSD Checklist-Specific Version); all $r_s > .72$. The PSSI-5 also demonstrates good convergent validity with measures of depression and trait anxiety. A probable cut-off score for PTSD diagnosis is a total score of 23 (Foa et al., 2016).

Quick Inventory of Depressive Symptomatology- Clinician Version (QIDS-C16; Rush et al., 2003). The QIDS is a 16-item semi-structured clinician-administered measure depression symptoms and symptom severity. Questions assess symptoms experienced over the past two week period and are anchored to a period when the individual being assessed was feeling more like their normal self / not depressed. For individuals not experiencing significant symptoms of depression and who feel as though their current state of mental health is their normal state, no comparison would be indicated. Assessment questions target domains of depressive symptomatology including sleep, appetite, mood, suicidal thinking, energy, concentration, anhedonia, and psychomotor symptoms. Responses range from 0 to 3, with the meaning of these responses tailored to each symptom question. For example, for the question assessing energy, a “0” response means *no change in usual level of energy*, whereas a “3” response means *unable to carry out most of usual daily activities due to lack of energy.*” Total score is calculated by summing the most severe item of the four sleep items, mood item, the most severe appetite item, the most severe weight item, concentration item, outlook on self item, suicide item, anhedonia item, energy item, and the most severe psychomotor item. The QIDS demonstrates good internal consistency ($\alpha = .86$), and good convergent validity with the Hamilton Rating Scale for Depression ($r = .86$) and the Inventory of Depressive

Symptomatology ($r = .96$). A score of 0 – 5 suggests no depression present; 6 – 10 suggests mild depression; 11 – 15 suggests moderate depression; 16 – 20 suggests severe depression, and 21+ suggests very severe depression (Rush et al., 2003).

Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). The MINI is a commonly used structured clinical interview that assesses a range of psychiatric disorders. Disorders covered include depressive disorders including bipolar disorders, anxiety disorders including OCD, substance use disorders, psychotic disorders, eating disorders, and antisocial personality disorder. Responses to questions are simply “yes” or “no,” and assessor are guided accordingly as to whether the individual meets diagnostic criteria for a given disorder. Administration of the MINI allows for assessment of comorbid conditions for eligible participants in addition to assessing for exclusionary diagnoses. The MINI demonstrates good sensitivity, 0.70 or greater for the majority of diagnoses). The MINI shows good diagnostic reliability and validity across diagnoses when compared to the SCID-IV, including for MDD ($K = 0.84$), PTSD ($K = 0.78$), OCD ($K = 0.63$) and lifetime psychotic disorder ($K = 0.76$) (Sheehan et al., 1998).

Self-report Baseline Measures

We included a range of self-report measures in order to assess participants' baseline characteristics including psychopathology and trait factors. These allowed further assessment of trauma exposure, depression severity, trait anxiety, and use of imagery in daily life. We also included several state measures that allow for assessment of change over the course of the study. These measures included a measure of state anxiety administered prior to acquisition and extinction sessions, a measure of affect administered immediately following film viewing to assess changes induced by film content, and a measure of how individuals processed the film in

order to examine possible state predictors of intrusive memories. Additionally, we included the Health & Medication Questionnaire that assesses information relevant to individuals' cortisol and sAA levels.

Health, & Medication Questionnaire. Factors known to influence cortisol and sAA levels were assessed, specifically sleep, teeth brushing, food consumption, cigarette smoking, caffeine intake, menstrual period, stress level, and current medications.

Brief Trauma Questionnaire (BTQ; Schnurr et al., 1995). The BTQ is a 10-item self-report measure derived from the Brief Trauma Interview (BTI; Schnurr et al., 1995). Each of the 10 items asks about a specific type of trauma exposure (e.g., combat exposure). When a “yes” to exposure to a particular type of trauma is indicated, two yes/no follow-up questions are asked: *Did you think your life was in danger or that you might be seriously injured? Were you seriously injured?* This measure served to assess additional trauma exposure. Interrater reliability for the BTI ranged from $K = .74 - 1.00$ (Schnurr et al., 1995).

Beck Depression Inventory- II (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II assesses presence and intensity of sleep, mood, appetite, worthlessness, suicidality, level of interest/engagement, and self-perception. Responses are symptom-specific and are rated on a 0 to 3 scale, with 0 representing the absence of that particular symptom and 3 representing high severity (e.g., 0 = *I don't criticize or blame myself more than usual*; 3 = *I blame myself for everything bad that happens*). Total BDI-II scores are calculated by summing the totals of all individual items, with higher scores representing higher severity of depression. The BDI-II has demonstrated good concurrent validity with other self-report measures of depression and anxiety, including the State-Trait Anxiety Inventory (trait version) ($r = .77$; Storch, Roberti, & Roth,

2004), and the Hamilton Psychiatric Rating Scale for Depression ($r = .71$; Beck, Steer, & Brown, 1996).

Spontaneous Use of Imagery Scale (SUIS; Reisberg, Pearson, & Kosslyn, 2003).

This 12-item self-report measure is used to assess how individuals use mental imagery in their daily lives. This measure was included given the relationship between mental imagery and intrusive memories (e.g., Morina, Leibold, & Ehrling, 2013). This measure focuses only on the use of visual imagery, and does not assess other spontaneous sensory experiences. Each item assesses how often a particular scenario fits an individual's typical experience, with responses rated on a 1 (*never appropriate*) to 5 (*always appropriate*) scale. For example, "When going to a new place, I prefer directions that include detailed descriptions of landmarks (such as the size, shape, and color of a gas station) in addition to their names." Total score is calculated by summing all items, with higher scores indicating those with higher image vividness. The SUIS is reported to have good internal consistency ($\alpha = .83$; McCarthy-Jones, Knowles, & Rowse, 2012). Additional psychometrics have not been reported at present (Nelis, Holmes, Griffith, & Raes, 2014).

Thoughts and Feelings Questionnaire (TFQ; Ehlers, 1998). This questionnaire captures conceptual and data-driven processing in response to emotional stimuli. Individuals are asked about the way in which they processed the film segment, including how well they tracked what was happening, how absorbed they were in the sensory material rather than the chronology, etc. This measure is important given that individuals who process stimuli in a primarily data-driven way (i.e., primarily focused on sensory images, emotions, etc.) may be more likely to experience intrusive memories of the content. The measure includes 14 total items, 8 of which correspond to the data-driven subscale and 6 of which correspond to the conceptual subscale.

The two subscales are scored separately, summing all items. Items are answered on a 0 (*not at all*) to 4 (*very strongly*) scale. An example of a data-driven item is, “My mind was full of impressions and my reactions to them,” whereas an example of a conceptual item is, “I tried to figure out what would happen next.” The TFQ shows good internal consistency ($\alpha = .70$; Ehlers, 1998). No other psychometrics have been published to date.

Additional Post-Film Questions. Four additional questions relevant to film viewing experience were asked after acquisition in order to assess for predisposing factors that may make someone more or less prone to developing intrusive memories from a graphic film segment. These questions were: 1) “How enjoyable do you find violent, graphic movies?” with responses rated on a 0 (*not at all*) to 6 (*very enjoyable*) Likert scale. 2) “How often do you seek out violent, graphic movies to watch?” also rated on a 0 (*never*) to 6 (*often*) scale. 3) “Did you pay attention during the movie?” with yes/no responses. 4) “Did you turn your head or look away at any point during the movie?” with yes/no responses, followed up with “If yes, how many times?”

State Emotion Measures

State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The measure is a self-report measure of both state anxiety and trait anxiety via two separate subscales (STAI-S and STAI-T, respectively). The STAI-T allows for assessment of overall baseline anxiety, whereas the STAI-S allows for a more concise assessment of anxiety in that given moment. The measure includes 40 total items that assess feelings of anxiety, contentedness, tension, etc. The STAI-T was administered once prior to acquisition; the STAI-S was administered prior to acquisition and extinction sessions as a measure of state anxiety coming into sessions. All items are rated on a scale from 0 (*not at all*) to 4 (*very much so*). Examples of items from the STAI-T include “I wish I could be as happy as others seem to be,” “I

feel secure,” and “I worry too much over something that does not really matter.” Sample questions from the STAI-S include “I feel calm,” “I feel tense,” and “I feel frightened.” The two subscales are scored separately; subscale scores are calculated by summing the 20 corresponding items, with reverse scoring where indicated. Higher total scores are indicative of higher anxiety. The STAI-T demonstrates good test-retest reliability ($r = .73 - .86$; Spielberger et al., 1983) and correlates well with other measures of trait anxiety ($r = .52 - .80$; Spielberger et al., 1983).

Subjective Units of Distress (SUDs; Wolpe, 1969). This self-report measure of subjective state distress is a single question (i.e., “What is your SUDs level?”) and responses are on a 0 to 100 scale. The SUDs scale allows for repeated assessment of participants’ distress in response to film content, and also in response to retrieval cue material. This rating is additionally used as a subjective rating in conjunction with participants’ cortisol/sAA data. Zero represents a completely calm and relaxed state, and 100 represents the most distress an individual has ever felt or could imagine feeling. Participants were asked to give SUDs ratings each time they give a saliva sample, and every 2 min during the film acquisition segment. In addition, participants randomized to an extinction condition gave SUDs ratings in response to the retrieval cue, and every 5 min during the 30 min extinction segment. Peak SUDs during acquisition and extinction phases were defined as the highest SUDs rating reported during each segment. This measure of distress is associated with objective measures of physiological arousal (heart rate, $r = .39$; peripheral vasoconstriction, $r = .84$; Thyer, Papsdorf, Davis, & Vallecorsa, 1984).

Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). The PANAS is a 20-item self-report measure that captures both positive (PA) and negative (NA) affective experiences. The PANAS allows for assessment of an individual’s state affect in a given moment, and was administered immediately after participants viewed the acquisition film

segment, and again immediately following extinction content for those randomized to an extinction condition. The positive subscale assesses the extent to which an individual experiences desirable mood states, such as interest, enthusiasm, and excitement; the negative subscale assesses the extent to which one experiences undesirable mood states, such as shame, irritability, and fear. Items responses are rated on a scale from a 5-point Likert scale from 1 (*slightly or not at all*) to 5 (*extremely*). The two subscales demonstrate good convergent validity with the BDI (NA: $r = .58$; PA: $r = -.36$) and with the Hopkins Symptom Checklist (NA: $r = .74$; PA: $r = -.19$).

Salivary alpha amylase (sAA) and cortisol. Saliva samples were collected using the SalivaBio swab (as opposed to passive drool) method. Approximately 50 μ L were collected using standard salivette sampling devices (Sarstedt, Numberg, Germany). Participants were explicitly instructed to place the salivette between their gum and their cheek, and leave it in place for two min. Research assistants instructed participants to spit the salivette back into the storage tube at the end of the two-min period. Immediately after all session samples were completed, samples were stored in a -20 C freezer until all data collection was completed. Samples were then shipped to Dresden Lab Service in Dresden, Germany, where they were thawed and centrifuged at 2000 x g for 5 min. Concentrations of cortisol in each sample were determined by interpolation from a standard curve, which is created by mapping standard cortisol concentrations against an optical density ratio (e.g., Felmingham, Tran, Fong, & Bryant, 2012). For sAA, an enzyme kinetic method was used. Briefly, a series of dilutions and incubations were conducted, with linear regression used to translate increases in absorbance to sAA concentrations (Segal & Cahill, 2009; Granger et al, 2007).

Intrusive Memory Assessment

Intrusive memory frequency and distress 72 hr after acquisition were the main dependent variables of interest. Intrusive memories were assessed via telephone. A definition of intrusive measures was provided: “An intrusive memory is a memory of an event that pops into your mind spontaneously, out of the blue, without any obvious cue or trigger. These memories are usually intense and very vivid, like brief snapshot images of a particular moment.” Four different types of intrusive memories are captured: sensory-based cued, sensory-based uncued, conceptual cued, and conceptual uncued. Examples of both cued (e.g., watching a news story about a child who drowned, and having an intrusive image pop into your head as you walk across a bridge) and uncued intrusive memories (e.g. an image of a wounded child popping into your head as you make breakfast in the morning), and examples of both sensory-based intrusive memories (intense, vivid, snapshot-like) and conceptual intrusive memories (e.g., recalling what it was like to view the film) are provided. Frequency and distress of intrusive memories were assessed separately. Distress responses were rated on a 0 (*not at all distressing*) to 8 (*extremely distressing*). In cases where participants reported having experienced more than one intrusive memory in a given category, distress ratings were based on the *most* distressing intrusive memory. Overall total number of intrusive memories were calculated, as well as subtotals for sensory-based and conceptual intrusive memories. Cued and uncued were totaled together to create a sum total of intrusive memories. Two different distress ratings were calculated: maximum distress rating (i.e., single highest distress rating), and average distress rating across all categories (i.e., accounting for distress level for all intrusive memories).

Procedure

Intake Assessment (Day 1). Individuals who were deemed eligible through phone screening procedures were invited for an initial intake assessment. Evaluators were clinically-

trained assessors, with prior training in the measures being administered and demonstrated reliability on the PSSI-5, the QIDS, and the MINI, showing >80% reliability to a standard on these measures. The assessors completed the PSSI-5, the QIDS, and the MINI and collected basic demographic information (e.g., age, race, ethnicity, education level, sex, and gender). Participants, regardless of eligibility, were offered a list of clinical referrals should they decide to seek treatment for a mental health issue. Ineligible individuals were explained reason for ineligibility and were compensated for their time (\$25/hr).

Acquisition (Day 1). Prior to beginning study procedures, SUDs anchors were explained, and explained how to rate their SUDs when prompted throughout the study. Participants were then asked to rate their SUDs levels, and provided a saliva sample (“Saliva 1”), Next, they completed baseline questionnaires, which included the health and medication questionnaire, the BTQ, BDI-II, STAI, and SUIS. A second SUDs level and saliva sample (“Saliva 2”) were collected following completion of baseline questionnaires, approximately 20 – 30 min after beginning questionnaires. Time of saliva samples were tracked. Participants were told that they would view a brief film and be asked to pay attention closely to the film. They were asked to rate their SUDs immediately prior to film viewing (“Pre-viewing SUDs”), and were oriented that SUDs ratings would be prompted throughout the film. Every 2 min throughout the 10 min acquisition clip, a research assistant then asked participants to rate their SUDs level. A final SUDs rating was collected immediately after the film viewing. Participants then received an explanation about phone assessment scheduling and were given a brief overview of the extinction phase of the study. Participants then gave a final saliva sample and SUDs rating (“Saliva 3”), and completed two post-film questionnaires (PANAS, TFQ) and answered the

additional post-film questions. They then scheduled their acquisition phone assessment with a research assistant.

Randomization (Day 1). Participants were randomized via random number generator to determine their condition assignment (film extinction, nature image extinction, assessment only). Randomization was conducted blocked for PTSD/MDD and control participants, to ensure similar condition distribution across groups. Participants were told individually prior to leaving the lab whether they would need to return to the lab on Day 3 for additional study procedures. No other details were provided.

Acquisition phone assessment (Day 2). A research assistant phoned each participant approximately 24 hr after acquisition and the participant completed the intrusive memory assessment. Participants were reminded, if applicable, of their session the following day.

Day 3. Forty-eight hrs after the acquisition, participants randomized to the extinction conditions returned to the lab. Participants provided an initial SUDs rating, gave their first saliva sample (“Saliva 4”), and completed the STAI-S. Participants in both extinction conditions then viewed the CS retrieval cue for 8 s and were instructed to focus on the image until it disappeared. Participants were asked to rate their SUDs, in order to capture distress elicited by the cue itself. After SUDs rating, research assistants directed participants to play Tetris on their computer for 10 min. Participants then rated how effective Tetris was at reducing any film-related images and thoughts that may have been elicited by the cue presentation. The second saliva sample and SUDs rating were then collected (“Saliva 5”).

Though the content of film viewing differed by extinction condition (see below), participants in both extinction conditions were told that they would view approx. 30 min worth of content. SUDs levels were recorded immediately prior to viewing, every 5 min during, and

immediately after extinction film viewing. In both conditions, at the conclusion of film viewing, a third saliva sample was collected. All participants then completed post-film questionnaires (PANAS, TFQ).

In the assessment only condition, participants did not return on Day 3. Instead, they completed both phone assessments in line with timing of participants who completed extinction procedures (i.e., 24 hr after acquisition, 72 hr after acquisition). Participants were scheduled for both phone assessments at the end of their acquisition session and were compensated for their time at the end of session.

72 hr phone assessment (Day 4). A research assistant again phoned each participant at 72 hrs after acquisition to administer their final intrusive memory assessment. The research assistant provided a comprehensive debriefing about study procedures and answered any questions.

All participants were paid for their time at a rate of \$25/hr. Payment was provided at the participant's final in-person session (Day 1 acquisition for assessment-only participants; Day 3 for all other participants).

Data Analysis

Data reduction. Data were screened prior to analyses to check for missing data and outliers. A means test was done looking for differences between cases missing data and cases without. Data from participants who do not complete all study procedures were excluded from analyses. At this point in data collection, only one participant had missing data and was excluded from analysis. Initial group and condition differences were assessed. Normality, homoscedasticity, and linearity assumptions were tested, and no transformations were needed for violated assumptions.

Data analytic strategy. Given the small sample size at this time, we examined basic descriptive data to see how the paradigm fared in the full trauma-exposed sample. We first examined whether the manipulation was effective in a trauma-exposed sample. We then examined patterns of distress during extinction between the two extinction conditions, and also between the PTSD/MDD and control groups. We then looked at patterns of intrusive memory frequency and distress 24 and 72 hr post-acquisition, first across all participants and then between the two groups. We next examined patterns of intrusive memory frequency and distress 72 hr after acquisition between participants in the assessment only condition and participants in any extinction condition (i.e., combined extinction conditions). Lastly, we examined relationships between baseline psychopathology and intrusive memory frequency and distress 24 and 72 hr after acquisition.

One participant in the assessment only condition completed all study procedures but was a clear outlier on primary dependent variables and was thus excluded from data analysis. Final sample size all analyses was 14.

Results

Clinical Description

Most participants in the PTSD/MDD group met criteria for both PTSD and MDD; one participant met criteria for MDD but not PTSD, and three participants met criteria for PTSD alone. Overall, PTSD levels were above the clinical cutoff of 21 as indicated by PSSI-5 psychometrics (Foa et al., 2016). Depression levels on average were at a moderate level, with severity ranging from mild to severe in the PTSD/MDD group. As a reminder, participants in the control group did not meet criteria for current PTSD, MDD, or any other Axis I diagnosis.

Manipulation Check

The 6 min acquisition film was effective in eliciting an increase in distress during the film (pre-viewing SUDs: $M = 13.57$, $SD = 15.50$, post-viewing SUDs: $M = 45.71$, $SD = 29.28$; $t(13) = -5.25$, $g = 1.40$) and in evoking a range of expected negative emotions on the PANAS (1-5 range for each item; upset: $M = 2.38$, $SD = 1.20$; afraid: $M = 2.06$, $SD = 1.29$; scared: $M = 2.25$, $SD = 1.34$). Critically, the acquisition film clip effectively elicited intrusive and distressing memories 24 hr after film exposure. The majority, 79.6%, of participants reported at least one intrusive memory 24 hr after the acquisition session, with an average total number of intrusive of 4.00 ($SD = 3.72$). Participants also generally reported distress associated with their intrusive memories 24 hr after acquisition (distress: $M = 3.02$, $SD = 1.21$). These intrusive memories were both cued (42.2%) and uncued (57.8%). The most commonly reported intrusive memory, which came in both cued and uncued forms for participants, was the image of the mutilated body at the end of the acquisition scene, consistent with our prior studies using this same film footage.

Patterns of Extinction Learning in Experimental Conditions

Figure 11 shows average SUDs levels across the extinction period, displaying a notable difference in distress levels over the 30 min between the image extinction ($n = 5$) and film extinction ($n = 5$) conditions. For average SUDs, participants in the image extinction seem to demonstrate what appears to be a more “typical” extinction curve compared to participants in the film extinction condition. There was a clear rise in distress that came down over the latter half of extinction for participants in the image extinction condition; whereas, the trajectory of distress that looks predominantly like gradually increasing distress over the entirety of the extinction period.

When examining the patterns during extinction between the Control group ($n = 3$) and the PTSD/MDD group ($n = 11$), combining the film and image extinction conditions, the

PTSD/MDD group may be showing a more typical extinction curve than the Control group. See Figure 12.

Intrusive Memories 24 and 72 hr After Acquisition

Across conditions (condition: film extinction, image extinction, assessment only) and groups (PTSD/MDD and Control), intrusive memory frequency from 24 hr after acquisition to 72 hr after acquisition showed a pattern of only a slight decrease (24 hr: $M = 3.21$, $SD = 2.69$; 72 hr: $M = 3.00$, $SD = 2.39$; $d = 0.08$). See Figure 13. However, maximum intrusive memory distress showed a stronger pattern of reduction from 24 to 72 hr post-acquisition (24 hr: $M = 3.09$, $SD = 1.30$; 72 hr: $M = 2.50$, $SD = 1.09$, $d = 0.85$). See Figure 14. Average intrusive memory distress also showed a similar pattern of decrease between 24 hr and 72 hr post-acquisition phone assessments (24 hr: $M = 2.86$, $SD = 1.14$; 72 hr: $M = 2.15$, $SD = 1.27$, $d = 1.09$).

As would be expected, individuals in the PTSD/MDD group ($M = 3.82$, $SD = 2.64$) compared to those in the Control group ($M = 1.00$, $SD = 1.73$) showed a pattern of more initial intrusions, $d = 1.12$. At 72 hr after acquisition, this pattern persisted but was not as strong (PTSD/MDD: $M = 3.00$, $SD = 1.33$; Control: $M = 2.00$, $SD = 3.46$, $d = 0.54$). See Figure 15. In terms of intrusive memory distress in the PTSD/MDD and Control groups, given that only one out of the three individuals in the Control group reported an intrusive memory, we did not examine how distress levels compared 24 and 72 hours after acquisition.

Effects of Intervention vs. Assessment Only on Intrusive Memories

A key part of the current study design was to examine what happened to intrusive memories elicited by the paradigm allowing for spontaneous reduction of intrusions (i.e., assessment only) compared to extinction intervention conditions. As such, we examined

intrusive memories 72 hr after acquisition combining both PTSD/MDD and Control groups and combining image and film extinction conditions in order to compare any extinction ($n = 10$) to assessment only ($n = 4$).

Intrusive memory frequency 72 hr after acquisition showed a pattern of decrease in the assessment only condition (24 hr: $M = 3.75$, $SD = 3.50$, 72 hr: $M = 2.50$, $SD = 1.92$, $d = 0.89$) but not the extinction conditions (24 hr: $M = 3.00$, $SD = 2.49$; 72 hr: $M = 3.20$, $SD = 2.62$, $d = 0.07$). See Figure 16. Preliminary pattern of changes in maximum intrusive memory-related distress from 24 to 72 hr after acquisition appeared similar between the assessment-only condition (24 hr: $M = 3.00$, $SD = 1.00$; 72 hr: $M = 2.67$, $SD = 0.58$, $d = 0.64$) and extinction conditions (24 hr: $M = 3.13$, $SD = 1.46$; 72 hr $M = 2.44$, $SD = 1.24$, $d = 0.90$). See Figure 17. When examining *average* intrusive memory-related distress rather than *maximum* intrusive memory-related distress, as seen in Figure 18, in contrast to the assessment only condition (24 hr: $M = 2.67$, $SD = 0.76$; 72 hr: $M = 2.33$, $SD = 0.29$, $d = 0.64$) the extinction conditions showed a stronger pattern of decrease in intrusive memory-related distress from 24 to 72 hr after acquisition (24 hr: $M = 2.94$, $SD = 1.29$; 72 hr: $M = 2.09$, $SD = 1.48$, $d = 1.29$).

Psychopathology and Intrusive Memories

Relationships between baseline psychopathology and intrusive memory frequency and distress were examined, given that this is the first study to use the film fear learning paradigm in a sample of trauma-exposed individuals with and without PTSD and MDD. See Table 12. Overall, few relationships were noteworthy. The degree of re-experiencing symptoms related to one's index trauma appeared related to the emergence (i.e., 24 hr intrusive memory frequency) but not the persistence (72 hr intrusive memory frequency) of film-related intrusions. Depression severity was also modestly correlated with 24 hr but not 72 hr intrusive memory

frequency. No clear relationships between intrusive memory-related distress and baseline psychopathology measures were evident.

Discussion

In this study, one of the purposes was to extend the reconsolidation film paradigm using complex, multisensory, and ecologically valid stimuli to trauma-exposed samples in order to continue translational efforts in understanding whether fear memory reconsolidation is a phenomenon with likely clinical utility. Studies to date investigating reconsolidation as an opportunity for adaptive memory updating have typically employed simple stimuli with little personal or emotional relevance and in healthy samples without psychiatric diagnoses, and have measured outcome using objective physiologic indices such as skin conductance response (e.g., Elsey & Kindt, 2017; Fernandez et al., 2017; Kredlow et al., 2016). Given mixed findings and considerable debate regarding boundary conditions and methodological differences that may explain such inconsistent findings, it is essential to expand this research to clinical samples. If effects cannot be replicated in clinical samples using what we know about the nuances of initiating reconsolidation processes from animal and human experimental models, then translation of reconsolidation as a clinically useful phenomenon is unlikely.

There is preliminary evidence that the paradigm was feasible in a trauma-exposed sample, including individuals who are experiencing clinical levels of psychopathology. Individuals with depression and/or PTSD participated in the study protocol. Only one participant in the PTSD/MDD group dropped out after the acquisition session. As expected, participants in the PTSD/MDD group reported more intrusive memories the day following acquisition than did participants without any current psychiatric diagnoses. The average number of intrusive memories reported by the PTSD/MDD group was comparable to those reported in the first study

in an undergraduate sample. Distress levels related to intrusive memories 24 and 72 hr after acquisition, also appeared comparable to distress levels associated with intrusive memories in the previous study with undergraduates. In brief, the paradigm appears to be feasible for trauma-exposed individuals already experiencing some level of intrusive memories and psychopathology. This is particularly important given that distressing film paradigms are commonly used as analogue traumatic events in translational PTSD research, yet the range of different films (e.g., length, format, content, etc.) make comparisons of findings across studies difficult (e.g., Weidmann, Conradi, Groger, Fehm, & Fydrich, 2009). Furthermore, researchers naturally may hesitate to show trauma-relevant material to trauma survivors for fear of doing harm (e.g., Griffin, Resick, Waldrop, & Mechanic, 2003), but this study and others (e.g., Rabenhorst, 2006; Walker, Newman, Koss, & Bernstein, 1997) suggest that these types of paradigms are tolerable and can be used without causing aversive effects or undo stress on participants.

One of the key questions with this study was comparing two different versions of extinction learning within the reconsolidation window. Shifting the paradigm to being more ecologically valid, by definition, some degree of experimental control is lost. With the extinction task used in the prior studies (Marks & Zoellner, 2014; Study 1 here), the extinction process mirrored prolonged exposure therapy in PTSD by repeatedly showing the acquisition clip and gradually honing in on its most distressing content, similar to what clinicians do when revisiting a traumatic memory (Foa et al., 2007). However, based on patterns of distress seen in Study 1 examining cue valence, it was unclear whether substantial new learning occurred that would then facilitate advantages of reconsolidation processes (e.g., Lee et al., 2017; Treanor et al., 2017; Tronson & Taylor, 2007).

The image extinction condition, in which the scene immediately preceding the mutilation (CS) no longer predicted the actual mutilation scene (US), participants showed a more classic extinction curve, where distress increased initially and then decreased by the end of extinction. Participants in the film extinction condition showed what looks like a slow and steady increase in distress over the 30 min period, including through the end of extinction. First and perhaps most obviously, the two conditions are markedly different in what participants are experiencing. The film extinction segment consists of many repeated exposures to the initial analogue trauma, whereas the image extinction segment consists of 20-second brief segments that remind participants of the analogue trauma without any direct exposure to the mutilated body. Alternatively, perhaps participants in the image extinction condition really did fear the eventual presentation of the mutilated body for the majority of the extinction process, despite 12 presentations of the 20 sec film clip immediately preceding the mutilated body scene in the absence of the mutilated body scene itself. This would be consistent with more innate, emotionally-relevant stimuli being more resistant to extinction (e.g., Mineka & Ohman, 2002; Ohman & Soares, 1993; Lovibond, Siddle, & Bond, 1993). Extinction curves look quite different in studies where ecologically irrelevant stimuli (e.g., yellow squares) are presented in the absence of a shock; graphs of physiological arousal during extinction in these studies show that arousal starts high and decreases fairly steadily over the extinction period (e.g., e.g., Schiller et al., 2010; Kindt & Soeter, 2013; Oyarzun et al., 2012). Of note, these extinction trajectories are based on objective measures (i.e., skin conductance) rather than subjective distress of anticipation of the US, and extinction periods are typically quite short (about 5 - 12 min) compared to the present study. Though it is still not well understood how fear-relevant stimuli fit in with extinction and reconsolidation, it is evident from the pharmacological literature that

the “fear relevance” of stimuli is not a stand-alone boundary condition for reconsolidation. In other words, the presence of fear-relevant stimuli does not necessarily mean that reconsolidation disruption will not occur. Several studies using pharmacological reconsolidation blockades have effectively disrupted post-retrieval reconsolidation of fear-relevant memories in order to decrease fear responses (e.g., Soeter & Kindt, 2011; Sevenster, Beckers, & Kindt, 2012). That said, there are more idiographic differences in how individuals respond to behavioral post-retrieval intervention with fear-relevant stimuli, which may make such an intervention less effective than pharmacological intervention in disrupting the reconsolidation of fear memories.

The pattern of distress during extinction also raises an interesting question of extrapolation between extinction and exposure therapy. Exposure-based interventions are thought to be based on the fear extinction literature (e.g., Bouton, 1988; Hofmann, 2008), yet this does not mean that extinction learning and exposure interventions are interchangeable. In certain anxiety disorders, the extension from extinction to exposure application makes clear sense. For example, a client was bitten (US) by a dog (CS+) and developed a phobia of dogs. She is repeatedly exposed to interactions with dogs who do not bite her (CS-), and her fear reaction to dogs decreases over time. In a client with PTSD, the application can also be quite straightforward; a client is robbed at gunpoint (US) while leaving her office one night (CS+). For this client, exposure therapy involves repeatedly approaching her office area (CS-), being out at night (CS-), and men (CS-), and she learns that these three conditioned stimuli are typically not associated with being assaulted. In the film fear learning paradigm, this exposure-extinction connection may be a bit less clear. The present study designed manipulated the type of new extinction learning as it relates to decreasing intrusive memories and intrusive memory distress. In the image extinction condition, participants may have learned over time that the image of the

man rushing down the hallway and pounding the elevator button no longer predicted the next image of the discovery of a mutilated body. In the film extinction condition, repeated presentation may have elicited different new learning more along the lines of, “This scene is awful but I can handle it,” or “I feel distressed but it is just a movie.” Though it is impossible to discern precisely what each participant learned based on SUDs ratings and PANAS scores, these two kinds of learning may affect reconsolidation processes and intrusive memories differently. If a leading hypothesis is that reconsolidation serves to keep memories “contextually relevant” (e.g., Dudai, 2004; Nader & Hardt, 2009), the image extinction condition certainly suggests that this film has now changed and no longer includes the horrific mutilation scene. In the film extinction condition, the new learning or relevance may be more variable, given a less clear disentangling of CS and US. Some participants may be so frustrated by having to view an awful scene over and over that their subjective ratings of distress capture frustration rather than fear. Others may experience boredom while viewing the same scene over and over, and their distress ratings may capture this instead. That said, we do not see substantially more variability in SUDs levels over the course of extinction in the film extinction condition as we would expect to see if idiographic differences were at play. In sum, the two versions of extinction are quite drastically different, and there are multiple factors at play including amount of exposure to distressing film content, presence of pleasant nature images, and clear-cut CS-US disassociation learning that all may contribute to differences seen between conditions here.

Another key question is whether extinction interventions following acquisition are superior to no intervention at all. It is well-established that spontaneous remission of learned fear responses can occur due to the passage of time, changes in one’s environment, unintentional exposure, etc. (e.g., Davey, 1989; De Silva & Rachman, 1981). As would be expected, intrusive

memories evoked by the film fear learning paradigm decrease when left alone, suggesting that the intrusive memories assessed 24 hr after exposure to the acquisition film are in fact normal, non-pathological experiences that likely do not map onto the kinds of intrusive memories seen clinically. Indeed, much of the intrusive memory literature to date focuses on intrusive memory *development* rather than intrusive memory *persistence* (e.g., Marks et al., 2018). Analogue studies designed to examine various predictors of intrusive memories often fail to account for intrusive memory distress and rather focus solely on the number of intrusive memories participants experience after some kind of analogue trauma exposure. This neglects the fact that intrusive memories are part of the normal human experience (e.g., Bernstein, 2001; Bywaters et al., 2004; Watkins et al., 2004). In these short paradigms, longer-term follow-up periods may be ideal, such as that of Schiller and colleagues (2010) who brought participants back one year after initial acquisition and extinction to test for return of fear. That said, long-term follow-up analyses are typically underpowered given most participants do not return to the lab, and findings may be coincidental given that experimental paradigms generally are not salient enough to have such a long-lasting effect. Although these studies are the first to incorporate reconsolidation with intrusive memories, few intrusive memory studies have extended beyond 3-month follow-up periods (e.g., Sundermann, Hauschildt, & Ehlers, 2013); the majority of studies tend to assess intrusive memories over the course of days or a week (e.g., Holmes et al., 2009; Kubota, Nixon, & Chen, 2015). As the field continues to struggle with translational questions regarding fear memory reconsolidation, we must consider whether we are assessing persistent rather than normative intrusive memory processes.

Intrusive memory frequency and intrusive memory distress do not necessarily behave similarly or move together. For example, when looking between participants with PTSD and/or

MDD and those who were in the control group, individuals with PTSD and/or MDD reported a higher frequency of intrusive memories on both days, whereas distress was fairly similar between the two groups across assessments. Differences were also seen across experimental conditions at 72 hrs after acquisition; the image extinction condition reported less frequent but more distressing intrusive memories than the other two conditions. In Study 1 and in Marks and Zoellner (2014), changes in intrusive memory frequency across experimental conditions were seen but differences in intrusive memory distress were not. Much of the prior intrusive memory literature has focused primarily on intrusive memory frequency. It essentially seems that trying to find predictors of the intrusive memory *development* using *frequency* as the primary construct to assess may be misguided (see Marks et al., 2018 for discussion); when, in fact, intrusive memory distress is more consistently predictive of PTSD (e.g., Michael, Ehlers, Halligan, & Clark, 2005; Kleim, Ehlers, & Gluckman, 2007; Ehlers & Steil, 1995). In brief, this preliminary data here adds to evidence that it should not be assumed that the presence of intrusive memories is pathological nor that individuals are upset by such memories. A comparable issue exists with studies that have used fear-irrelevant stimuli in these paradigms (e.g., Oyarzun et al., 2012; Schiller et al., 2010); while we know how physiologically reactive to stimuli individuals are, and how durable their extinction learning is when retested, standard outcome measures assessed in typical fear conditioning paradigms are missing critical information. For example, studies typically have not assessed action tendencies, which indicate whether participants avoid or withdraw from an aversive stimulus (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013). There are multiple dimensions to the definition of “fear”, including subjective experience, physiological arousal, and behavioral response (e.g., Frijida, 1986; Gross, 2014). Physiological arousal is the primary dimension consistently assessed, and behavioral responses and subjective

experiences are commonly ignored. Does arousal matter functionally, if an individual is not bothered enough to try to avoid an aversive stimulus? In the case of intrusive memories, does the presence of an intrusive memory matter functionally, if an individual is not distressed by its presence? In line with much-needed shifts in the fear conditioning literature, intrusive memory research needs to shift focus to what predicts the persistence of distressing intrusive memories, and whether memory reconsolidation is a viable way of more effectively decreasing intrusive memory distress.

This study is certainly not without limitations. First and most obviously is the sample size; continuing data collection is ongoing and this is by no means the final data analysis or discussion of this study. Within this small sample size, we are additionally limited by the skewed group sizes. The control group has only three participants, and only one of the three reported intrusive memories 24 and 72 hr after the acquisition session. In addition, though the PTSD/MDD sample reported re-experiencing symptoms and met criteria for PTSD and/or MDD, the PTSD/MDD group reported generally comparable levels of trait anxiety as the control group. This further exemplifies the importance of balancing the samples sizes, as the trauma-exposed controls typically report significantly lower levels of trait anxiety than clinical samples. With comparable levels of trait anxiety, the two samples may be more similar than different in their vulnerability to developing persistent intrusive memories, particularly in light of some findings suggesting that trait anxiety predicts intrusive memory frequency (e.g., Laposa & Alden, 2008; Logan & O’Kearney, 2012; Regambal & Alden, 2009). A second limitation is that the current study design does not compare post-retrieval extinction (i.e., within the reconsolidation window) to extinction as a stand-alone intervention, since both extinction conditions viewed the film retrieval cue 10 min prior to extinction procedures. While this design was intentional, it does

limit any conclusions that can be made directly related to reconsolidation processes. Instead, the focus was to hone in on several of the key issues that continue to challenge the translation of reconsolidation from “bench to bedside.” For example, knowing whether the image version of extinction learning is superior to the film version, that version can be used as a model of how best to translate reconsolidation moving forward. That said, exposure to distressing film content now varies considerably across extinction conditions; part of what needs to be better understood is whether enough “new learning” in this paradigm occurs with repeated exposure to the film content, or whether less exposure with more clear delineation of CS and US is better suited to take advantage of reconsolidation processes, as these two types of extinction may look quite different in a clinical setting.

It would be useful to know what participants were leaving extinction thinking and feeling, as this might give additional useful insights into what learning has actually occurred. Open-ended questions regarding what participants’ experiences were of extinction would provide nuanced information that may be useful to understand whether substantial new learning occurs during extinction that would facilitate enhanced reconsolidation. For example, it is nearly impossible to say whether a participant who reports moderate to high amounts of distress, interest, strength, alertness, and nervousness has experienced any shifts in their experience of the stimuli compared to acquisition. An additional statement as simple as “It wasn’t as bad as I thought it would be,” combined with a multiple choice question asking participants to check all experiences that apply would help be more confident be able to say this person learned something new during extinction. Clinically, it is common to use a combination of distress ratings and client dialogue to gauge session outcome and to guide in identifying where a given exposure session needs adjustment. In experimental work, getting a more open-ended statement

from participants at the end of follow-up would fit well with translational efforts. That said, it will be very useful to see how different patterns of extinction are related or unrelated to intrusive memory distress after extinction, and how these patterns compare to no intervention following acquisition.

It would also be useful to gather additional between-session data on memory retrieval processes, given that retrieval strength of memories can change each time a memory is retrieved (Bjork & Bjork, 1992). Though the current study design assessed *involuntary* retrieval between acquisition and extinction and in the 24 hr after extinction, voluntary retrieval was not assessed, nor was information about appraisals of intrusive memories, which very likely affect further retrieval of an intrusive memory (e.g., Williams & Moulds, 2008; Halligan, Michael, Clark, & Ehlers, 2002). Future work could also consider manipulation of prediction error, given that expectancy violation appears to be a key part of the new learning process that occurs during extinction, and also because it is a boundary condition for reconsolidation to occur (i.e., modification of original memory) (e.g., Beckers & Kindt, 2017). Additional extinction trials may be required in order for distress to decrease.

With such a small sample size, minimal clinical implications can be gleaned at this point in time. Nevertheless, some of the patterns and preliminary data observed so far suggest a couple of tentative clinical implications when considered in conjunction with prior findings. It is possible that the assessment only condition may fare similarly to the extinction conditions at the 72 hr assessment time point, which reinforces the common observation that intrusive memories are indeed normal phenomena that often diminish naturally over time (e.g., McFarlane, 1988; Shalev, 1992). This could have implications for individuals seeking treatment in the acute aftermath of a traumatic event, when psychoeducation and normalization rather than intervention

to decrease intrusive memories are thought to be the key components needed to decrease an individual's distress during that stage (Shalev, 2002). There are also tentative implications for assessing multiple facets of intrusive memories; if particularly distressing images or moments that come to a client's mind can be identified, we can make more informed decisions about where exposure sessions need to focus on intrusive memory distress is critical in distinguishing psychopathology from more typical human experiences. **What is the implication then? Spell out. Does it change what memories we focus on, does it change what we already pay clinical attention to?**

General Discussion

Research in understanding how memory reconsolidation may be advantageous in clinical settings has taken off in the past decade (e.g., Auber et al., 2013; Beckers & Kindt, 2017; Drexler & Wolf, 2018; Fernandez et al., 2018; Kredlow et al., 2016; Lee et al., 2017; Treanor et al., 2017). Findings from many of the animal studies examining post-retrieval interventions that could lead to adaptive changes in the retrieved memory were promising (e.g., Clem & Huganir, 2010; Monfils et al., 2009; Nader et al., 2000; Rao-Ruiz et al., 2011). Further, the idea that such a simple manipulation (i.e., memory destabilization plus modification within a particular timeframe) could potentially lead to meaningful changes in how a fearful memory is restored to long-term memory is for obvious reasons quite attractive. As the field matures, however, it has become somewhat "stuck" in how to move forward toward clinical translation of reconsolidation processes; and perhaps more importantly, there is not a clear sense of whether memory reconsolidation can in fact translate to complex fear memories that are multisensory, overgeneralized, and highly distressing. The title of a recently published review article sums up the state of current research quite succinctly: "Behavioral disruption of memory reconsolidation:

From bench to bedside and back again” (Drexler & Wolf, 2018). As a field, the possibility of clinical implications based predominantly on rodent research that emerged in the early 2000’s, and several studies thereafter begun to examine reconsolidation in clinical settings (e.g., Brunet et al., 2008; Soeter & Kindt, 2015), despite the ongoing struggle in defining the many nuances of reconsolidation and the specific conditions required in order for new learning within the reconsolidation window to be enhanced.

It is perhaps this quest for boundary condition criteria that keeps the field spinning in place, given that for every study where a particular boundary condition is illustrated, contradictory findings of that same boundary condition also exist (e.g., Beckers & Kindt, 2017; Fernandez, Bavassi, Forcato, & Pedreira, 2016). It is also quite possible that many researchers continue to look back to several of the early studies examining extinction learning as momentum in the field was building (e.g., Clem & Haganir, 2010; Monfils et al., 2009; Rao-Ruiz et al., 2011), without fully accounting for the studies that have struggled to find effects. This is to a certain extent with good reason, as Schiller and colleagues’ (2010) data suggesting that post-retrieval extinction effects showed retention of updating one year after extinction occurred is clearly compelling. At the same time, there have been over ten reviews summarizing memory reconsolidation over the past five years alone describing an increasing number of nuances involved in boundary conditions of reconsolidation without clear directions as to how this phenomenon can be engaged in clinical settings (e.g., Auber et al., 2013; Beckers & Kindt, 2017; Drexler & Wolf, 2018; Elsey & Kindt, 2017; Exton-McGuinness et al., 2015; Fernandez et al., 2017; Kredlow et al., 2016; Lee et al., 2017; Merlo, Milton, & Everitt, 2015; Otis et al., 2015; Schwabe, Nader, & Pruessner, 2014; Treanor et al., 2017).

Future research should work hard to focus on boundary conditions that are controllable and modifiable in a clinical setting. For example, the age of a memory once an individual presents for treatment is not changeable. Similarly, initial memory storage strength is not modifiable; once a memory is fully encoded and consolidated, storage strength is thought to be permanent (Bjork & Bjork, 1992). However, boundary conditions such as new learning that violates one's expectancies, characteristics of the retrieval cue such as context specificity (e.g., Besnard, 2012; Chan et al., 2010), and the frequency of memory retrieval (e.g., Wichert, Wolf, & Schwabe, 2013) are posited boundary conditions that are at least somewhat more able to be controlled. In addition to emphasizing boundary conditions that have some degree of practical clinical applicability, it is important to continue using more ecologically valid paradigms like the ones here and those of Kunze and colleagues (2015) and Soeter and Kindt (2015) and to extend such paradigms to clinical samples. This is particularly critical given that individuals with psychopathology differ from healthy individuals in experimental fear learning paradigms, demonstrating delayed extinction and stronger fear expectancy (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007), larger psychophysiological responses to fear stimuli (e.g., Orr et al., 2000), and distinct deficiencies in neurological responding during fear extinction (e.g., Bremner et al., 2005). These differences may become all the more pronounced as paradigms shift to be more trauma-relevant. Just as fear learning paradigms in rodents likely engage processes distinct from processes engaged when fear is consciously elicited in human fear learning paradigms (LeDoux, 2014), distinct processes of action in psychopathology, specifically in anxiety and stressor-related disorders, may require unique boundary conditions in order to effectively harness reconsolidation processes to reduce fear and anxiety-based suffering.

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Table 1. *Participant characteristics (N = 173)*

<u>Demographics/Psychopathology</u>	<u>M (SD) or Percentage (%)</u>	<u>Range</u>
Age (years)	19.27 (1.66)	18 - 35
Gender (% female)	56.6	
Race (% Caucasian)	35.3	
Ethnicity (% Non-Hispanic or Latino)	90.2	
Criterion A exposure (PDS-5) (%)	36.4	
PTSD severity (PDS-5) (<i>n</i> = 62)	8.63 (8.78)	0 - 44
Depression (BDI-II)	16.90 (12.47)	1 - 59
Trait anxiety (STAI-T)	42.39 (11.37)	20 – 77

Note. PDS-5 = Posttraumatic Diagnostic Scale; BDI-II = Beck Depression Inventory; STAI-T = State Trait Anxiety Inventory

Table 2. *Descriptive statistics of primary dependent variables by condition.*

	<u>24 hr Intrusions <i>M (SD)</i></u>		<u>72 hr Intrusions <i>M (SD)</i></u>	
	<u>Total #</u>	<u>Max Distress</u>	<u>Total #</u>	<u>Max Distress</u>
Pre Neutral CS (<i>n</i> = 56)	1.75 (<i>1.86</i>)	2.46 (<i>1.60</i>)	0.96 (<i>1.57</i>)	2.11 (<i>1.53</i>)
Pre Negative CS (<i>n</i> = 39)	1.26 (<i>1.62</i>)	2.45 (<i>1.57</i>)	1.31 (<i>1.63</i>)	1.94 (<i>1.45</i>)
Pre Scrambled (<i>n</i> = 36)	1.75 (<i>1.65</i>)	2.82 (<i>1.10</i>)	1.24 (<i>1.83</i>)	2.07 (<i>1.41</i>)
Delayed Neutral CS (<i>n</i> = 42)	2.14 (<i>1.98</i>)	2.31 (<i>1.35</i>)	1.00 (<i>1.41</i>)	1.85 (<i>1.32</i>)

Note. Raw means and standard deviations are reported.

Table 3. Sex and sAA output (AUCg) predicting maximum intrusive memory distress 24 hr after acquisition.

	<u>B</u>	<u>SE</u>	<u>B</u>	<u>t</u>	<u>p</u>
sex	-.43	.13	-.30	-3.41	.001
cort	.002	.001	.13	1.45	.15
sAA	-5.39E-5	.000	-.18	-1.93	.06
cort*sAA	7.00E-8	.000	.03	.28	.78
sex*cort	.000	.001	-.01	-.10	.92
sex*sAA	2.52E-5	.000	.08	.90	.37
sex*cort*sAA	2.55E-7	.000	.11	1.01	.32

Note. Overall, $F(7, 113) = 3.22, p = .004$. Cort = cortisol; sAA = salivary alpha amylase; sex coded as -1 = female, 1 = male.

Table 4. *Sex predicting maximum intrusive memory distress 24 hr after acquisition.*

	<u>B</u>	<u>SE</u>	<u>B</u>	<u>t</u>	<u>p</u>
sex	-.44	.14	-.31	-3.24	.002
cort	.001	.003	.05	0.50	.62
sAA	.000	.000	-.15	-1.68	.10
cort*sAA	2.36E-6	.000	.15	1.42	.16
sex*cort	-.001	.003	-.02	-.24	.81
sex*sAA	1.16E-5	.000	.02	.19	.85
sex*cort*sAA	.000	.000	.03	.24	.81

Note. Overall, $F(7, 113) = 2.65$ $p = .02$. Cort = cortisol; sAA = salivary alpha amylase; sex coded as -1 = female, 1 = male.

Table 5. Increase in sAA and the interaction of increases in cortisol and sAA during acquisition predict intrusive memories 72 hr after acquisition.

	<u>B</u>	<u>SE</u>	<u>B</u>	<u>t</u>	<u>p</u>
sex	.14	.17	.07	.87	.39
cort	-.001	.004	-.02	-.23	.82
sAA	.000	.000	.23	2.66	.01
cort*sAA	5.87E-6	.000	.25	2.62	.01
sex*cort	-.003	.004	-.06	-.69	.49
sex*sAA	6.97E-5	.000	.07	.86	.39
sex*cort*sAA	1.92E-6	.000	.08	.86	.39

Note. Overall, $F(7, 135) = 2.34$ $p = .03$. Cort = cortisol; sAA = salivary alpha amylase; sex coded as -1 = female, 1 = male.

Table 6. *Day 2 cortisol and sAA magnitude of increase (AUCi) predict higher intrusive memories 72 hr after acquisition.*

	<u>B</u>	<u>SE</u>	<u>B</u>	<u>t</u>	<u>p</u>
sex	.08	.16	.04	.51	.61
cort	.009	.003	.28	2.88	.01
sAA	.000	.000	.25	2.98	.01
cort*sAA	2.59E-6	.000	.10	1.08	.28
sex*cort	.003	.003	.09	.94	.35
sex*sAA	1.87E-5	.000	.02	.23	.82
sex*cort*sAA	2.95E-6	.000	.11	1.24	.22

Note. Overall, $F(7, 141) = 3.62, p = .001$. Cort = cortisol; sAA = salivary alpha amylase; sex coded as -1 = female, 1 = male.

Table 7. *sAA* magnitude of increase (*AUCi*) predicts higher maximum intrusive memory distress 72 hr after acquisition

	<u>B</u>	<u>SE</u>	<u>B</u>	<u>t</u>	<u>p</u>
sex	-.19	.15	-.13	-1.28	.20
cort	.004	.003	.16	1.26	.21
sAA	.000	.000	.27	2.63	.01
cort*sAA	-1.09E-6	.000	-.06	-.53	.60
sex*cort	.004	.003	.16	1.28	.20
sex*sAA	.000	.000	.16	1.57	.12
sex*cort*sAA	3.50E-7	.000	.02	.17	.87

Note. Overall, $F(7, 96) = 2.19, p = .04$; Cond = cue condition, cort = cortisol; sAA = salivary alpha amylase; sex coded as -1 = female, 1 = male.

Table 8. *Correlation table of baseline demographics, psychopathology, and intrusive memories (N = 173).*

	1	2	3	4	5	6	7	8	9	10	11	12
1. Age	--											
2. Sex	-.06	--										
3. Race	.04	-.00	--									
4. Ethnicity	.00	.08	.35	--								
5. Crit A exposure	.17	.01	.07	.10	--							
6. PTSD severity (PDS-5)	.00	.12	.18	.01	.00	--						
7. Depression severity (BDI-II)	.02	.13	-.04	.10	.21	.49	--					
8. Trait anxiety (STAI-T)	.05	.12	-.11	.09	.15	.55	.77	--				
9. Subjective Use of Imagery Scale (SUIS)	-.05	.24	.05	-.06	-.05	.26	.17	.10	--			
10. Day 1 total intrusions	.13	.01	-.10	-.01	.10	.17	.18	.16	.06	--		
11. Day 2 total intrusions	.02	-.02	-.15	.01	-.03	.07	.05	.11	.06	.21	--	
12. Day 1 max distress	.12	.26	-.25	.02	.08	.07	.20	.29	-.04	.50	.18	--
13. Day 2 max distress	-.01	.12	-.30	.02	.05	.20	.12	.23	-.03	.34	.41	.61

Note. PDS-5 = Posttraumatic Diagnostic Scale; BDI-II = Beck Depression Inventory; STAI-T = State Trait Anxiety Inventory- Trait Version.

Table 9. Correlation table of peri-film, post-film factors, and intrusive memories ($N = 173$)

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Day 1 peak SUDs	--												
2. Data-driven processing (TFQ)	.34	--											
3. Conceptual processing (TFQ)	-.09	-.27	--										
4. Positive affect (PANAS)	.27	.07	.18	--									
5. Negative affect (PANAS)	.67	.34	-.06	.32	--								
6. Day 1 intrusions	.11	.01	-.01	.04	.20	--							
7. Day 1 max intrusion distress	.54	.33	-.24	.25	.59	.49	--						
8. Day 2 peak SUDs	.46	.29	-.16	.21	.46	.01	.50	--					
9. Day 2 data-driven (TFQ)	.34	.57	-.24	.14	.31	.01	.48	.46	--				
10. Day 2 conceptual (TFQ)	.08	-.07	.21	.15	.02	.05	.05	.00	-.04	--			
11. Day 2 positive affect (PANAS)	.05	-.04	-.04	.35	.01	-.04	.13	.26	.22	.26	--		
12. Day 2 negative affect (PANAS)	.35	.34	-.21	.23	.50	-.01	.50	.76	.60	-.01	.43	--	
13. Day 2 intrusions	.11	.06	.03	.12	.25	.21	.18	.23	.04	.04	.14	.10	--
13. Day 2 max intrusion distress	.42	.32	-.18	.21	.50	.34	.61	.50	.34	-.04	.08	.43	.41

Note. SUDs = Subjective Units of Distress Scale; TFQ = Thoughts and Feelings Questionnaire; PANAS = Positive and Negative Affect Scale.

Table 10. *Participant characteristics (N = 14)*

<u>Demographics</u>	<u>M (SD) or Percentage (%)</u>	<u>Range</u>
Age (years)	34.00 (13.61)	19 - 61
Gender (% female)	50.0%	
Race (% Caucasian)	73.3	
Ethnicity (% Non-Hispanic or Latino)	86.7	
Education (years)	15.47 (4.29)	12 – 29
Index Trauma Type		
Sexual assault	35.7	
Physical assault	21.4	
Childhood sexual assault	14.3	
Car accident	7.1	
Combat exposure	7.1	
Other	7.1	
Freq of other trauma exposure	2.86 (2.11)	

Table 11. *Baseline psychopathology in clinical sample (N = 11)*

Psychopathology	<i>M (SD)</i> or Percentage (%)	Range
Diagnoses		
PTSD	27.3%	
MDD	9.1%	
Both PTSD & MDD	63.6%	
PSSI-5		
Re-experiencing	6.25 (1.36)	0 – 20
Avoidance	3.92 (1.38)	0 – 8
Negative mood/cognition	10.58 (4.87)	0 – 28
Arousal	8.92 (4.25)	0 – 24
Total score	29.67 (7.90)	0 - 80
QIDS total	11.75 (4.60)	0 – 27
STAI-T total	49.77 (13.64)	20 – 77
>2 Axis I diagnoses	50.0%	

Table 12. Means and standard deviations by group and condition.

	<u>24 hr Intrusions M (SD)</u>		<u>72 hr Intrusions M (SD)</u>	
	<u>Total #</u>	<u>Max Distress</u>	<u>Total #</u>	<u>Max Distress</u>
PTSD/MDD (<i>n</i> = 11)				
Image Extinction	3.50 (2.52)	3.75 (1.50)	3.25 (3.20)	3.25 (1.26)
Film Extinction	3.25 (2.99)	2.00	3.25 (3.06)	1.50 (0.58)
Assessment Only	5.00 (3.00)	(1.00)	3.33 (1.16)	2.67 (0.58)
Control (<i>n</i> = 3)				
Image Extinction	0	--	0	--
Film Extinction	3.00	4.00	6.00	3.00
Assessment Only	0	--	0	--

Table 13. *Bivariate correlations of baseline psychopathology and intrusive memory variables.*

	1	2	3	4	5	6	7
1. Re-experiencing (PSSI5 subscale)	--						
2. PTSD severity (PSSI-5 total)	.85	--					
3. Depression severity (QIDS)	.78	.84	--				
4. Trait anxiety (STAI-T)	.19	.42	.56	--			
5. 24 hr intrusion freq	.65	.43	.51	-.14	--		
6. 24 hr intrusion max distress	-.09	-.06	.20	-.11	.39	--	
7. 72 hr intrusion freq	.16	.03	.10	-.41	.44	.45	--
8. 72 hr intrusion max distress	-.20	-.06	.15	-.28	.38	.85	.34

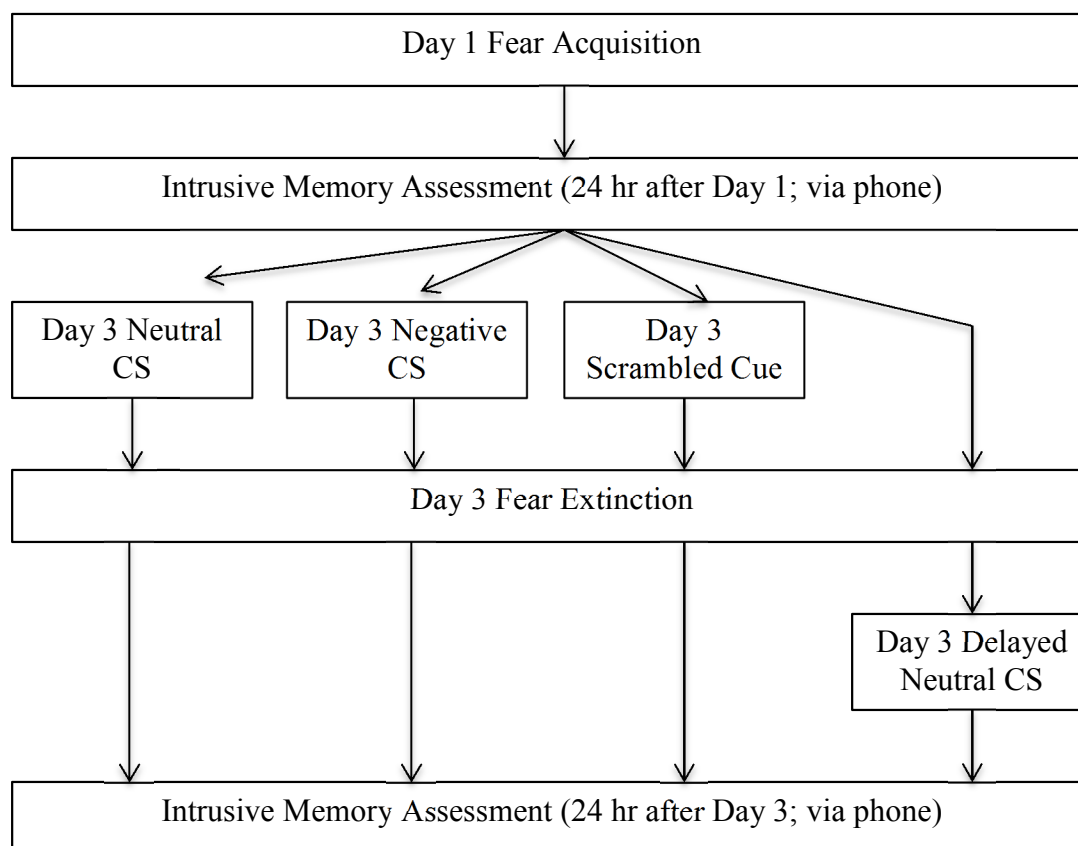
Figure 1. *Study 1 flow diagram*

Figure 2. *Effect of cue condition on number of intrusive memories 24 hr after extinction.*

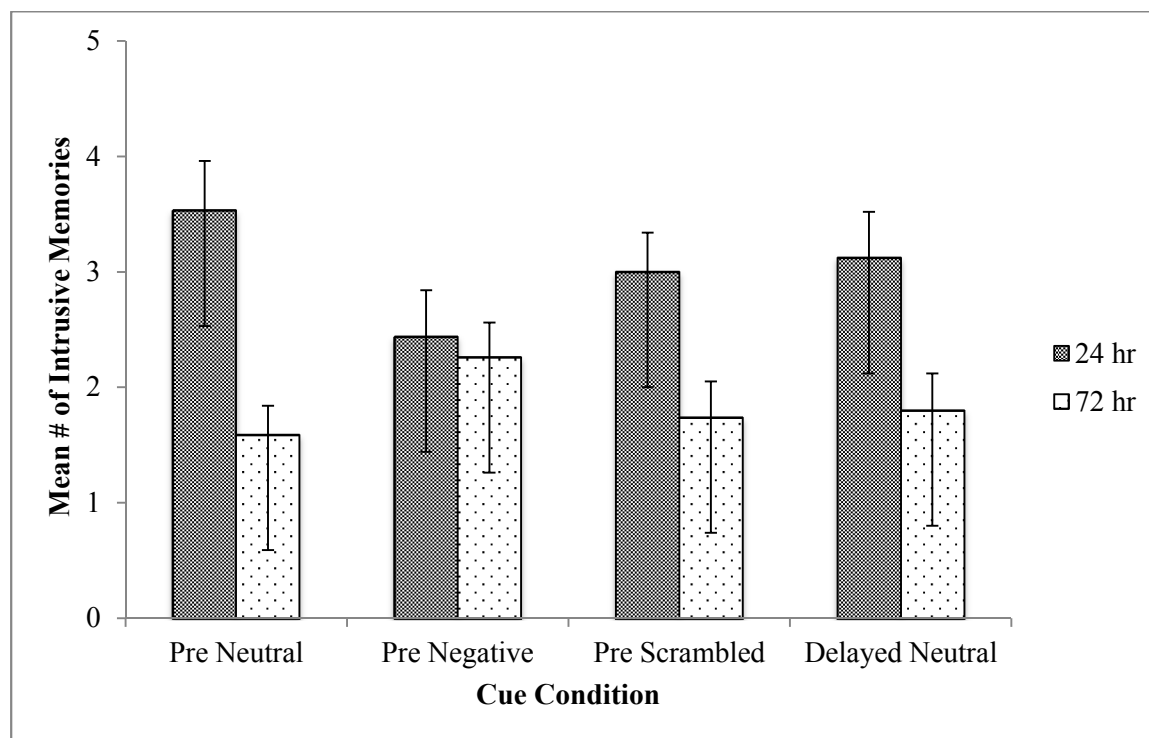


Figure 3. *Effect of cue condition maximum intrusive memory distress 24 hr after extinction.*

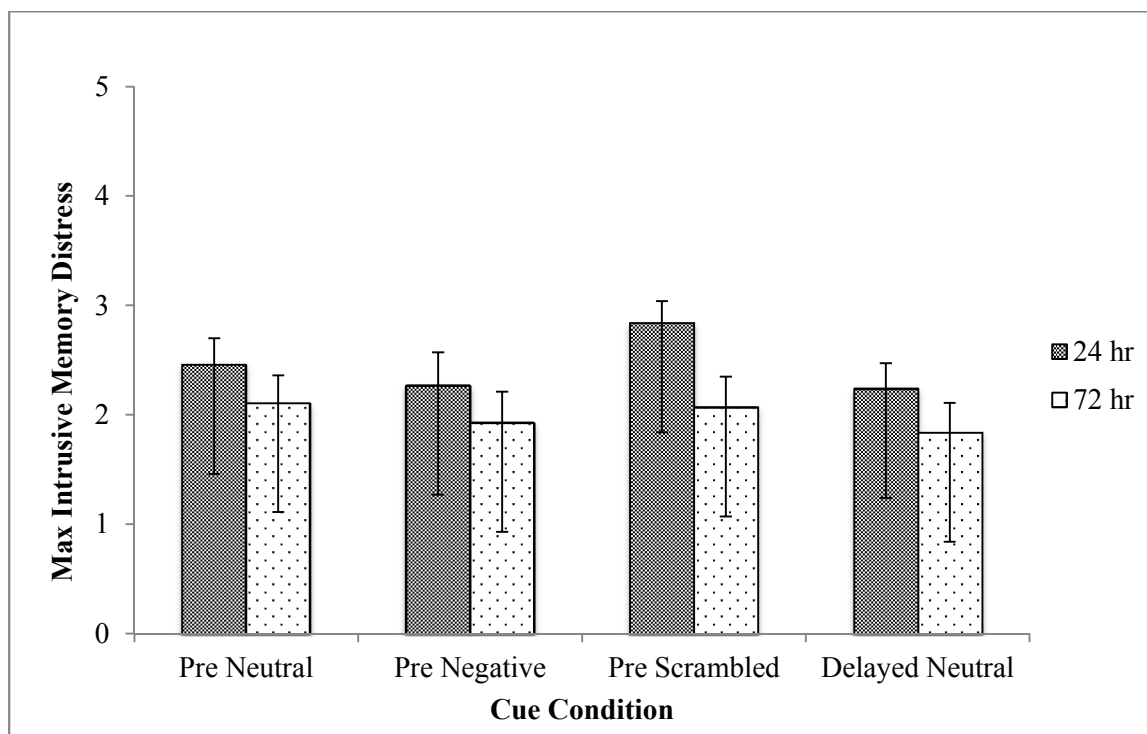


Figure 4. Sex but not cortisol or sAA output (AUCg) variables predicts intrusive memory distress 24 hr after acquisition.

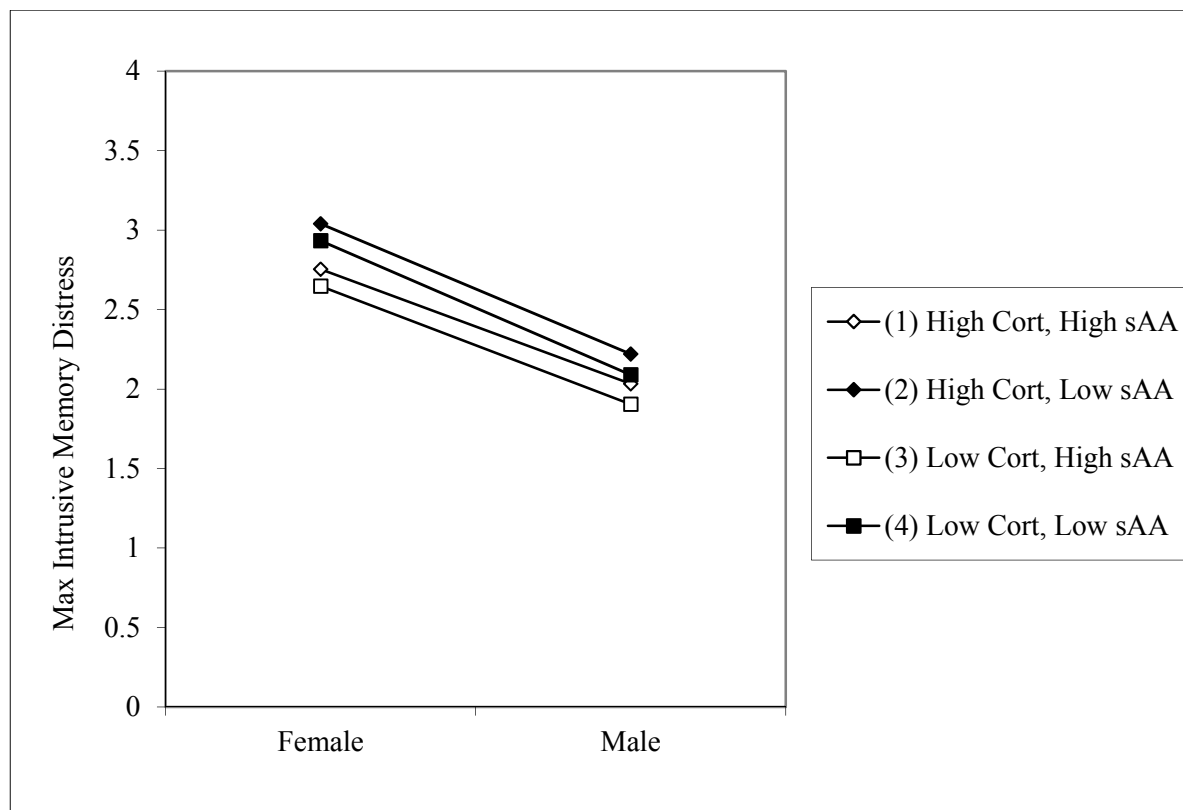


Figure 5. Sex but not increases in cortisol or sAA (AUCi) variables predicts intrusive memory distress 24 hr after acquisition.

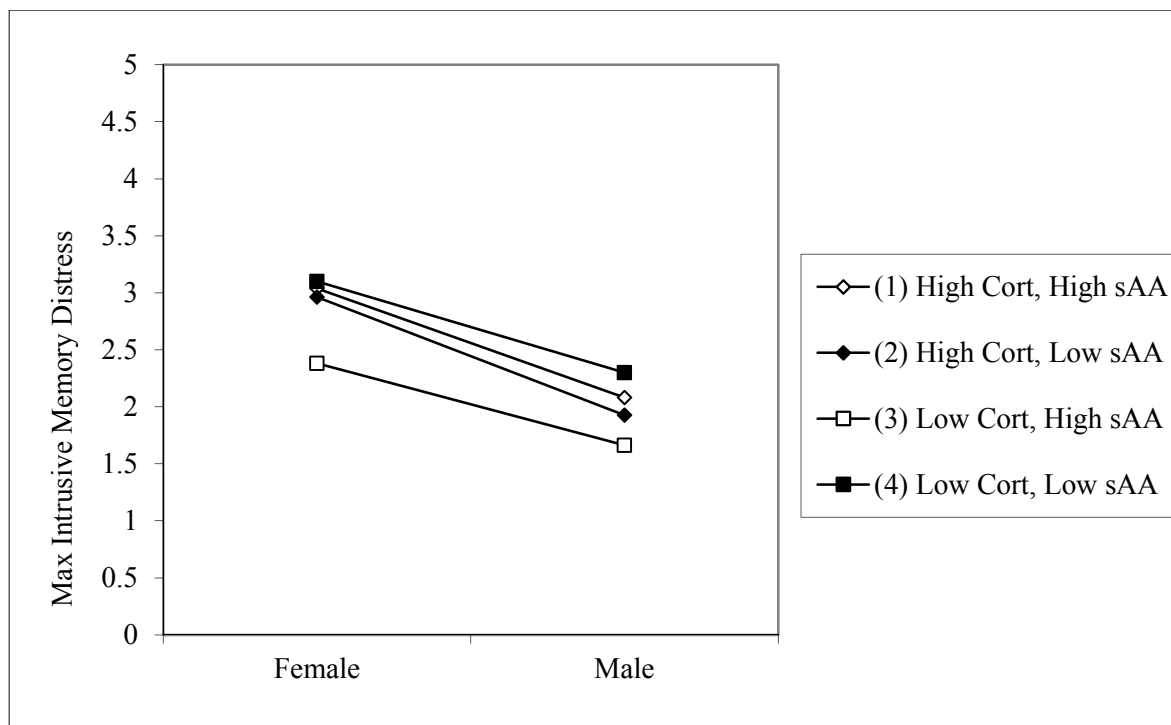


Figure 6. Increase in cortisol and two-way interaction between increases in cortisol and sAA during acquisition predict intrusive memory frequency 72 hr post-acquisition

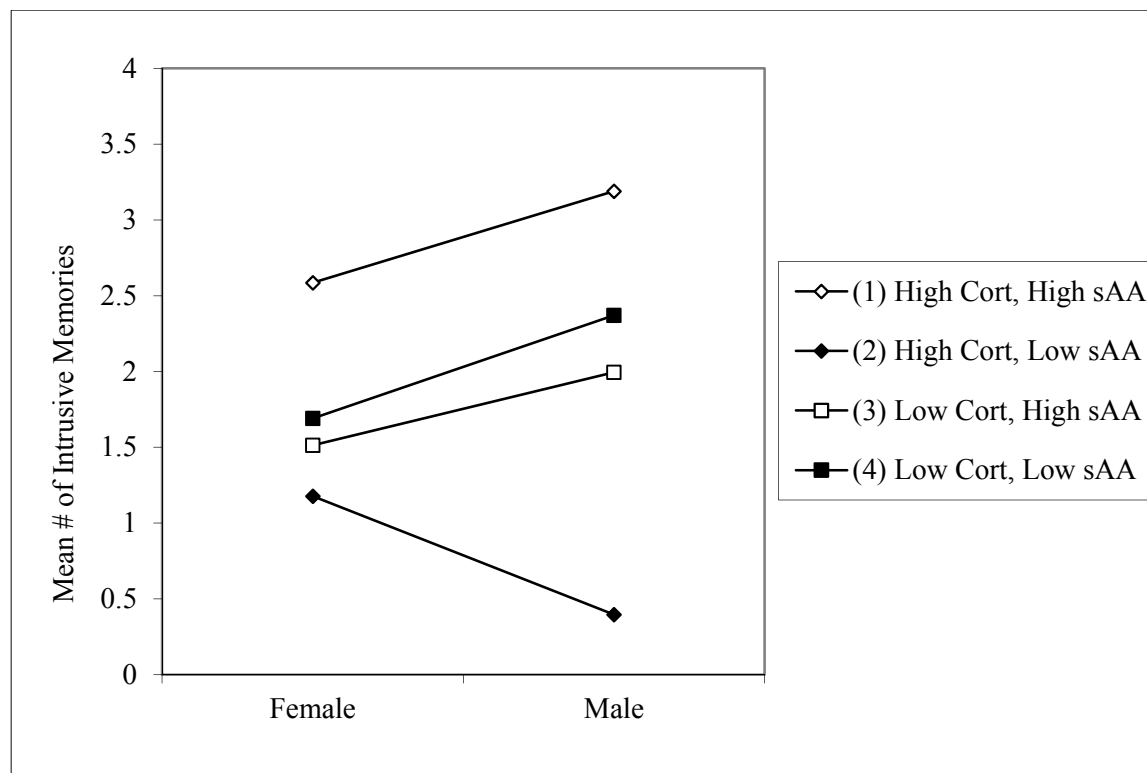


Figure 7. *Main effects of cortisol and sAA increases (AUCi) during extinction predict intrusive memory frequency 72 hr post-acquisition*

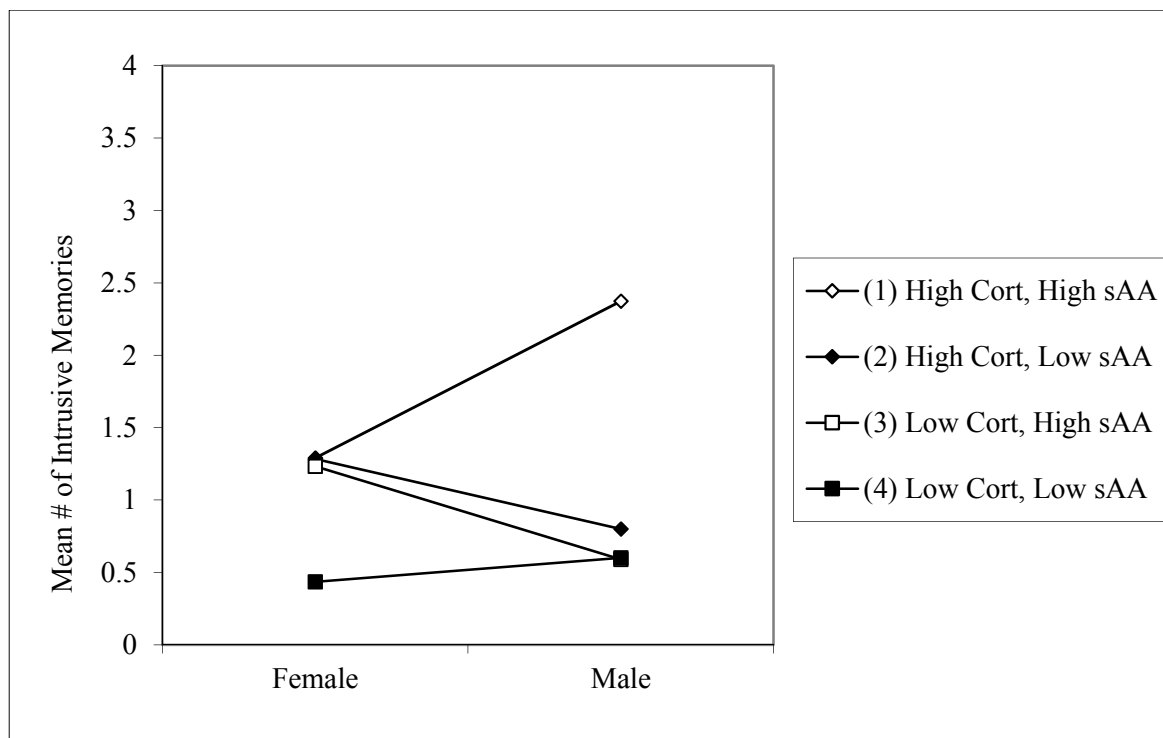


Figure 8. Increase in sAA during extinction (AUCi) predicts maximum intrusive memory distress 72 hr after acquisition.

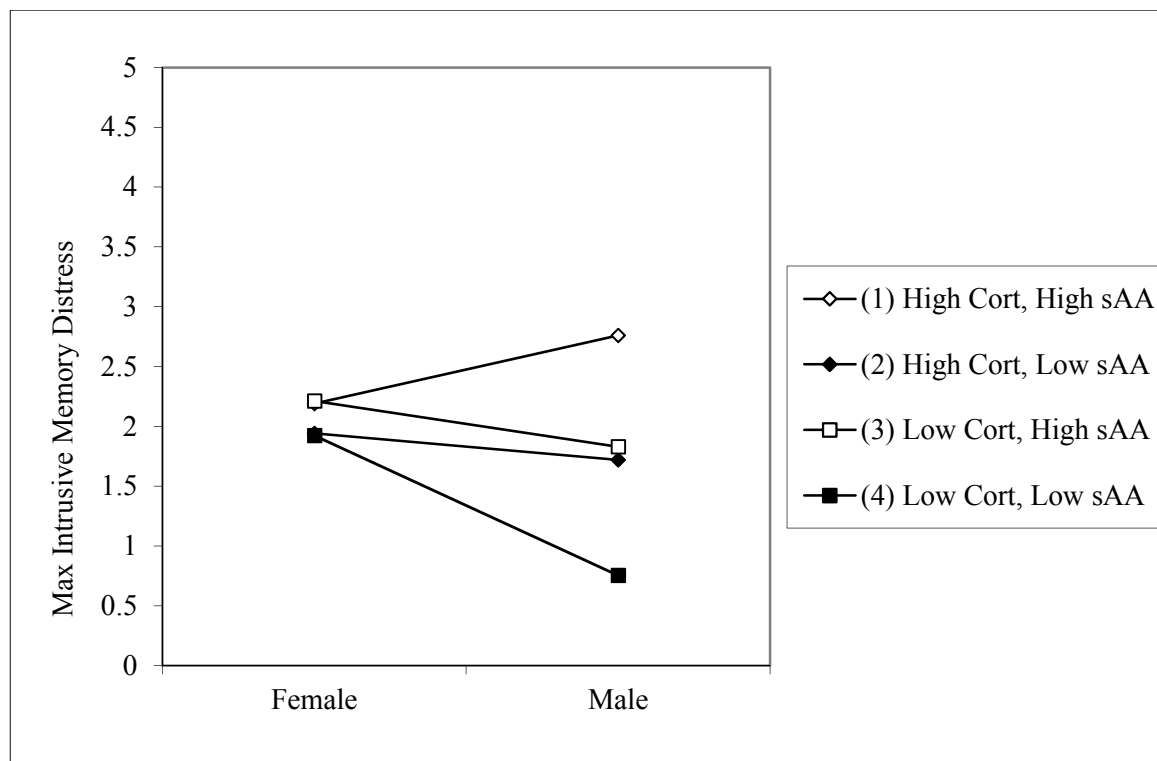
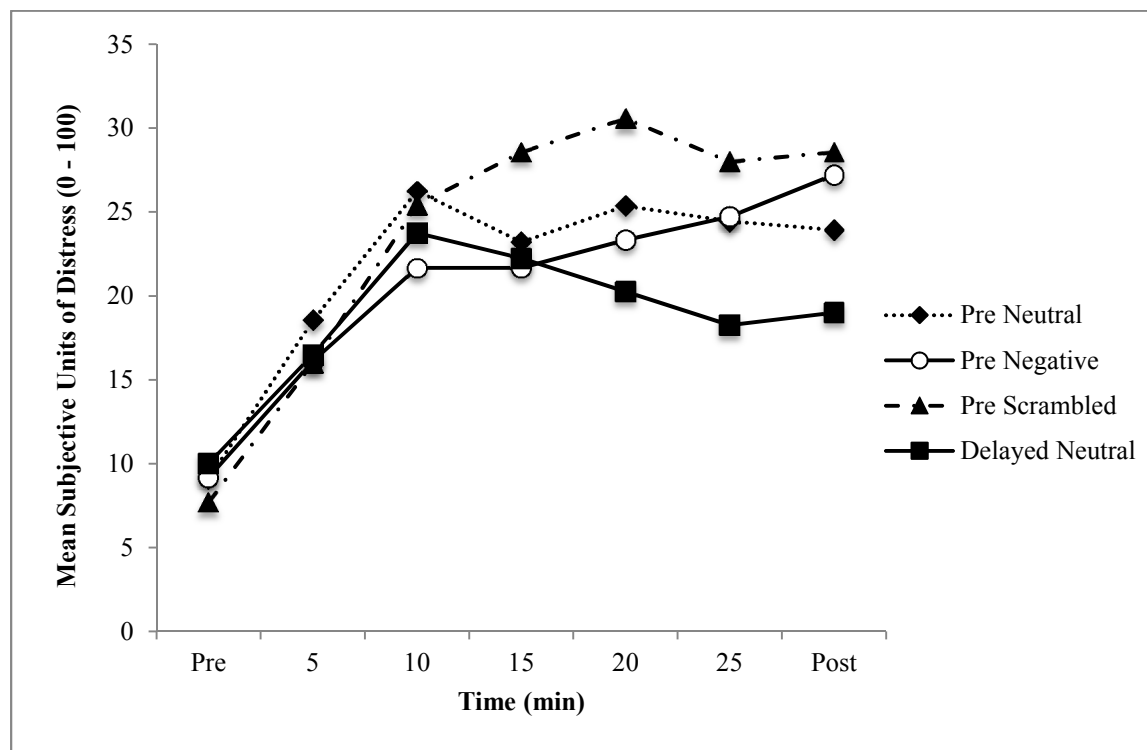


Figure 9. Trajectories of distress during extinction by cue condition.



Note. Raw means displayed here.

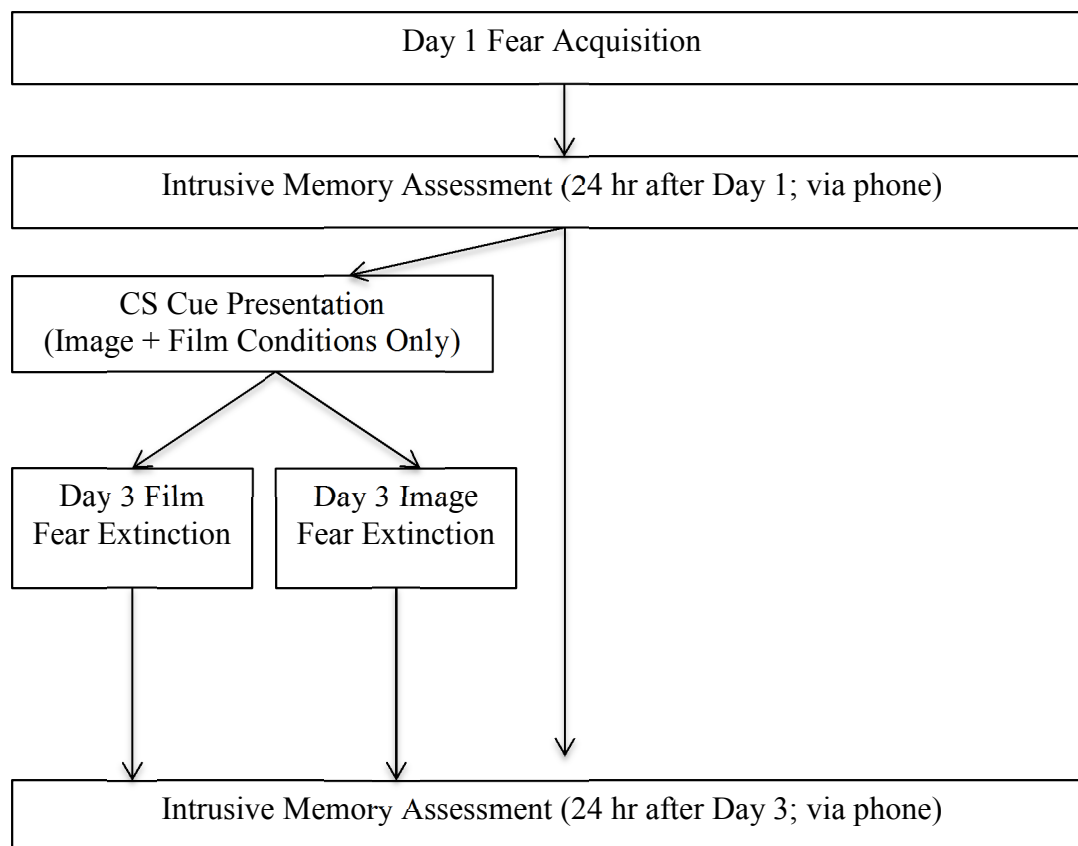
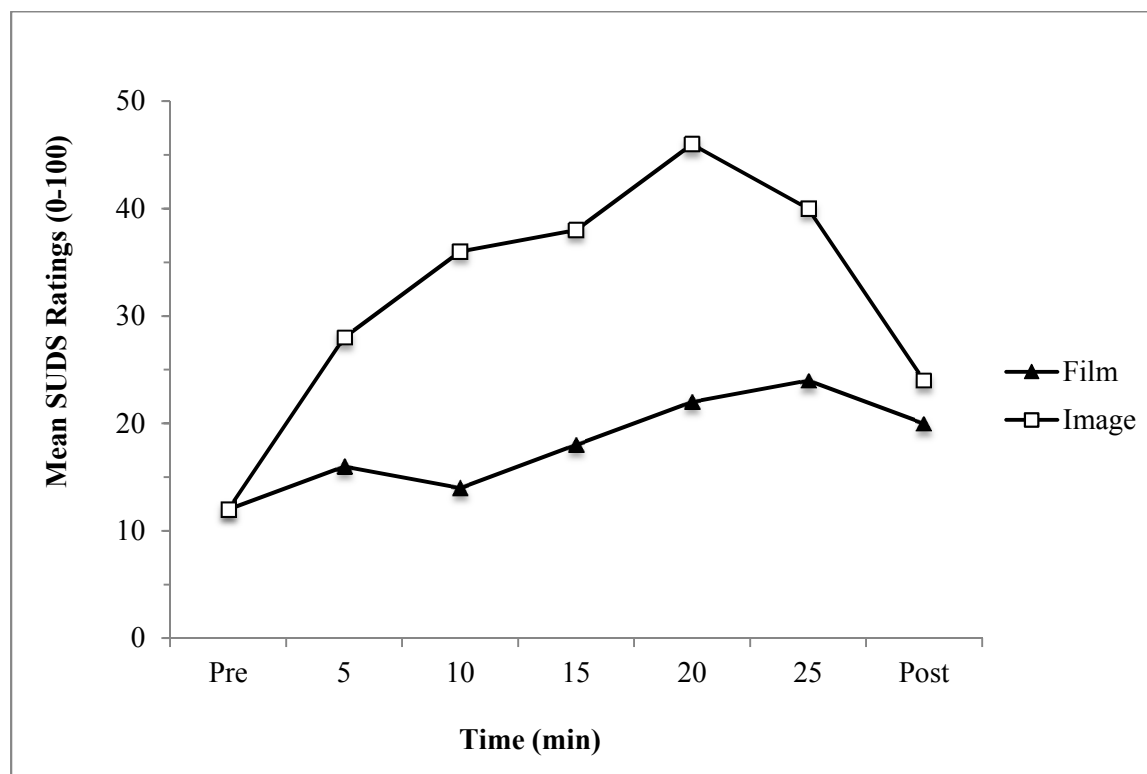
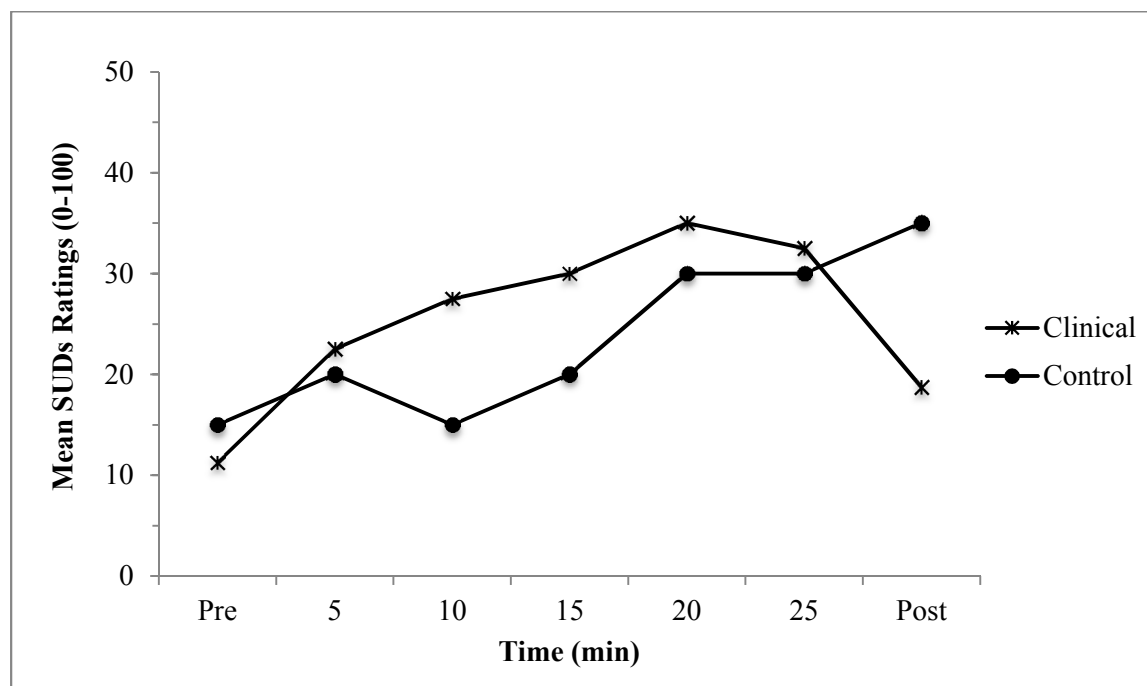
Figure 10. *Study 2 flow diagram.*

Figure 11. *Patterns of distress during extinction between image and film extinction conditions*



Note. Raw means displayed here.

Figure 12. *Patterns of distress during extinction between clinical and control participants.*



Note. Raw means displayed here.

Figure 13. *Differences in intrusive memory frequency 24 and 72 hrs after acquisition.*

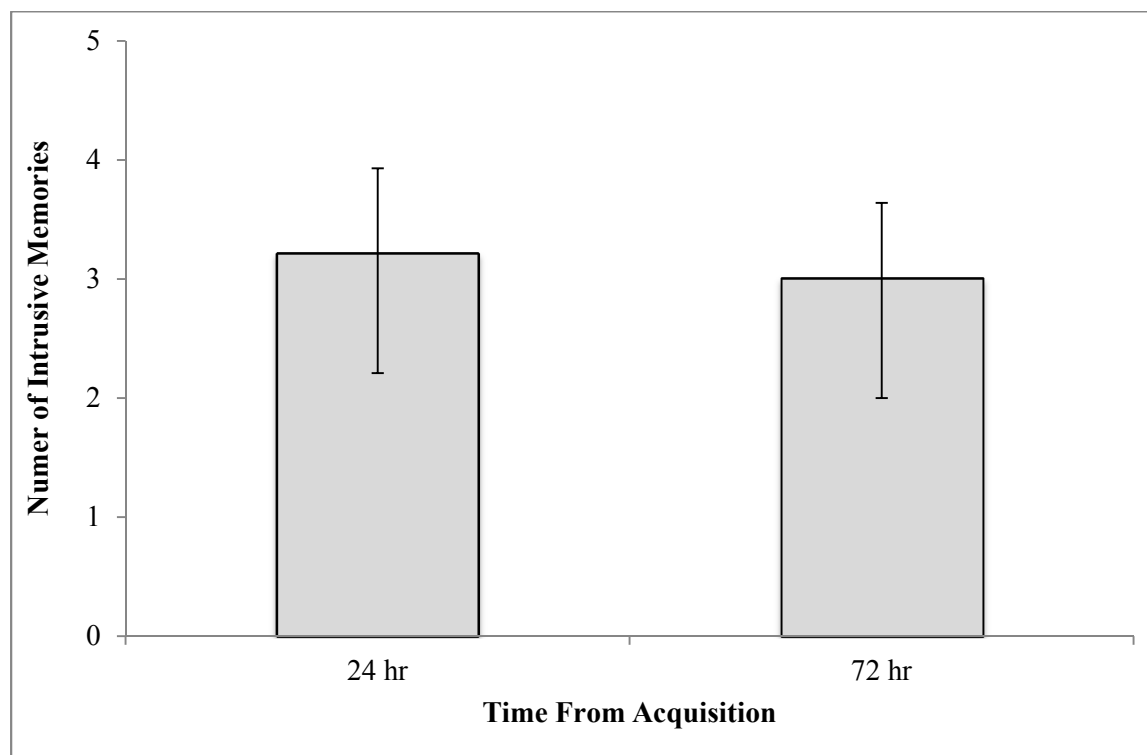


Figure 14. *Differences in maximum intrusive memory distress 24 and 72 hrs after acquisition.*

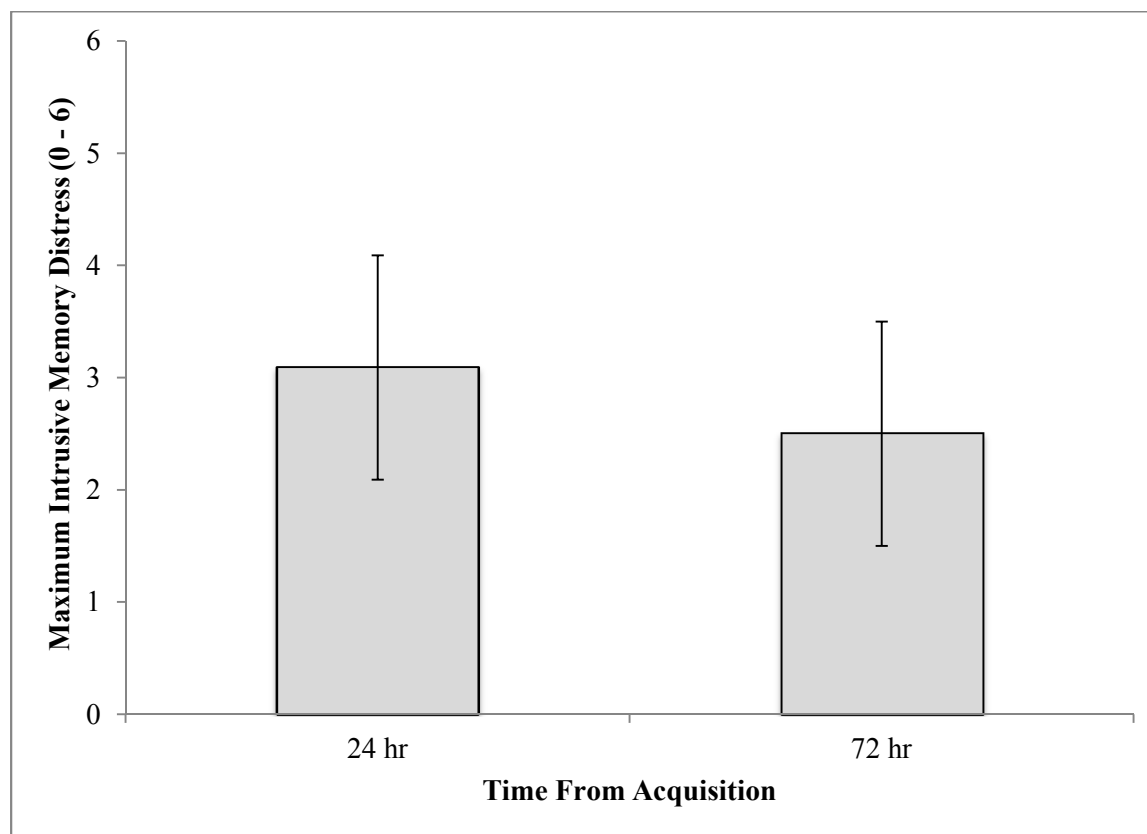


Figure 15. *Differences in intrusive memory frequency change between clinical and trauma-exposed control samples.*

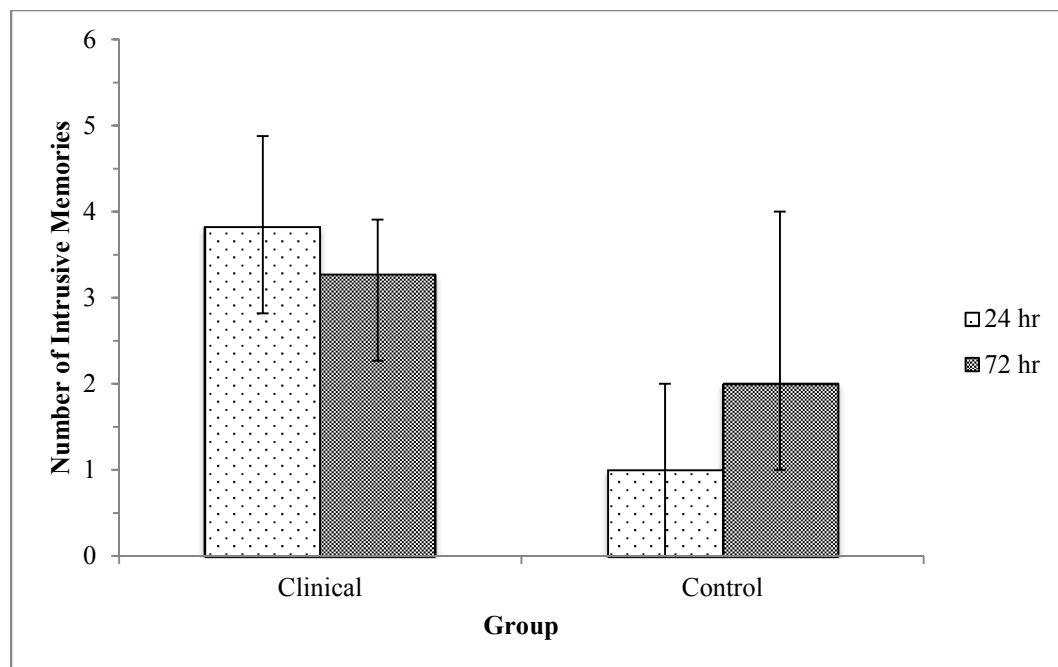


Figure 16. *Differences between extinction and assessment conditions in number of intrusive memories 72 hr after acquisition.*

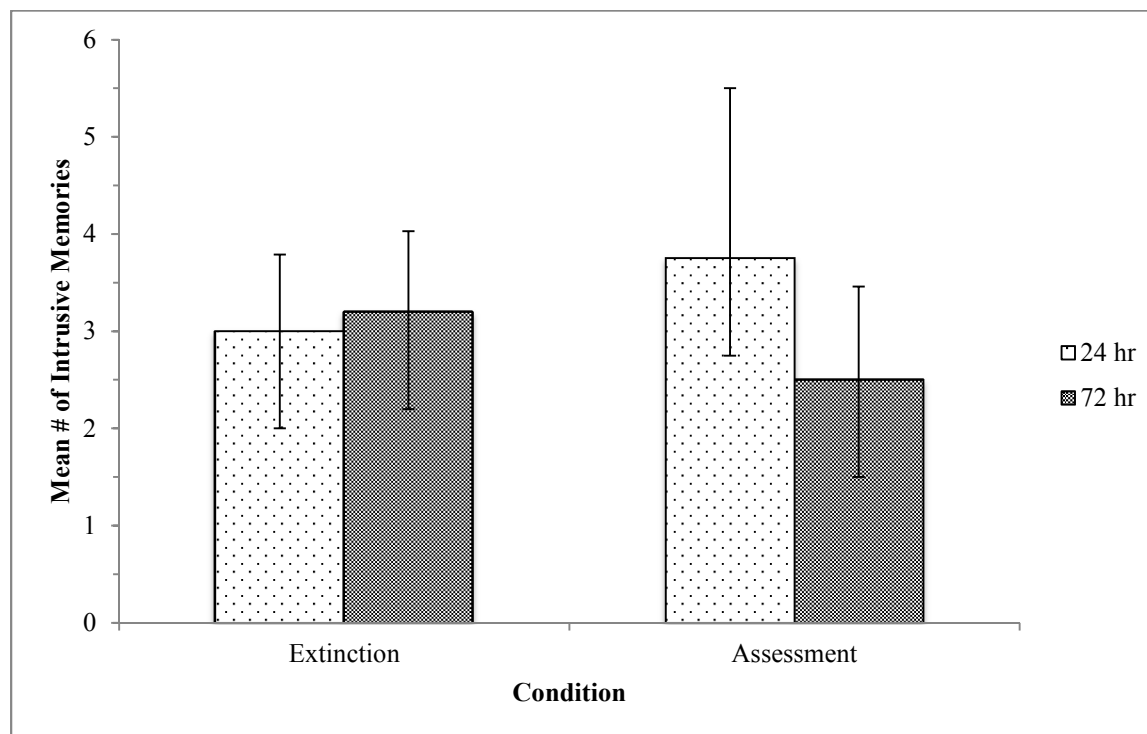


Figure 17. *Differences between extinction and assessment conditions in maximum intrusive memory distress 72 hr after acquisition.*

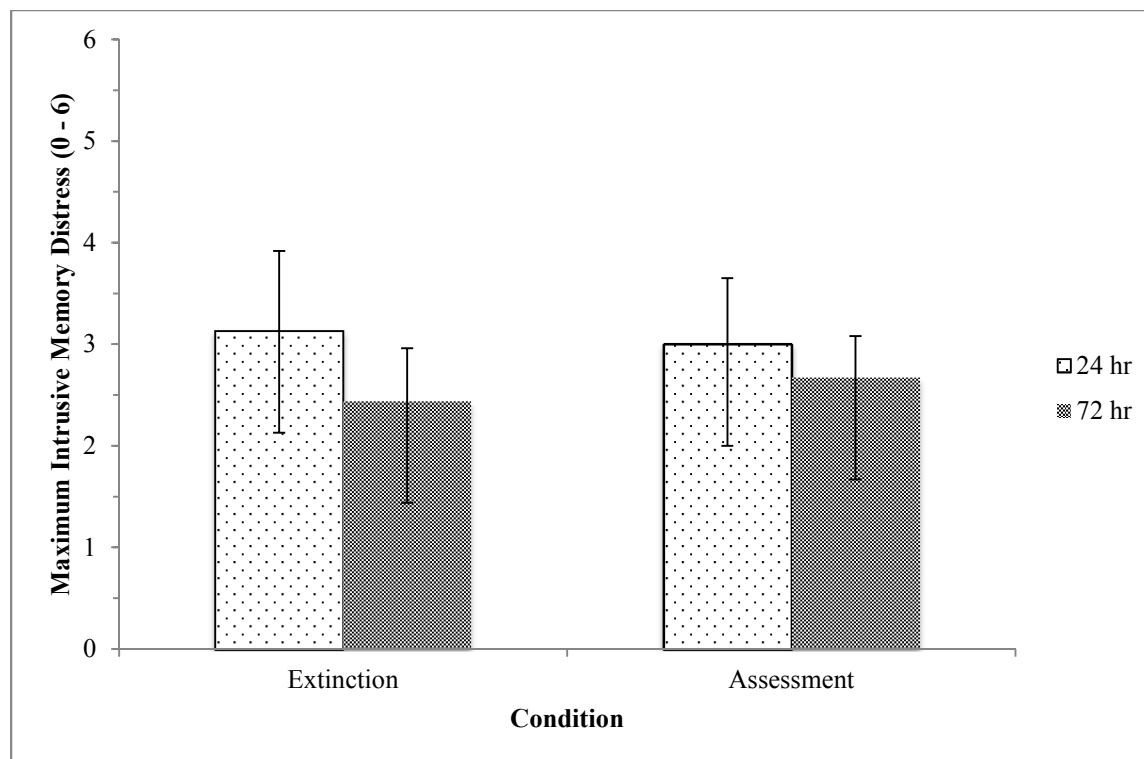


Figure 18. *Differences between extinction and assessment conditions in average intrusive memory distress 72 hr after acquisition.*

