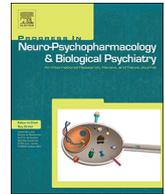




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The clinical applications and practical relevance of human conditioning paradigms for posttraumatic stress disorder

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ABSTRACT

The classical conditioning paradigm of fear learning has spawned a number of experimental variations for the explanation of posttraumatic stress disorder (PTSD) etiology. These paradigms include extinction learning and recall, fear inhibition, fear generalization, and conditioned avoidance. As such, each of these paradigms have significant applications for understanding the development, maintenance, treatment, and relapse of the fear-related features of PTSD. In the present review, we describe each of these conditioning-based paradigms with reference to the clinical applications, and supported by case examples from patients with severe PTSD symptoms. We also review the neurobiological models of conditioning and extinction in animals, psychiatrically healthy humans, and PTSD patients, and discuss the current balance of evidence suggesting a number of biological, behavioral, and cognitive mechanisms/moderators of the conditioning and extinction process in experimental and clinical contexts.

1. Introduction

As many as 70% of the population may experience a traumatic event at some point in their lifetime (Resnick et al., 1993), and a small subset of these individuals will go on to develop symptoms of posttraumatic stress disorder (PTSD). Studies in military samples show lifetime prevalence rates of 19% due to war-related trauma, and lifetime PTSD rates in civilians can vary dramatically by country and trauma type (Karam et al., 2014; Kessler et al., 1995), and can be as high as 15% (Kessler et al., 1995; Ramchand et al., 2010). PTSD can be a chronic and debilitating condition resulting in significantly reduced quality of life, and comorbidity with depression and substance abuse. Hallmark symptoms of the disorder typically include distressing intrusive memories, avoidance of trauma reminders, hyperarousal, and negative alterations in cognition and mood (DSM-5; American Psychiatric Association, 2013). A primary treatment technique for PTSD (as well as other anxiety disorders with specific triggers or cues) is prolonged exposure therapy. During exposure therapy, the client is repeatedly exposed to the feared stimulus or situation via a series of *in vivo* exposures or narrative/mental imagery-based tasks. This treatment technique largely draws on, and is influenced by, the mechanisms of fear conditioning

and extinction (Rothbaum and Davis, 2003; Yehuda et al., 2015b), based on Pavlov's (1927) classical conditioning theory. As the natural response to trauma exposure is recovery (Bryant, 2003), a current argument is that impairments in fear conditioning and extinction processes contribute to the ongoing persistence or relapse of fear-related symptoms of PTSD (Briscone et al., 2014; Mineka and Oehlberg, 2008; Pitman et al., 2012; Zuj et al., 2016b). Indeed, a number of different conditioning paradigms have been developed over the past few decades that provide unique explanations for different clinical situations of posttraumatic stress.

Variations in fear conditioning paradigms (such as tests of extinction recall, generalization, and avoidance) all present unique translational explanations for the development, persistence, treatment, and relapse of the fear-related features of PTSD (Johnson et al., 2012; Zoladz and Diamond, 2013; Norrholm and Jovanovic, 2018). The current review describes the specific translational relevance of each of the various fear learning paradigms for clinical situations. Although these paradigms carry important implications for a number of psychiatric conditions, this review focuses on evidence from research in PTSD populations. To further highlight the clinical relevance of this field of experimental psychopathology, we illustrate the translational nature of

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many of these paradigms with anonymized real-world examples from clinical patients with PTSD.¹ The importance of conditioning paradigms for various clinical scenarios is highlighted by recent evidence of a correlation between fear extinction performance and the success of laboratory- and clinic-based treatment approaches (Ball et al., 2017; Forcadell et al., 2017; Waters and Pine, 2016), supporting the idea that extinction is a key process in exposure-based treatments for anxiety disorders (Pitman et al., 2012).

PTSD is a broad and dynamic condition, often characterized by considerable individual differences in symptom presentation. In addition to hallmark symptoms of intrusive memories, avoidance behaviors, and hyperarousal, PTSD can also be characterized by symptoms of anger (McHugh et al., 2012), emotional numbing (Felmingham et al., 2014), dissociation (Armour et al., 2014), and sleep disturbances (Germain, 2013). Although this review acknowledges the wide-range of symptoms that can present in PTSD, we will be focusing on the fear-related features of PTSD, and the critical relevance of experimental fear conditioning paradigms (Jovanovic and Norrholm, 2016). In doing so, we will begin with a brief review of the translational cortical models of fear processing from animal research to humans with and without anxiety disorders, followed by a discussion of conditioning paradigms and their relevance for PTSD development, treatment, and relapse. Finally, we conclude with a brief discussion of additional factors known to mediate/moderate the extinction process. Throughout this review, we provide anonymous reports from clients to illustrate the significance of each of these experimental paradigms for explaining PTSD symptomatology. This review is not aimed at identifying a ‘common practice’ for fear conditioning methodologies (for a thorough review of design considerations in human fear conditioning, see Lonsdorf et al., 2017), but is intended to highlight the relevance of fear conditioning paradigms for various clinical situations.

1.1. Fundamental concepts in fear conditioning and extinction

Fear conditioning and extinction is based on Pavlov’s (1927) classical conditioning theory of behavioral learning. This theory argues that a previously neutral stimulus becomes a conditioned stimulus (CS) through repeated pairings with an aversive event (e.g., a mild electric shock (Zeidan et al., 2012), or a sudden blast of air to the larynx (Norrholm et al., 2006)). Through association, the CS elicits a conditioned response (CR) in the absence of the unconditioned stimulus (US). Extinction occurs when this threat response subsides through repeated presentations of the CS in the absence of the US. Irrespective of the timing of extinction relative to conditioning, extinction does not appear to erase or override the conditioning memory (Archbold et al., 2010), but instead results in the formation of a new inhibitory memory to prevent the expression of the CS-US fear association (Bouton, 2002; Delamater, 2004; Myers and Davis, 2002). The conditioned response may, however, return due to certain environmental or contextual factors (e.g., unsignaled US presentations termed reinstatement; the passage of time termed spontaneous recovery). Consistent evidence shows fear extinction learning and/or memory to be impaired in individuals with PTSD (e.g., Blechert et al., 2007; Norrholm et al., 2015; Norrholm et al., 2011).

Conditioned fear responses are typically quantified by a variety of physiological and behavioral measures, among the most common of which are skin conductance response (SCR), acoustic startle, and self-reported US-expectancy ratings (Briscone et al., 2014). Skin conductance refers to the electrodermal activity of the sweat glands – a direct measure of sympathetic arousal (Boucsein, 1992). Studies have reliably found increased SCRs to the US-reinforced CS+ during fear

acquisition, compared to a second CS that is never reinforced, termed the CS- (e.g., Orr et al., 2000; Phelps et al., 2004; Zuj et al., 2016a). Alternatively, fear-potentiated startle (FPS), or the relative increase in the frequency or magnitude of the acoustic startle response in the presence of a cue (CS+) that has been paired with an aversive outcome (US), reflects an automatic behavioral startle response to aversive stimuli that is a widely used translational tool to model fear and anxiety (Davis, 1992; Jovanovic and Norrholm, 2016). Similar to SCR, considerable research has found FPS to reliably increase in relation to the CS+ as compared to a participant’s own baseline acoustic startle response and relative to the CS- (e.g., Glover et al., 2011; Guthrie and Bryant, 2006; Norrholm et al., 2015). Indeed, Guthrie and Bryant (2006) found increased pre-trauma startle responses during fear extinction to be a significant predictor of posttraumatic stress reactions in trainee firefighters. Fear-potentiated startle, rather than SCR, has also been argued to be a more useful translational tool for neuroscience due to clear cortical relationships with the amygdala (Davis and Whalen, 2001; Glover et al., 2011; Kindt and Soeter, 2013). It is important to note that psychophysiological based fear acquisition/extinction methods, including those discussed in the present review, have been identified by the United States National Institute of Mental Health (NIMH, 2016) Research Domain Criteria (RDoC) workgroup as a recommended negative valence system task paradigm for assessing acute fear.

In addition to SCR and FPS, self-report US-expectancy ratings are considered a valid measure of human fear extinction and threat expectancy (Boddez et al., 2013), and are widely used in conjunction with psychophysiological measures (Kindt and Soeter, 2013; Norrholm et al., 2011; Vervliet et al., 2007; Zuj et al., 2017b). Further, increased US-expectancy ratings during fear extinction in Dutch soldiers prior to deployment was found to be a significant predictor of PTSD symptoms post-deployment (Lommen et al., 2013). Studies have also shown different patterns of conditioning and extinction for different response measures. For example, Blechert et al. (2008) have found extinction learning to be very rapid in SCR amplitude data, and slower in US-expectancy ratings, suggesting a disparity between psychophysiological arousal and cognitive threat expectancy.

1.2. From rodents to humans: understanding the cortical networks of fear

Biological fear networks are remarkably translational, with initial animal research in rodents informing our understanding of the cortical fear networks in humans (for reviews, see Myers and Davis, 2007; Pitman et al., 2012). The amygdala is the premier subcortical structure in activating sympathetic threat systems (LeDoux, 2000), based on excitatory or inhibitory projections from prefrontal and hippocampal networks. In short, sensory recognition of environmental (or internal) threat activates two systems simultaneously. Threat is recognized by cognitive pathways and subjectively labeled (and experienced) as fear, while efferent cortical projections from the amygdala increase arousal in biological and physiological systems required for a response to the threat (LeDoux and Brown, 2017). An important discussion relevant to this review has been raised by LeDoux (2014) with respect to the meaning of the term ‘fear’ as it applies to the processes of threat detection in lower mammals and the emotional state of fear in humans. For the sake of this review and to maintain consistency with the expansive corpus of literature in this area, we will use the overarching term ‘fear’ across the translational bridge of our discussions. While the amygdala is important in activating these biological and physiological systems, this is contingent on the information relayed from certain cortical and subcortical systems. Different neural structures play markedly different roles in the excitation or inhibition of the amygdala in various situations, and these relationships are summarized in Fig. 1.

Rodent research shows that the amygdala receives inhibitory projections from the infralimbic cortex based on understanding of CS-US contingencies, with increased infralimbic cortical activation associated

¹ Anonymous patient statements are provided by the authors through clinical encounters with previously traumatized individuals presenting with signs and symptoms of PTSD.

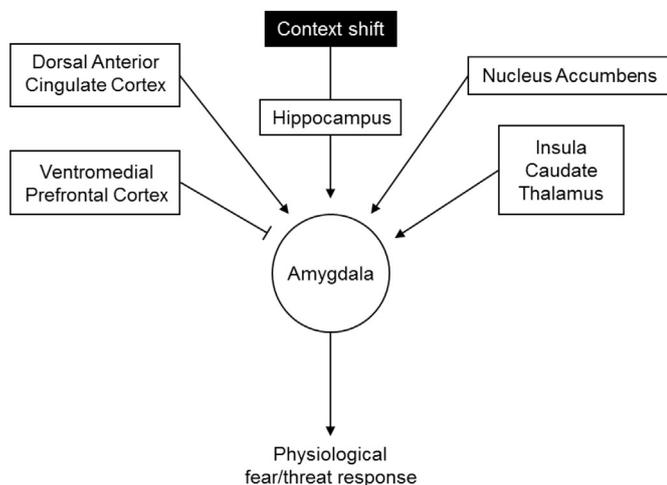


Fig. 1. Different conditioning paradigms also show unique variations in the neural pathways of fear expression. Greater discussion of corresponding fear-related behavioral and neural activity can be found in Myers and Davis (2007). Simply put, the amygdala is a central structure in the biological and physiological expression of fear, based on the incoming excitation/inhibition from various subcortical structures. Increased activation of the dorsal anterior cingulate cortex leads to excitation of the amygdala, and the expression of *conditioned fear* responses, while increased ventromedial prefrontal cortex activity inhibits the amygdala, which is a key network in *fear inhibition/extinction*. During *contextual* changes, such as a different environment to the therapeutic environment, increased activity in the hippocampus works to excite or inhibit the amygdala, and subsequent fear expression/inhibition. *Generalization* stimuli that are closely related to the CS- are associated with increased ventromedial prefrontal cortex activity to inhibit the amygdala, while generalization stimuli closely related to the CS+ are associated with greater activity in the insula, caudate nucleus, and the thalamus (reviewed in Dymond et al., 2015). Finally, *avoidance* behaviors are primarily associated with connections from the basal nucleus of the amygdala to the nucleus accumbens (LeDoux et al., 2017).

Box 1

Clinical vignette: Fear Acquisition.

John is a 33-year old, male U.S. Air Force veteran who was deployed to the Middle East three times as a flight support officer. Following his deployments, John remained on Active Duty serving at a stateside joint military installation for three years. As is common with many service members, John interacted with his colleagues both during their tours of duty and while off duty at various social events. A year after his military service ended, John came to the PTSD clinic with symptoms of PTSD and sought treatment for these symptoms as well as comorbid depression and alcohol abuse. During his initial assessment, John reported a significant traumatic event that occurred during the previous Christmas holiday season in which a friend and colleague had committed suicide by self-inflicted gunshot wound in John's presence at his friend's home. John reported significant distress and anxiety, both emotional and physical in nature, in the presence of sirens and flashing lights; posttraumatic sequelae that developed at the time of the traumatic event as John remained on the scene as first responders arrived and tended to his recently deceased friend and colleague. Exposure to sirens and flashing lights on police, fire, and rescue vehicles repeatedly evoked classical symptoms of panic and anxiety in John including racing heart, excessive perspiration, shallow, rapid breathing, as well as nausea and vomiting. In addition to these somatic features, John also found himself becoming emotionally upset with bouts of sadness and crying both during and in the immediate aftermath of exposure to sirens and flashing lights. Per John's report, these physical and emotional responses to cues related to emergency services subsided after he was removed from the situations for an extended period of time, often in the safety of his home.

with extinction learning (Barrett and Gonzalez-Lima, 2018) and extinction recall (Milad and Quirk, 2002). While extinction learning is associated with greater activation of inhibitory networks between the infralimbic cortex and basolateral amygdala, selective inhibition of this network impairs extinction learning (Bloodgood et al., 2018; Laurent and Westbrook, 2009; Milad and Quirk, 2002; Milad et al., 2004; Quirk et al., 2000). Alternatively, the prelimbic cortex acts in opposition to the infralimbic cortex, whereby greater activation is associated with greater conditioned responding and poorer extinction (Burgos-Robles et al., 2009; Fenton et al., 2014; Sierra-Mercado et al., 2011) which is specific for learned, but not innate threat responding (Corcoran and

Quirk, 2007). In addition, the hippocampus plays a crucial role in contextual processing, with lesion studies showing greater freezing in safe as well as dangerous contexts (reviewed in Maren et al., 2013).

Similarly in humans, the amygdala appears to play a key role in the excitation (or inhibition) of biological and physiological systems for threat responding (Cheng et al., 2006; Cheng et al., 2003; Cheng et al., 2007; Duvarci and Pare, 2014; Knight et al., 2004; LaBar et al., 1998; Morris and Dolan, 2004; Pare and Duvarci, 2012), with Sehlmeier et al. (2011) showing amygdala activity increasing towards the end of fear acquisition and then subsequently decreasing throughout extinction learning. These findings demonstrate the excitatory and inhibitory processes of the amygdala during threat responding and the extinction of threat responses. Further, the infralimbic and prelimbic cortices in rodents appear to be functionally analogous to the ventromedial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (dACC) in humans, respectively. Specifically, vmPFC activation inhibits amygdala projections and subsequent threat responding (Milad et al., 2006; Milad et al., 2007b; Motzkin et al., 2015), while activation in the dACC results in greater amygdala activation, encouraging conditioned responding (Cheng et al., 2003; Knight et al., 2004; Linnman et al., 2011; Milad et al., 2007a). Further, the hippocampus only appears to show greater activation in conditioning paradigms with multiple contexts and various contingencies for extinction (Lang et al., 2009; Milad et al., 2007b), with non-contextual conditioning studies showing no modulation of the hippocampus (Phelps et al., 2004).

Further support for the above neurocircuitry of emotional fear processing has been found in populations with PTSD. For instance, greater dACC activity in PTSD has been associated with poorer extinction learning (Rougemont-Bücking et al., 2011) and extinction recall (Milad et al., 2009). Shvil et al. (2014), however, found this effect only in men with PTSD. Furthermore, Sripada et al. (2013) found a relationship between avoidance symptoms in PTSD and greater activity in the amygdala, vmPFC and hippocampus, among other emotion-related regions (i.e., insula and dorsomedial PFC).

2. Paradigms and phases of associative fear learning

In this section, we discuss the clinical relevance of the different experimental models based on a fear conditioning framework. As such, this review discusses (1) *acquisition/conditioning* as an analogue for the development of post-traumatic stress symptoms; (2) *extinction learning* as an influential explanation for the natural recovery of symptoms, but also for the maladaptive persistence of symptoms; (3) *extinction memory/recall* paradigms as a model for treatment resistance and symptom remission; (4) *return of fear* manipulations for the relapse of symptoms post-treatment and delayed-onset of PTSD symptoms; (5)

fear inhibition as a model for the inability to transfer learned safety contingencies; (6) *reversal learning* for the new learning of attributing positive valences to previously negative stimuli, and vice versa; (7) *instrumental avoidance* paradigms and maladaptive attempts to avoid stressful fear symptoms; and (8) the *generalization* of fear responses to benign stimuli that were not present during the traumatic event. In the final section, we acknowledge a number of genetic, biological, behavioral, and cognitive factors that have been shown to moderate/mediate some of these processes.

2.1. Fear acquisition/conditioning

Fear acquisition refers to the initial associative learning process of the CS-US relationship. During fear acquisition in experimental settings, a neutral stimulus (e.g., colored geometric shapes, lights) is paired with the US (e.g., mild electric shock, aversive airblast). Through repeated pairings, the CS+ comes to predict the US and elicits a distinct fear response when compared to a safety signal (a similar stimulus never paired with the US, termed the CS-). Studies are somewhat mixed regarding levels of differential conditioning between PTSD and traumatized or non-traumatized control groups. PTSD-specific effects in fear acquisition are mixed, with some studies finding elevated psychophysiological responding to the safety cue (Acheson et al., 2015; Handy et al., 2018; Jovanovic et al., 2010; Peri et al., 2000), greater CS+/-discrimination (Blechert et al., 2007; Orr et al., 2000), or no differences at all (Glover et al., 2012).

Despite these mixed findings for PTSD-specific patterns of responding during fear acquisition, a recent meta-analysis by Duits et al. (2015) found a small effect that patients with anxiety disorders display increased fear expression to the CS- during fear acquisition. As discussed by Duits et al. (2015), this finding can be interpreted in one of two ways: (1) individuals with PTSD may have a greater propensity to generalize fear to similar neutral stimuli, and (2) this effect may be reflective of impaired inhibition processes. Both are equally likely explanations, and greater fear expression to the CS- during acquisition is likely to be due to a combination of generalization and inhibitory processes. Indeed, fear generalization has been described as “balancing excitation versus inhibition” (Dymond et al., 2015, p.565), and will be discussed in greater detail below.

Translationally, the fear acquisition phase is considered a laboratory model for trauma exposure. A traumatic event acts as a naturally occurring US that evokes unconditioned responses of intense arousal and fear. Indeed, there is consistent evidence of heightened physiological arousal (as indexed by acoustic startle and heart rate responses) in the acute aftermath of trauma as a significant predictor of increased post-traumatic stress at follow-up in motor vehicle accident survivors (Bryant et al., 2000), firefighters (Guthrie and Bryant, 2005), and assault victims (Griffin, 2008). Further, patients with PTSD present with elevated physiological arousal at rest (Peri et al., 2000), and greater fear-potentiated startle to the CS+ during late acquisition is associated with high levels of re-experiencing and hyperarousal symptoms (Norrholm et al., 2011). These studies suggest that individuals with PTSD show heightened physiological arousal in the acute phase post-trauma, which is argued to reflect the propensity for stronger unconditioned responses (Bryant et al., 2000; Shalev et al., 1998). In turn, this heightened peri- and post-traumatic arousal may manifest into greater fear-related symptoms, namely re-experiencing and hyperarousal (Norrholm et al., 2011).

Although fear conditioning can provide a theoretical explanation for the *development* of the fear-related clinical features of PTSD, it cannot however, fully explain the persistence of these symptoms, or explain why some individuals do not develop PTSD. Indeed, a study by Bryant et al. (2013) found that during 3-, 12-, and 24-month follow-ups, many individuals moved between symptom-free, sub-syndromal, and clinical PTSD classifications. Specifically, the rates of PTSD at each time-point remained relatively stable, however participant membership fluctuated

between the different diagnostic categories at each time-point. In support, many individuals with severe PTSD symptoms in the weeks following a trauma recover in the following months (for a review, see Bryant, 2003). Due to the normative response to trauma being recovery, and the dynamic trajectory of PTSD onset, persistent fear-related PTSD symptoms are likely due to mechanisms of impaired extinction, avoidance, and/or inhibition, rather than conditioning.

It is important to note here that we do not suggest that PTSD is a “fear-conditioning disorder” as its heterogeneous presentation spans several neurobiological, cognitive, emotional, and social domains including frequently observed guilt, shame, anger, and irritability. These symptoms are likely mediated by cortical and subcortical (e.g., striatal) brain regions that lie outside of the limbic circuitry implicated in fear learning (McHugh et al., 2012; Briscione et al., 2014; Norrholm and Jovanovic, 2018).

2.2. Fear extinction learning

Fear extinction occurs following fear acquisition (either immediately, or following a delay), whereby the CS+ is repeatedly presented without the US. Over time, this results in a reduction in conditioned fear responses to the CS+, until there is minimal discriminability between the CS+ and CS-. It is important to note here that in experimental situations, most participants extinguish conditioned responses (for a discussion of non-extinguishers, see Norrholm et al., 2008), however, it is the rate/pattern of extinction that is of most interest. Compared to trauma-exposed and non-exposed controls, individuals with PTSD tend to show slower rates of extinction learning (Acheson et al., 2015; Blechert et al., 2007; Zuj et al., 2017b; Zuj et al., 2017c), or greater physiological arousal during extinction (Fani et al., 2012; Norrholm et al., 2011; Orr et al., 2000; Peri et al., 2000).

One way in which impaired fear extinction learning can present in PTSD is fear load. Fear load refers to a pattern of fear expression whereby individuals with PTSD display greater fear expression in the early phases of extinction learning, compared to control groups (Norrholm et al., 2015; Norrholm et al., 2011), and is argued to be an intermediate phenotype of PTSD symptom development. That is, PTSD participants display greater levels of fear at the beginning of extinction learning, compared to controls. Indeed, fear load draws a number of parallels with risk factors of PTSD, such as genetics (Norrholm et al., 2013) and sex hormones (Glover et al., 2012). Fear load is also associated with an increased attentional bias to threat (Fani et al., 2012), which has been found to be specific to PTSD in Australian soldiers, compared to soldiers with a mild traumatic brain injury without PTSD (Zuj et al., 2017a). Further, Galatzer-Levy et al. (2017) identified increased fear load to be a specific trajectory of acquisition and extinction, characterized by high levels of fear-potentiated startle during acquisition and extinction, and little reduction in startle during extinction. This trajectory appeared to be distinct from other trajectories characterized by complete extinction of fear-potentiated startle (Galatzer-Levy et al., 2017). It is likely that this non-extinction trajectory may be associated with treatment-resistant PTSD symptoms.

Trauma-focused cognitive behavioral therapies, such as prolonged exposure therapy, are considered to work via fear extinction mechanisms to reduce the distress associated with trauma-related thoughts and behaviors (McLean and Foa, 2011; Rauch et al., 2012; Yehuda et al., 2015b). During prolonged exposure therapy, the patient is gradually exposed to reminders of the traumatic event, resulting in increased physiological arousal and anxiety. Over the course of treatment sessions, recounting the traumatic event produces lower levels of fear and anxiety, much the same way this process occurs in experimental extinction sessions. Although prolonged exposure therapy is considered the gold standard of treatment for PTSD, reports indicate that there are large dropout rates due to the huge levels of distress caused by initial stages of treatment (Schnurr et al., 2007; Simmons et al., 2013; Yehuda et al., 2015a). This elevated level of distress in the beginning of

exposure therapy can be conceptualized as fear load, whereby reminders of the traumatic event are initially met with intense physiological hyperarousal.

2.3. Fear extinction recall

In clinical settings, the extinction of a distressing conditioned response to emotional trauma reminders occurs in two ways: within-session (as discussed above), and between-session. Regarding the latter, symptom reduction during a session of exposure-based therapy needs to carry over into subsequent sessions for long-term symptom management. In laboratory settings, this involves assessing the recall of fear extinction in the days following extinction learning (e.g., Milad et al., 2008). Multi-day conditioning, extinction, and extinction recall paradigms have found deficient between-session recall of extinction in participants with PTSD, with no impairments in acquisition or within-session extinction (Milad et al., 2008; Milad et al., 2009; Shvil et al., 2014). Similarly, these findings have also been found in patients with obsessive-compulsive disorder, compared to controls (Milad et al., 2013). Furthermore, recent evidence shows that adolescents, who are at greater risk for the development of anxiety disorders, show impaired extinction recall compared to adults (Ganella et al., 2017b) and this appears to be linked to reduced activity in regions of the prefrontal cortex (Ganella et al., 2017a; Ganella et al., 2017b). Recent evidence also suggests that transcranial magnetic stimulation of the PFC enhances extinction recall (Rajj et al., 2017), further supporting the inhibitory function of the vmPFC on amygdala circuits. Extinction recall paradigms are an important experimental model for the maintenance of symptom reduction following sessions of exposure therapy.

2.4. Return of fear following extinction learning

As described previously in this review, conditioned fear memories (e.g., CS-US associations) are not erased following extinction learning and can be elicited through the processes of spontaneous recovery (after the passage of time; Pavlov, 1927), reinstatement (following the un-signaled presentation of the US without the CS; Rescorla and Heth, 1975), or renewal (following a change in context from the extinction learning environment; Bouton and Bolles, 1979). The clinical analogues of the laboratory phenomena of spontaneous recovery, reinstatement, and renewal are time elapsed since the conclusion of extinction-based exposure therapy, exposure to a stressful life event, and experiences within contexts different from that within which therapy occurred, respectively (Norrholm, 2012).

2.5. Fear inhibition

Fear inhibition is related to fear extinction with a notable exception being that inhibition paradigms typically compare subject responses to a reinforced “danger” cue (e.g., CS+) with responses to a non-reinforced “safety” cue (e.g., CS-). Fear extinction, by definition, refers to a decrease in fearful responding to a previously reinforced CS+ following a change in the experimental contingency (i.e., presentation of the same CS is no longer followed by an aversive outcome). Fear inhibition has been reliably investigated by Jovanovic et al. (2010) using psychophysiological indices previously described using a learning paradigm termed AX+/BX-. As part of this approach, a neutral stimulus (termed the X cue) is paired with a cue (termed the A cue) that is paired with an aversive airblast US. This compound is referred to as the AX+ compound and its presentation is repeatedly followed by the US. In addition, a second cue (termed the B cue) that is not paired with the US is presented with the same neutral X cue, and this compound is referred to as BX-. Subsequently, the previously reinforced A cue and non-reinforced B cue are paired together (termed the AB compound) and presented to determine the degree to which the inhibitory properties of the B cue are transferred to the excitatory A cue. Healthy controls

routinely show this transfer of inhibition (Jovanovic et al., 2005). In PTSD patients, however, a failure of transfer of inhibition has been reported by this group as evidenced by similar levels of fear responding to both the excitatory AX compound and the inhibition test compound AB (Jovanovic et al., 2009). These results suggested that PTSD may be related to an impairment in transferring learned safety (a goal of treatment for trauma-, stressor-, and anxiety-related disorders).

As discussed in section 2.6, Sam’s ability to reduce his fearful responses to riding in a motor vehicle at home following his vehicle-based traumatic event while deployed can also be explained, to some degree, by reversal learning. Reversal learning occurs when an individual successfully determines that a cue that previously predicted a negative outcome later predicts a neutral or positive outcome. In Sam’s case, the cue (i.e., motor vehicle) remained largely constant but the context (i.e., United States versus Afghanistan) qualitatively changed. The study of reversal learning in PTSD populations is in its infancy but represents a potential area of increased focus for clinical interventions.

2.6. Reversal learning

Fear learning, as assessed by acquisition and extinction paradigms, is context-dependent and conditioned fear responses emerge in the presence of both discrete cues and the contexts in which these cues are presented (Norrholm and Jovanovic, 2018; VanElzakker et al., 2014). In addition to the extinction phenomena discussed previously, an emerging area of interest with regard to PTSD and clinically-relevant learning mechanisms is reversal learning. In a typical reversal learning procedure, participants learn that the valence (i.e., positive or negative outcome) of a paired association between cue and context initially predicts a neutral or aversive consequence (e.g., cue A is followed by a US). Subsequently, this reinforced cue is then presented with a different, often positive, outcome on later trials. To successfully learn the new associations presented in a reversal learning paradigm, participants need to reverse their association expectation of either the original cue or original context while keeping the valence of the other dimension constant to isolate reversal learning on a single dimension (cue or context).

The potential validity of increased focus on reversal learning was illustrated in a recent study by Levy-Gigi et al. (2014) who assessed this type of learning in trauma-exposed firefighters, crime scene investigators, and non-traumatized control participants. As described above, the authors presented reversal associations of cue and context independently and tested the ability of each group to learn the contingency reversals. Previously traumatized firefighters exhibited a decreased capacity to learn that a context that initially predicted a negative outcome, when presented with a different cue, was subsequently followed by a positive outcome. Conversely, previously traumatized crime scene investigators showed an impaired ability to learn that a cue that initially predicted a negative outcome when the context remained constant. The authors discuss these results in terms of the specific occupation-related tasks required by each of these professions; firefighters may be more attuned to contextual features of the environments to which they are exposed whereas crime scene investigators may recruit more discrete cue-specific features of the contexts within which they work. The results of this work suggest that clinical focus, as it relates to the fear-related symptoms of trauma-, stressor-, and anxiety-related disorders should not be limited to fear-related cues, or triggers, but also the multiple contexts within which they appear.

2.7. Avoidance and avoidance extinction

While deficits in the learning and memory for fear extinction is one mechanism by which fear might persist, another is avoidance. Avoidance refers to any active or passive behavior that increases the distance between an individual and an aversive event or situation (for an excellent review, see Pittig et al., 2018). In relation to PTSD, this

Table 1

The applications and relevance of conditioning paradigms for behavioral and clinical situations.

Conditioning paradigms	Behavioral/clinical analogues
Fear acquisition	The development of conditioned anxiety- and fear-provoking triggers.
Fear extinction learning	When unimpaired = natural recovery. When impaired = symptom persistence. Important mechanism of exposure-based treatment.
Fear extinction recall	When unimpaired = symptom improvement. When impaired = poor between-session treatment response. Important mechanism of exposure-based treatment
Return of fear	Post-treatment relapse of symptoms.
Fear inhibition	Impaired ability to transfer learned safety contingencies. Important mechanism of exposure-based treatment.
Reversal learning	New learning that a previously threatening stimulus/context signals safety.
Avoidance	Active maintenance of symptoms. Protection from recovery.
Fear generalization	Symptom persistence and the transfer of conditioned fear/anxiety to different (but perceptually or conceptually similar) stimuli.

typically involves reminders of a traumatic event. For example, an individual involved in a nasty cycling accident on an ordinary stretch of road may actively avoid that area to prevent anxious thoughts and feelings about the potential for another accident, or to avoid memories of the previous accident. Avoidance behaviors are a common technique of managing symptoms in anxiety disorders due to the direct negative reinforcement of reducing anxious thoughts and feelings (LeDoux et al., 2017; Mineka, 1979). This, however, leads to a distorted ability to recognize safe vs. dangerous situations, and becomes a maladaptive strategy of managing symptoms (LeDoux et al., 2017). Maladaptive avoidance behaviors can lead to a flow-on effect of additional comorbidities with PTSD, as Possemato et al. (2015) found that greater use of maladaptive avoidance-based coping strategies was associated with an increased risk of alcohol use in veterans with PTSD. For an account of various theoretical explanations of avoidance behaviors in associative and instrumental learning paradigms, see Lovibond (2006).

Avoidance paradigms typically begin with a Pavlovian conditioning phase, followed by an avoidance phase. During instrumental avoidance tasks, participants are presented with an additional cue indicating the CS+ can be avoided (e.g., via a spacebar press, or multiple rapid presses). Research in healthy controls shows that when an extinction phase follows avoidance training, the presentation of an avoidance cue during extinction prevents participants from extinguishing, known as ‘protection from extinction’ (Lovibond et al., 2009). The act of initiating the avoidance cue arbitrarily removes any expectancy of the US, and extinction therefore cannot occur (Lovibond et al., 2009). Recent evidence in healthy controls also shows that greater reinforcement of avoidance (i.e., higher chance that avoidance behaviors will cancel the US) results in persistent fear responses throughout an extinction learning phase (Xia et al., 2017).

In clinically ecological paradigms, there is evidence that individuals with greater levels of anxiety show increased instrumental avoidance behaviors to reduce the likelihood of experiencing the aversive US. Dymond et al. (2014) found that individuals with high spider fear require fewer acquisition trials to develop an avoidance response to an image of a spider, compared to individuals with lower levels of spider fear. Further, anxious children in a choice-based fear learning task are more likely to choose a safety signal instead of a threat signal, indicating avoidance of threat (Lau and Viding, 2007). Avoidance symptoms in veterans with PTSD also show associations with neural networks of emotion during fear conditioning and extinction (Sripada et al., 2013).

During exposure therapy for PTSD and other anxiety disorders, initial reports suggested that within- and between-session habituation of physiological arousal/anxiety is necessary for long-term symptom reduction (Foa and Kozak, 1986). That is, disrupting the habituation process during the session when anxiety levels become too high was viewed as a form of negative reinforcement, promoting avoidance and ongoing symptoms. Recent reports, however, suggest that within-session habituation does not predict behavioral avoidance at follow-up (Craske et al., 2008; Kircanski et al., 2012). These findings indicate some uncertainty regarding how avoidance might be targeted during the treatment process, however it is likely that the natural recovery from negative posttraumatic stress reactions may be ‘protected’ by the use of avoidance behaviors (Lovibond et al., 2009).

2.8. Fear generalization

An important experimental and clinical understanding is that conditioned fear and arousal can be caused by stimuli that were not present during a traumatic event (Dymond et al., 2015). The concept of generalization refers to the extension of conditioned responses to stimuli that may be perceptually, symbolically, or contextually related to the original CS (for a review of different generalization techniques, see Dymond et al., 2015). Recent investigations show reduced vmPFC-amygdala connectivity to generalized stimuli resembling the safety signal in patients with PTSD, compared to controls (Morey et al., 2015). Indeed, Lissek et al. (2014) found that healthy participants show greater hippocampal-vmPFC connectivity in a gradient-response relationship with generalization stimuli as the stimuli show a closer perceptual relationship with the safety signal (the neural mechanisms of fear generalization in relation to PTSD are reviewed in Lopresto et al., 2016). While little research has investigated classically conditioned fear generalization in PTSD, this model has important clinical relevance for the development and persistence of anxious symptoms (Lissek, 2012), as patients with PTSD frequently generalize anxiety and fearful responses to safe stimuli that were not present during the trauma.

2.9. Summary

While empirical research of some of these experimental paradigms is limited in clinical samples, these models nonetheless provide important explanations for a variety of fear-related features of PTSD and other anxiety disorders. As summarized in Table 1, the biological and experimental models outlined above provide unique descriptions for the development and persistence of fear-related symptoms (via conditioning, impaired extinction, and over-generalization mechanisms), treatment and the maintenance of treatment responses (extinction learning and recall mechanisms), the post-treatment relapse of symptoms (return of fear paradigms), avoidance behaviors of trauma-related stimuli (via instrumental avoidance paradigms), and fearful responding to safe stimuli (via inhibition and generalization paradigms). As highlighted at the beginning of this review, PTSD is a complex psychiatric conditioning with significant variability in symptom presentation. As such, the above sections are directed at explaining the clinical relevance of these paradigms for the fear-related features of PTSD (see Fig. 2). (See Boxes 2–4.)

3. Mediators and moderators of conditioning and extinction processes

The aforementioned sections have detailed different paradigms of Pavlovian fear learning, and their direct clinical relevance in the development, treatment, and relapse of PTSD symptoms. In addition, there has been increased attention toward identifying various boundary conditions of fear learning, with important implications for theory development and the treatment of fear-related symptoms. For example, a

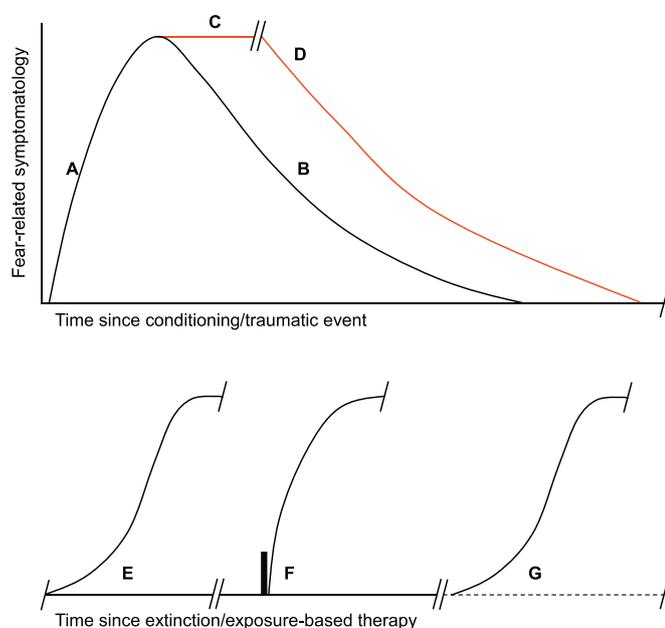


Fig. 2. Following a traumatic event, the majority of people develop *conditioned* fear-related symptoms (A) of post-traumatic stress, and make conscious behavioral attempts to *avoid* reminders of the traumatic event. In the example of patient John, these symptoms may also *generalize* to reminders of the traumatic event, such as emergency vehicles. However, the normative response to trauma is recovery, and the majority of trauma-exposed individuals will experience a gradual *extinction* of fear responses and *avoidance* behaviors (B). In those who develop chronic PTSD (C), symptoms may persist indefinitely, and require *extinction-based prolonged exposure therapy* for symptom management (D). Fear-related symptoms may, however, return following extinction. In particular, symptoms may return due to: (E) the passage of time since treatment (*spontaneous recovery*); (F) an environmental trigger, or a spontaneous panic attack (*reinstatement*); or (G) the experience of trauma reminders in a different context to the previous extinction/treatment context (*renewal*).

large body of research shows significant effects of sleep quality on fear extinction potential (reviewed in Pace-Schott et al., 2015a, 2015b), and therapies targeting nightmares also improve PTSD symptoms (Krakow et al., 2001). Sleep quality, therefore, appears to act as a moderator (or mediator) of fear extinction learning, and treatment response might be enhanced by also focusing on a patients' quality of sleep. In the following section, we briefly review the evidence of known moderators and mediators of Pavlovian fear learning. As this section covers a number of rich research areas, this section is brief, with appropriate

Box 2

Clinical vignette: Fear Extinction Learning.

The patient introduced in Box 1, John, was assigned to prolonged exposure treatment that consisted of weekly sessions with a therapist as well as between-session *in vivo* exposure exercises according to the clinical protocol published by Foa et al. (2007). The session-by-session procedures included as part of this type of treatment will not be reviewed in detail here but the reader is referred to the latter work of Foa and others. During his treatment sessions, John repeatedly recounted his traumatic experience, in the safety of the clinical space, having witnessed the suicide of a friend and fellow service member. This included detailed descriptions of the sensory and emotional experiences that encompassed this distressing event. As is typical with this type of treatment, John reported his Subjective Units of Distress (SUDS) level at regular intervals during the sessions as well at the beginning and end of his recollections. John and his therapist created a hierarchy of cues, places, and situations in which to be exposed during his *in vivo* exposures. This was done in a graded fashion with the patient “building up” to the contexts and situations that are reported to be most distressing. For John, this hierarchy involved moving from limited exposure to emergency-related sounds played through audio devices and handheld flashing lights, as are often seen on emergency vehicles before progressing to exposures in and around first responder facilities such as fire and police facilities. John did well with this treatment regimen as evidenced by clinician- and self-reported symptom inventories, self-reported reductions in his SUDS level over the course of his 8-week course of therapy, and increased exposure to situations in close proximity to rescue vehicles. By the end of treatment, John reported an increased quality of life, reduced alcohol consumption, and re-engagement with many of the activities that he had long avoided.

acknowledgement to the relevant reviews of many of these fields. Similarly, the central role that fear extinction learning and memory appears to play in linking many of these fields of research to PTSD has been reviewed previously (Zuj et al., 2016b).

3.1. Genetic mechanisms

BDNF is involved in the synaptic plasticity of the emotional circuitry of the brain (namely the amygdala, PFC, and hippocampus), and higher serum BDNF levels have been associated with greater PTSD symptom severity (Hauck et al., 2009; Hauck et al., 2010; Matsuoka et al., 2013; Rakofsky et al., 2012). Additionally, carriers of the Met allele of the BDNF Val66Met polymorphism show poor response to exposure therapy (Felmingham et al., 2013) and poorer extinction learning (Soliman et al., 2010). Recently, Felmingham et al. (2018) found the BDNF Val66Met polymorphism to be a significant moderator between PTSD symptoms and extinction learning, with greater PTSD symptoms and poorer fear extinction only in Met allele carriers, but not Val carriers.

COMT is an enzyme involved in the synaptic degradation of dopamine, epinephrine, and norepinephrine within the PFC and hippocampus (Bomyea et al., 2012). Homozygosity of the Val158Met polymorphism (Val/Val or Met/Met carriers) is associated with greater and lower levels of dopamine degradation, respectively (Tunbridge et al., 2006). In comparison, Val/Met carriers appear to show balanced dopamine degradation at the synapse. There is consistent evidence that homozygous Val/Val or Met/Met carriers show greater PTSD symptoms than heterozygous Val/Met carriers (Boscarino et al., 2011; Clark et al., 2013; Deslauriers et al., 2018; Kolassa et al., 2010; Valente et al., 2011). COMT Val158Met homozygosity is also associated with impaired fear extinction (Lonsdorf et al., 2009) and fear inhibition to safety signals (Deslauriers et al., 2018; Norrholm et al., 2013; Wendt et al., 2014).

Studies indicate that carriers of the ‘short’ allele of the serotonin transporter gene, 5-HTTLPR, show stronger conditioned fear responses during acquisition (Hermann et al., 2012; Lonsdorf et al., 2009). In clinical situations, the 5-HTTLPR-s allele also shows significant gene × environment interactions to increase risk for PTSD. Specifically, 5-HTTLPR-s shows significant associations with high trauma exposure and interpersonal experiences (e.g., low social support) to increase risk for PTSD (Gressier et al., 2013; Kilpatrick et al., 2007; Koenen et al., 2009). Although, Wald et al. (2013) found that in the military, the 5-HTTLPR-s allele interacted with increased combat exposure and attentional threat biases as protective factors for PTSD.

FK506 binding protein 5 (FKBP5) is important in modulating glucocorticoid receptor sensitivity, influencing the activity of cortisol and the negative feedback loop of the hypothalamic-pituitary-adrenal axis

Box 3

Clinical vignette: Return of Fear.

Patient John successfully completed prolonged exposure therapy for his PTSD symptoms and returned to many of his daily activities including steady employment as an air traffic support technician at the local airport. He was not seen in the PTSD clinic for 18 months after which time he returned to the clinic with relapse of his PTSD symptoms. He again reported physical and emotional reactivity in the presence of emergency response-related cues. During his return assessment visit, John disclosed that he had recently undergone short-term, invasive treatment for a localized, benign tumor in his abdomen. He stated that his PTSD symptoms returned shortly after his discharge from the hospital. Per his report, his exposure to the various medical clinics and procedures reminded him of his traumatic experience with his colleague's suicide and that these intrusive memories were coupled with his own thoughts of death, dying, and mortality. During the few days in which he waited for the results of his biopsy and in the days leading up to his surgery, he felt as if his life was endangered by the new medical diagnosis. These thoughts and feelings evoked visceral, panic-like symptoms. Clinically speaking, a significant medical crisis can precipitate a relapse of PTSD symptoms. In experimental fear learning terms, this is analogous to reinstatement of fear when a successfully extinguished participant is presented with the fear-eliciting unconditioned stimulus in the absence of the cues previously paired to the US. It is also important to note here, that John's relapse may also be partially explained by a generalization of fear, that he previously acquired to emergency response-related cues, to the cues to which he was exposed during his hospital stay. John underwent a brief, 4-week course of exposure and talk therapy after which time he reported a reduction in his relapsed PTSD intrusive and hyperarousal symptoms.

(Bomyea et al., 2012; Zannas and Binder, 2014). Research suggests that, similar to the 5-HTTLPR-s allele, FKBP5 is not associated with PTSD risk in isolation (Binder et al., 2008; Xie et al., 2010), but interacts with childhood trauma to increase risk for PTSD (Xie et al., 2010). Specifically, the RS9470080 SNP of FKBP5 has been associated with childhood trauma as a G × E risk for PTSD (Xie et al., 2010), but has also been associated with hyperarousal symptoms and impaired extinction learning in a sample with PTSD (Galatzer-Levy et al., 2017). Rodent models of PTSD have also shown that reduced fear acquisition and enhanced fear extinction learning and memory are associated with reduced FKBP5 expression in the amygdala (Sawamura et al., 2016) and the infralimbic cortex (Criado-Marrero et al., 2017). The biological processes relating FKBP5 to fear memory and PTSD have been reviewed by Maddox et al. (2013)

3.2. Biological mechanisms

The hormonal stress response can be simply described in terms of two systems: (1) the sympathetic nervous system, releasing fast-acting catecholamines such as adrenaline and noradrenaline; and (2) the hypothalamic-pituitary-adrenal (HPA) axis, which is a slow-response system regulating the stress response of the sympathetic nervous system, and acting to return physiological systems to pre-threat levels (for a review, see Szeszko et al., 2018). Individuals with PTSD have been shown to display elevated noradrenaline levels, relative to

controls (Geraciotti et al., 2001; Pietrzak et al., 2013; Wingenfeld et al., 2015; Yehuda et al., 1998; Yehuda et al., 1992; although see Zuj et al., 2018). Noradrenaline is considered an important modulator of emotional memory consolidation (Mueller and Cahill, 2010), and rodent studies show yohimbine administration (resulting in increased noradrenaline secretion) immediately prior to extinction learning results in enhanced extinction (Cain et al., 2004; Morris and Bouton, 2007). Similarly, yohimbine administration immediately prior to conditioning in human subjects results in a conditioned fear that is resistant to extinction (Soeter and Kindt, 2012). Using behavioral tests, such as a cold presser test, immediately before acquisition or extinction learning results in stronger conditioned fear or enhanced extinction learning, respectively (Antov et al., 2015; Antov et al., 2013). Zuj et al. (2018), however, recently found that the relationship between extinction learning and PTSD symptom severity does not change as a factor of endogenous salivary α -amylase (as a proxy for noradrenaline levels), suggesting that the relationship between conditioning/extinction, PTSD, and noradrenaline is unclear.

Evidence has been somewhat inconsistent regarding PTSD-related cortisol secretion, with research showing persistent PTSD to be associated with increased cortisol (Groer et al., 2014), reduced cortisol (Bicanic et al., 2013; Wabbeh and Oken, 2013; Yehuda et al., 2009; Yehuda et al., 2007a; Yehuda et al., 2007b), or no differences, compared to control groups (Shalev et al., 2008; Zuj et al., 2017c). A meta-analysis conducted by Morris et al. (2012), however, found that PTSD

Box 4

Clinical vignette: Fear Inhibition and Reversal Learning.

Sam was a 35 year old U.S. Army Veteran who was deployed to Afghanistan from 2005 – 2007. As a transportation and logistics specialist, Sam often travelled within the combat theatre as part of armoured vehicle convoys. During one mission in late 2006, the vehicle within which Sam was riding was hit by an improvised explosive device (IED) and several of Sam's fellow members were significantly injured by shrapnel and concussive forces. Sam recalls feeling frightened and distressed at the time of this event but was able to serve the remainder of his deployment without any clinically significant consequences. Upon his return to the States in 2007, Sam reported to the PTSD clinic with PTSD symptoms most notably increased physiological and emotional arousal when driving or riding in a motor vehicle. Sam was treated with a few cognitive behavioural therapy regimens including cognitive processing therapy (CPT) and prolonged exposure (PE) therapy with varying degrees of success reported by Sam. Sam recalled that an aspect of cognitive therapy that was helpful was learning new ways to think about traumatic events and their aftermath. Over the course of therapy, Sam recognized that the sights, sounds, and smells (i.e., cues) present during his travels on American roads were qualitatively different from those that were present in Afghanistan. In addition, there was a clear familiarity of the roads he traveled at home. These factors provided a sense of safety for Sam, and as he progressed through treatment, the safety inherent with traveling by vehicle in the States transferred to his experiences of being in a car (initially reported by Sam to be a reminder of a Humvee cabin) and sitting in U.S. road traffic (initially reported by Sam to remind him of a military convoy). From a learning theory perspective, the reduction in Sam's reactivity to motor vehicle cues over time represents a form of fear inhibition in which the inhibitory properties of a safety signal are transferred to a danger signal that previously evoked fear.

appears to be associated with lower cortisol secretion compared to control groups (after controlling for extraneous variables). Regarding conditioning research, cortisol appears to be more closely related to the inhibition of responses. That is, cortisol may affect the ability to accurately inhibit responses to safe stimuli that do not pose a threat. Recently, Zuj et al. (2017c) found that cortisol reactivity (from baseline to US-exposure) was a significant moderator between PTSD and responding to the CS-. Specifically, higher cortisol reactivity – but not lower reactivity – was associated with lower PTSD symptom severity as fear inhibition increased. Following release, cortisol binds to glucocorticoid receptors and studies have shown that glucocorticoid administration facilitates extinction (Barrett and Gonzalez-Lima, 2004; Cai et al., 2006; de Quervain et al., 2009; Yang et al., 2006).

Women are almost twice as likely to develop PTSD compared to men (e.g., Glover et al., 2015), and research implicates the sex hormones estrogen and progesterone in this process, albeit inconsistently. For example, women who were exposed to a traumatic event during the luteal phase of the menstrual cycle (associated with elevated estrogen and progesterone) developed stronger intrusive memories of the trauma (Bryant et al., 2011). Similarly, women with PTSD have also shown impaired fear extinction recall during the mid-luteal phase compared to women without PTSD (Pineles et al., 2016). Alternatively, research in healthy women has found low estrogen levels to be associated with poorer extinction learning (Wegerer et al., 2014), extinction recall (Milad et al., 2010; Zeidan et al., 2011), and fear inhibition (Glover et al., 2013). Glover et al. (2012) also found that women with PTSD and low estrogen levels demonstrated poorer extinction learning compared to trauma-exposed controls. As such, while research clearly indicates an important role for the menstrual cycle and sex hormones as a mechanism/boundary condition of sex differences in extinction learning and memory, the nature of this relationship is currently unclear.

3.3. Behavioral mechanisms

Sleep is considered a crucial mechanism of emotional memory consolidation (Stickgold, 2005), including the process of recovery from PTSD (Germain, 2013). Numerous studies indicate that sleep quality has a significant impact on fear extinction learning and memory (for reviews on the topic, see Pace-Schott et al., 2015a, 2015b). Specifically, evidence shows that fear extinction memories generalize to previously conditioned but unextinguished stimuli (Pace-Schott et al., 2009). Extinction learning, memory, and generalization are also more effective in the morning compared to the evening (Pace-Schott et al., 2013), and this effect is stronger in participants with PTSD compared to trauma-exposed and non-exposed controls (Zuj et al., 2016a). In clinical situations, greater pre-trauma sleep disturbances are also shown to predict the development of PTSD (Bryant et al., 2010), and greater sleep disturbances also slow the rate of recovery via cognitive therapy for PTSD in those with comorbid depression (Lommen et al., 2016). Indeed, Lommen et al. (2016) found cognitive therapy improved sleep quality and reduced PTSD symptoms simultaneously, highlighting the important relationship between the two factors.

Prevalence rates show elevated levels of smoking in those with anxiety disorders (Lasser et al., 2000), with smoking being a significant predictor of post-treatment symptom return in PTSD and other anxiety disorders (Taylor et al., 2015). Rodent studies show that nicotine administration results in impaired contextual safety discrimination (Kutlu et al., 2014) and facilitates the spontaneous recovery of previously extinguished stimuli (Kutlu et al., 2016). Recent work by Haaker et al. (2017) in mentally healthy controls showed impaired within-session fear extinction was correlated with the frequency and chronicity of smoking, and smokers displayed impaired extinction recall the following day compared with non-smokers. A number of studies examining smoking behaviors in PTSD have revealed periods of abstinence are met with stronger cigarette cravings in PTSD (Beckham et al., 2013; Dedert et al., 2012), and that trauma reminders may also

signal strong cravings (Beckham et al., 1996). Research also shows that individuals with PTSD attempting to quit experience sooner lapses of smoking compared to non-PTSD quitting smokers, and this is attributed to negative affect and trauma reminders (Beckham et al., 2013). Aforementioned rodent studies suggest that smoking may impair fear extinction learning ability in humans (for a review, see Kutlu and Gould, 2015), and this may translate to response to exposure treatment in PTSD.

3.4. Cognitive mechanisms

PTSD has been described as a disorder of memory (McNally, 2006), often involving fragmented and intrusive memories of the traumatic event, and conditioning and extinction are important forms of emotional memory in PTSD. In a meta-analysis, Brewin et al. (2007) determined that the most consistent cognitive domain affected in PTSD is verbal learning and memory. Indeed, reductions in PTSD symptom severity is also associated with increases in verbal learning and memory (Yehuda et al., 2006). Recently, Gazendam and Kindt (2012) instructed participants to engage in a verbal worrying task, showing that the verbal task was associated with significantly poorer extinction than a control task. Research has also shown that conditioning and extinction are dependent on available cognitive resources, with greater demands on working memory systems resulting in reduced conditioning (Carter et al., 2003) and impaired extinction (Raes et al., 2009). Finally, recent research has found that conscious cognitive awareness of the US-CS+ contingency is essential for conditioning of SCR, but not startle (Sevenster et al., 2014), suggesting an important role of cognitive load and the availability of cognitive resources in appropriate conditioning and extinction.

4. Conclusion

In the present review, we discuss a number of paradigms of human fear learning, and highlight the relevance and applications of these paradigms for the fear-related features of PTSD. In doing so, we have discussed the applications of these paradigms for the development, maintenance, normal and treatment-assisted recovery of symptoms, as well as the post-treatment relapse of PTSD symptoms. To illustrate the applicability of these paradigms, we have provided a real-world case example of a patient with severe PTSD symptomatology. While PTSD is associated with additional features that cause significant reductions in daily functioning and quality of life (e.g., anger and dissociation), the current review aimed to provide explanations for various aspects of fear-related symptoms (e.g., avoidance behaviors and hyperarousal). While some of these paradigms have been studied extensively in PTSD patients (e.g., conditioning, extinction, and inhibition), other paradigms have been involved in limited studies with clinical populations (e.g., avoidance and generalization). Finally, we have provided a brief review of some of the biological, behavioral, and cognitive variables that are known to influence PTSD symptoms and the fear conditioning/extinction process, and may be important in therapy for PTSD.

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References

- Acheson, D.T., Geyer, M.A., Baker, D.G., Nievergelt, C.M., Yurgil, K., Risbrough, V.B., 2015. Conditioned fear and extinction learning performance and its association with psychiatric symptoms in active duty Marines. *Psychoneuroendocrinology* 51, 495–505.
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Author, Washington, DC.
- Antov, M.I., Wolk, C., Stockhorst, U., 2013. Differential impact of the first and second

- wave of a stress response on subsequent fear conditioning in healthy men. *Biological Psychology* 94 (2), 456–468.
- Antov, M.I., Melicherová, U., Stockhorst, U., 2015. Cold pressor test improves fear extinction in healthy men. *Psychoneuroendocrinology* 54, 54–59.
- Archbold, G.E., Bouton, M.E., Nader, K., 2010. Evidence for the persistence of contextual fear memories following immediate extinction. *The European journal of neuroscience* 31 (7), 1303–1311.
- Armour, C., Elklit, A., Lauterbach, D., Elhai, J.D., 2014. The DSM-5 dissociative-PTSD subtype: can levels of depression, anxiety, hostility, and sleeping difficulties differentiate between dissociative-PTSD and PTSD in rape and sexual assault victims? *J Anxiety Disord* 28 (4), 418–426.
- Ball, T.M., Knapp, S.E., Paulus, M.P., Stein, M.B., 2017. Brain activation during fear extinction predicts exposure success. *Depress Anxiety* 34 (3), 257–266.
- Barrett, D., Gonzalez-Lima, F., 2004. Behavioral effects of metyrapone on Pavlovian extinction. *Neurosci Lett* 371 (2–3), 91–96.
- Barrett, D.W., Gonzalez-Lima, F., 2018. Prefrontal-limbic Functional Connectivity during Acquisition and Extinction of Conditioned Fear. *Neuroscience* 376, 162–171.
- Beckham, J.C., Lytle, B.L., Vrana, S.R., Hertzberg, M.A., Feldman, M.E., Shipley, R.H., 1996. Smoking withdrawal symptoms in response to a trauma-related stressor among Vietnam combat veterans with posttraumatic stress disorder. *Addictive Behaviors* 21 (1), 93–101.
- Beckham, J.C., Calhoun, P.S., Dennis, M.F., Wilson, S.M., Dedert, E.A., 2013. Predictors of lapse in first week of smoking abstinence in PTSD and non-PTSD smokers. *Nicotine & Tobacco Research* 15 (6), 1122–1129.
- Bicanic, I.A., Postma, R.M., Sinnema, G., De Roos, C., Olff, M., Van Wesel, F., van de Putte, E.M., 2013. Salivary cortisol and dehydroepiandrosterone sulfate in adolescent rape victims with post traumatic stress disorder. *Psychoneuroendocrinology* 38 (3), 408–415.
- Binder, E.B., Bradley, R.G., Liu, W., Epstein, M.P., Deveau, T.C., Mercer, K.B., Tang, Y., Gillespie, C.F., Heim, C.M., Nemeroff, C.B., Schwartz, A.C., Cubells, J.F., Ressler, K.J., 2008. Association of FKBP5 polymorphisms and childhood abuse with risk of post-traumatic stress disorder symptoms in adults. *J. Am. Med. Assoc.* 299 (11), 1291–1305.
- Blecher, J., Michael, T., Vriends, N., Margraf, J., Wilhelm, F.H., 2007. Fear conditioning in posttraumatic stress disorder: Evidence for delayed extinction of autonomic, experiential, and behavioural responses. *Behaviour Research and Therapy* 45 (9), 2019–2033.
- Blecher, J., Michael, T., Williams, S.L., Purkis, H.M., Wilhelm, F.H., 2008. When two paradigms meet: Does evaluative learning extinguish in differential fear conditioning? *Learning and Motivation* 39 (1), 58–70.
- Bloodgood, D.W., Sugam, J.A., Holmes, A., Kash, T.L., 2018. Fear extinction requires infralimbic cortex projections to the basolateral amygdala. *Transl Psychiatry* 8 (1), 60.
- Boddez, Y., Baeyens, F., Luyten, L., Vansteenwegen, D., Hermans, D., Beckers, T., 2013. Rating data are underrated: validity of US expectancy in human fear conditioning. *J. Behav. Ther. and Exp. Psychiatr.* 44 (2), 201–206.
- Bomyea, J., Risbrough, V., Lang, A.J., 2012. A consideration of select pre-trauma factors as key vulnerabilities in PTSD. *Clinical Psychology Review* 32 (7), 630–641.
- Boscarino, J.A., Hoffman, S.N., Rukstalis, M., Stewart, W.F., 2011. Association of FKBP5, COMT and CHRNA5 polymorphisms with PTSD among outpatients at risk for PTSD. *Psychiatry Research* 188 (1), 173–174.
- Boucsein, W., 1992. Electrodermal activity. In: Ray, W.J. (Ed.), *Psychophysiology and Medicine*. Plenum Press, New York, pp. 1–420.
- Bouton, M.E., 2002. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biol Psychiatry* 52 (10), 976–986.
- Bouton, M.E., Bolles, R.C., 1979. Contextual control of the extinction of conditioned fear. *Learning and Motivation* 10, 455–466.
- Brewin, C.R., Kleiner, J.S., Vasterling, J.J., Field, A.P., 2007. Memory for emotionally neutral information in posttraumatic stress disorder: A meta-analytic investigation. *J. Abnormal Psychol.* 116 (3), 448–463.
- Briscone, M.A., Jovanovic, T., Norrholm, S.D., 2014. Conditioned fear associated phenotypes as robust, translational indices of trauma-, stressor-, and anxiety-related behaviors. *Frontiers in Psychiatry* 5, 88.
- Bryant, R.A., 2003. Early predictors of posttraumatic stress disorder. *Biological Psychiatry* 53 (9), 789–795.
- Bryant, R.A., Harvey, A.G., Guthrie, R.M., Moulds, M.L., 2000. A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. *J Abnorm Psychol* 109 (2), 341–344.
- Bryant, R.A., Creamer, M., O'Donnell, M., Silove, D., McFarlane, A.C., 2010. Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. *Sleep* 33 (1), 69–74.
- Bryant, R.A., Felmingham, K.L., Silove, D., Creamer, M., O'Donnell, M., McFarlane, A.C., 2011. The association between menstrual cycle and traumatic memories. *Journal of Affective Disorders* 131 (1–3), 398–401.
- Bryant, R.A., O'Donnell, M.L., Creamer, M., McFarlane, A.C., Silove, D., 2013. A multisite analysis of the fluctuating course of posttraumatic stress disorder. *JAMA Psychiatry* 70 (8), 839–846.
- Burgos-Robles, A., Vidal-Gonzalez, I., Quirk, G.J., 2009. Sustained conditioned responses in prefrontal neurons are correlated with fear expression and extinction failure. *J. Neurosci.* 29 (26), 8474–8482.
- Cai, W.H., Blundell, J., Han, J., Greene, R.W., Powell, C.M., 2006. Postreactivation glucocorticoids impair recall of established fear memory. *J. Neurosci.* 26 (37), 9560–9566.
- Cain, C.K., Blouin, A.M., Barad, M., 2004. Adrenergic transmission facilitates extinction of conditional fear in mice. *Learn. Mem.* 11 (2), 179–187 (Mar-Apr).
- Carter, R.M., Hofstotter, C., Tsuchiya, N., Koch, C., 2003. Working memory and fear conditioning. *Proc Natl Acad Sci U S A* 100 (3), 1399–1404.
- Cheng, D.T., Knight, D.C., Smith, C.N., Stein, E.A., Helmstetter, F.J., 2003. Functional MRI of human amygdala activity during Pavlovian fear conditioning: Stimulus processing versus response expression. *Behavioral Neuroscience* 117 (1), 3–10.
- Cheng, D.T., Knight, D.C., Smith, C.N., Helmstetter, F.J., 2006. Human amygdala activity during the expression of fear responses. *Behav Neurosci* 120 (6), 1187–1195.
- Cheng, D.T., Richards, J., Helmstetter, F.J., 2007. Activity in the human amygdala corresponds to early, rather than late period autonomic responses to a signal for shock. *Learning & memory (Cold Spring Harbor, N.Y.)* 14 (7), 485–490.
- Clark, R., DeYoung, C.G., Sponheim, S.R., Bender, T.L., Polusny, M.A., Erbes, C.R., Arbisi, P.A., 2013. Predicting post-traumatic stress disorder in veterans: Interaction of traumatic load with COMT gene variation. *Journal of Psychiatric Research* 47 (12), 1849–1856.
- Corcoran, K.A., Quirk, G.J., 2007. Activity in prefrontal cortex is necessary for the expression of learned, but not innate, fears. *The Journal of Neuroscience* 27 (4), 840–844.
- Craske, M.G., Kircanski, K., Zelikowsky, M., Mystkowski, J., Chowdhury, N., Baker, A., 2008. Optimizing inhibitory learning during exposure therapy. *Behaviour Research and Therapy* 46 (1), 5–27.
- Criado-Marrero, M., Morales Silva, R.J., Velazquez, B., Hernandez, A., Colon, M., Cruz, E., Soler-Cedeno, O., Porter, J.T., 2017. Dynamic expression of FKBP5 in the medial prefrontal cortex regulates resiliency to conditioned fear. *Learning & Memory* 24 (4), 145–152.
- Davis, M., 1992. The role of the amygdala in fear-potentiated startle: implications for animal models of anxiety. *Trends in Pharmacological Sciences* 13 (1), 35–41.
- Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. *Mol Psychiatry* 6 (1), 13–34.
- de Quervain, D.J., Aerni, A., Schelling, G., Roozendaal, B., 2009. Glucocorticoids and the regulation of memory in health and disease. *Front Neuroendocrinol* 30 (3), 358–370.
- Dedert, E.A., Calhoun, P.S., Harper, L.A., Dutton, C.E., McClernon, F.J., Beckham, J.C., 2012. Smoking withdrawal in smokers with and without posttraumatic stress disorder. *Nicotine & Tobacco Research* 14 (3), 372–376.
- Delamater, A.R., 2004. Experimental extinction in Pavlovian conditioning: behavioural and neuroscience perspectives. *The Quarterly journal of experimental psychology. B, Comparative and physiological psychology* 57 (2), 97–132.
- Deslauriers, J., Acheson, D.T., Maihofer, A.X., Nievergelt, C.M., Baker, D.G., Geyer, M.A., Risbrough, V.B., 2018. COMT val158met polymorphism links to altered fear conditioning and extinction are modulated by PTSD and childhood trauma. *Depress Anxiety* 35 (1), 32–42.
- Duits, P., Cath, D.C., Lissek, S., Hox, J.J., Hamm, A.O., Engelhard, I.M., van den Hout, M.A., Baas, J.M.P., 2015. Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depression and Anxiety* 32 (4), 239–253.
- Duvarci, S., Pare, D., 2014. Amygdala microcircuits controlling learned fear. *Neuron* 82 (5), 966–980.
- Dymond, S., Schlund, M.W., Roche, B., Whelan, R., 2014. The spread of fear: symbolic generalization mediates graded threat-avoidance in specific phobia. *Quarterly journal of experimental psychology* (2006) 67 (2), 247–259.
- Dymond, S., Dunsmoor, J.E., Vervliet, B., Roche, B., Hermans, D., 2015. Fear Generalization in Humans: Systematic Review and Implications for Anxiety Disorder Research. *Behav Ther* 46 (5), 561–582.
- Fani, N., Tone, E.B., Phifer, J., Norrholm, S.D., Bradley, B., Ressler, K.J., Kamkwalala, A., Jovanovic, T., 2012. Attention bias toward threat is associated with exaggerated fear expression and impaired extinction in PTSD. *Psychological Medicine* 42 (3), 533–543.
- Felmingham, K.L., Dobson-Stone, C., Schofield, P.R., Quirk, G.J., Bryant, R.A., 2013. The brain-derived neurotrophic factor Val66Met polymorphism predicts response to exposure therapy in posttraumatic stress disorder. *Biological Psychiatry* 73 (11), 1059–1063.
- Felmingham, K.L., Falconer, E.M., Williams, L., Kemp, A.H., Allen, A., Peduto, A., Bryant, R.A., 2014. Reduced amygdala and ventral striatal activity to happy faces in PTSD is associated with emotional numbing. *PLoS One* 9 (9), e103653.
- Felmingham, K.L., Zuj, D.V., Hsu, K.C.M., Nicholson, E., Palmer, M.A., Stuart, K., Vickers, J.C., Malhi, G.S., Bryant, R.A., 2018. The BDNF Val66Met polymorphism moderates the relationship between Posttraumatic Stress Disorder and fear extinction learning. *Psychoneuroendocrinology* 91, 142–148.
- Fenton, G.E., Pollard, A.K., Halliday, D.M., Mason, R., Bredy, T.W., Stevenson, C.W., 2014. Persistent prefrontal cortex activity contributes to enhanced learned fear expression in females. *Learning & Memory* 21 (2), 55–60.
- Foa, E.B., Kozak, M.J., 1986. Emotional processing of fear: exposure to corrective information. *Psychological Bulletin* 99 (1), 20–35.
- Foa, E.B., Hembree, E., Rothbaum, B.O., 2007. *Prolonged Exposure Therapy for PTSD: Emotional Processing of Traumatic Experiences, Therapist Guide*. Oxford University Press, New York.
- Forcadell, E., Torrents-Rodas, D., Vervliet, B., Leiva, D., Tortella-Feliu, M., Fullana, M.A., 2017. Does fear extinction in the laboratory predict outcomes of exposure therapy? A treatment analog study. *International Journal of Psychophysiology* 121, 63–71.
- Galatzer-Levy, I.R., Andero, R., Sawamura, T., Jovanovic, T., Papini, S., Ressler, K.J., Norrholm, S.D., 2017. A cross species study of heterogeneity in fear extinction learning in relation to FKBP5 variation and expression: Implications for the acute treatment of posttraumatic stress disorder. *Neuropharmacology* 116, 188–195.
- Ganella, D.E., Barendse, M.E.A., Kim, J.H., Whittle, S., 2017a. Prefrontal-Amygdala Connectivity and State Anxiety during Fear Extinction Recall in Adolescents. *Frontiers in Human Neuroscience* 11, 587.
- Ganella, D.E., Drummond, K.D., Ganella, E.P., Whittle, S., Kim, J.H., 2017b. Extinction of conditioned fear in adolescents and adults: A human fMRI study. *Frontiers in Human Neuroscience* 11, 647.

- Gazendam, F.J., Kindt, M., 2012. Worrying affects associative fear learning: A startle fear conditioning study. *PLoS ONE* 7 (4).
- Geraciotti, T.D., Baker, D.G., Ekhtor, N.N., West, S.A., Hill, K.K., Bruce, A.B., Schmidt, D., Rounds-Kugler, B., Yehuda, R., Keck, P.E., Kasckow, J.W., 2001. CSF norepinephrine concentrations in posttraumatic stress disorder. *The American Journal of Psychiatry* 158 (8), 1227–1230.
- Germain, A., 2013. Sleep disturbances as the hallmark of PTSD: where are we now? *The American Journal of Psychiatry* 170 (4), 372–382.
- Glover, E.M., Phifer, J.E., Crain, D.F., Norrholm, S.D., Davis, M., Bradley, B., Ressler, K.J., Jovanovic, T., 2011. Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. *Depress Anxiety* 28 (12), 1058–1066.
- Glover, E.M., Jovanovic, T., Mercer, K.B., Kerley, K., Bradley, B., Ressler, K.J., Norrholm, S.D., 2012. Estrogen levels are associated with extinction deficits in women with posttraumatic stress disorder. *Biological Psychiatry* 72 (1), 19–24.
- Glover, E.M., Mercer, K.B., Norrholm, S.D., Davis, M., Duncan, E., Bradley, B., Ressler, K.J., Jovanovic, T., 2013. Inhibition of fear is differentially associated with cycling estrogen levels in women. *Journal of Psychiatry & Neuroscience* 38 (5), 341–348.
- Glover, E.M., Jovanovic, T., Norrholm, S.D., 2015. Estrogen and extinction of fear memories: Implications for posttraumatic stress disorder treatment. *Biological Psychiatry* 78 (3), 178–185.
- Gressier, F., Calati, R., Balestri, M., Marsano, A., Alberti, S., Antypa, N., Serretti, A., 2013. The 5-HTTLPR polymorphism and posttraumatic stress disorder: a meta-analysis. *Journal of Traumatic Stress* 26 (6), 645–653.
- Griffin, M.G., 2008. A prospective assessment of auditory startle alterations in rape and physical assault survivors. *J Trauma Stress* 21 (1), 91–99.
- Groer, M.W., Kane, B., Williams, S.N., Duffy, A., 2014. Relationship of PTSD Symptoms With Combat Exposure, Stress, and Inflammation in American Soldiers. *Biological Research for Nursing* 17 (3), 303–310.
- Guthrie, R.M., Bryant, R.A., 2005. Auditory startle response in firefighters before and after trauma exposure. *Am J Psychiatry* 162 (2), 283–290.
- Guthrie, R.M., Bryant, R.A., 2006. Extinction learning before trauma and subsequent posttraumatic stress. *Psychosomatic Medicine* 68, 307–311.
- Haaker, J., Lonsdorf, T.B., Schumann, D., Bunzeck, N., Peters, J., Sommer, T., Kalisch, R., 2017. Where There is Smoke There is Fear-Impaired Contextual Inhibition of Conditioned Fear in Smokers. *Neuropsychopharmacology* 42 (8), 1640–1646.
- Handy, J.D., Avcu, P., Ko, N., Ortiz, A., Doria, M.J., Servatius, R.J., 2018. Facilitated acquisition of the classically conditioned eyeblink response in active duty military expressing posttraumatic stress disorder symptoms. *Behavioural Brain Research* 339, 106–113.
- Hauk, S., Gomes, F., Silveira Junior Ede, M., Almeida, E., Possa, M., Ceitlin, L.H., 2009. Serum levels of brain-derived neurotrophic factor in acute and posttraumatic stress disorder: a case report study. *Revista Brasileira de Psiquiatria* 31 (1), 48–51.
- Hauk, S., Kapczinski, F., Roesler, R., Silveira, E.D., Magalhaes, P.V., Kruehl, L.R.P., Schestatsky, S.S., Ceitlin, L.H.F., 2010. Serum brain-derived neurotrophic factor in patients with trauma psychopathology. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 34 (3), 459–462.
- Hermann, A., Kupper, Y., Schmitz, A., Walter, B., Vait, D., Hennig, J., Stark, R., Tabbert, K., 2012. Functional gene polymorphisms in the serotonin system and traumatic life events modulate the neural basis of fear acquisition and extinction. *Plos One* 7 (9), 11.
- Johnson, L.R., McGuire, J., Lazarus, R., Palmer, A.A., 2012. Pavlovian fear memory circuits and phenotype models of PTSD. *Neuropharmacology* 62 (2), 638–646.
- Jovanovic, T., Norrholm, S.D., 2016. Human psychophysiology and PTSD. In: Liberzon, I., Ressler, K. (Eds.), *Neurobiology of PTSD: From Brain to Mind*. Oxford University Press, New York.
- Jovanovic, T., Keyes, M., Fiallos, A., Myers, K.M., Davis, M., Duncan, E.J., 2005. Fear potentiation and fear inhibition in a human fear-potentiated startle paradigm. *Biol Psychiatry* 57 (12), 1559–1564.
- Jovanovic, T., Norrholm, S.D., Fennell, J.E., Keyes, M., Fiallos, A.M., Myers, K.M., Davis, M., Duncan, E.J., 2009. Posttraumatic stress disorder may be associated with impaired fear inhibition: Relation to symptom severity. *Psychiatry Research* 167 (1–2), 151–160.
- Jovanovic, T., Norrholm, S.D., Blanding, N.Q., Davis, M., Duncan, E., Bradley, B., Ressler, K.J., 2010. Impaired fear inhibition is a biomarker of PTSD but not depression. *Depression and Anxiety* 27 (3), 244–251.
- Karam, E.G., Friedman, M.J., Hill, E.D., Kessler, R.C., McLaughlin, K.A., Petukhova, M., Sampson, L., Shahly, V., Angermeyer, M.C., Bromet, E.J., de Girolamo, G., de Graaf, R., Demyttenaere, K., Ferry, F., Florescu, S.E., Haro, J.M., He, Y., Karam, A.N., Kawakami, N., Kovess-Masfety, V., Medina-Mora, M.E., Browne, M.A., Posada-Villa, J.A., Shalev, A.Y., Stein, D.J., Viana, M.C., Zarkov, Z., Koenen, K.C., 2014. Cumulative traumas and risk thresholds: 12-month PTSD in the World Mental Health (WMH) surveys. *Depress Anxiety* 31 (2), 130–142.
- Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry* 52 (12), 1048–1060.
- Kilpatrick, D.G., Koenen, K.C., Ruggiero, K.J., Acierio, R., Galea, S., Resnick, H.S., Roitzsch, J., Boyle, J., Gelernter, J., 2007. The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *American Journal of Psychiatry* 164 (11), 1693–1699.
- Kindt, M., Soeter, M., 2013. Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. *Biol Psychol* 92 (1), 43–50.
- Kircanski, K., Mortazavi, A., Castriotta, N., Baker, A.S., Mystkowski, J.L., Yi, R., Craske, M.G., 2012. Challenges to the traditional exposure paradigm: variability in exposure therapy for contamination fears. *Journal of Behavior Therapy and Experimental Psychiatry* 43 (2), 745–751.
- Knight, D.C., Smith, C.N., Cheng, D.T., Stein, E.A., Helmstetter, F.J., 2004. Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. *Cognitive, Affective, & Behavioral Neuroscience* 4 (3), 317–325.
- Koenen, K.C., Aiello, A.E., Bakshis, E., Amstadter, A.B., Ruggiero, K.J., Acierio, R., Kilpatrick, D.G., Gelernter, J., Galea, S., 2009. Modification of the association between serotonin transporter genotype and risk of posttraumatic stress disorder in adults by county-level social environment. *American Journal of Epidemiology* 169 (6), 704–711.
- Kolassa, I.-T., Kolassa, S., Ertl, V., Papassotiropoulos, A., De Quervain, D.J.F., 2010. The risk of posttraumatic stress disorder after trauma depends on traumatic load and the Catechol-O-Methyltransferase Val158Met polymorphism. *Biological Psychiatry* 67 (4), 304–308.
- Krakow, B., Hollifield, M., Johnston, L., Koss, M., Schrader, R., Warner, T.D., Tandberg, D., Lauriello, J., McBride, L., Cutchen, L., Cheng, D., Emmons, S., Germain, A., Melendrez, D., Sandoval, D., Prince, H., 2001. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: A randomized controlled trial. *Journal of the American Medical Association* 286 (5), 537–545.
- Kutlu, M.G., Gould, T.J., 2015. Nicotine modulation of fear memories and anxiety: Implications for learning and anxiety disorders. *Biochemical pharmacology* 97 (4), 498–511.
- Kutlu, M.G., Oliver, C., Gould, T.J., 2014. The effects of acute nicotine on contextual safety discrimination. *Journal of psychopharmacology (Oxford, England)* 28 (11), 1064–1070.
- Kutlu, M.G., Tumolo, J.M., Holliday, E., Garrett, B., Gould, T.J., 2016. Acute nicotine enhances spontaneous recovery of contextual fear and changes c-fos early gene expression in infralimbic cortex, hippocampus, and amygdala. *Learning & Memory* 23 (8), 405–414.
- LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., Phelps, E.A., 1998. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* 20 (5), 937–945.
- Lang, S., Kroll, A., Lipinski, S.J., Wessa, M., Ridder, S., Christmann, C., Schad, L.R., Flor, H., 2009. Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex. *European Journal of Neuroscience* 29 (4), 823–832.
- Lasser, K., Boyd, J.W., Woolhandler, S., Himmelstein, D.U., McCormick, D., Bor, D.H., 2000. Smoking and mental illness: A population-based prevalence study. *Jama* 284 (20), 2606–2610.
- Lau, J.Y., Viding, E.M., 2007. Anxiety-related biases in children's avoidant responses to a masked angry face. *Behav Res Ther* 45 (7), 1639–1645.
- Laurent, V., Westbrook, R.F., 2009. Inactivation of the infralimbic but not the prelimbic cortex impairs consolidation and retrieval of fear extinction. *Learning & memory (Cold Spring Harbor, N.Y.)* 16 (9), 520–529.
- LeDoux, J.E., 2000. Emotion circuits in the brain. *Annual Review of Neuroscience* 23, 155–184.
- LeDoux, J.E., 2014. Coming to terms with fear. *Proc Natl Acad Sci U S A* 111 (8), 2871–2878.
- LeDoux, J.E., Brown, R., 2017. A higher-order theory of emotional consciousness. *Proceedings of the National Academy of Sciences* 114 (10), E2016–E2025.
- LeDoux, J.E., Moscarello, J., Sears, R., Campese, V., 2017. The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm. *Mol Psychiatry* 22 (1), 24–36.
- Levy-Gigi, E., Richter-Levin, G., Keri, S., 2014. The hidden price of repeated traumatic exposure: different cognitive deficits in different first-responders. *Frontiers in Behavioral Neuroscience* 8, 281.
- Linnman, C., Rougemont-Bucking, A., Beucke, J.C., Zeffiro, T.A., Milad, M.R., 2011. Unconditioned responses and functional fear networks in human classical conditioning. *Behavioural Brain Research* 221 (1), 237–245.
- Lissek, S., 2012. Toward an account of clinical anxiety predicated on basic, neurally mapped mechanisms of Pavlovian fear-learning: the case for conditioned overgeneralization. *Depress Anxiety* 29 (4), 257–263.
- Lissek, S., Bradford, D.E., Alvarez, R.P., Burton, P., Espensen-Sturges, T., Reynolds, R.C., Grillon, C., 2014. Neural substrates of classically conditioned fear-generalization in humans: a parametric fMRI study. *Social Cognitive and Affective Neuroscience*. 9 (8), 1134–1142.
- Lommen, M.J.J., Engelhard, I.M., Sijbrandij, M., van den Hout, M.A., Hermans, D., 2013. Pre-trauma individual differences in extinction learning predict posttraumatic stress. *Behaviour Research and Therapy* 51 (2), 63–67.
- Lommen, M.J.J., Grey, N., Clark, D.M., Wild, J., Stott, R., Ehlers, A., 2016. Sleep and treatment outcome in posttraumatic stress disorder: Results from an effectiveness study. *Depression and Anxiety* 33 (7), 575–583.
- Lonsdorf, T.B., Weike, A.I., Nikamo, P., Schalling, M., Hamm, A.O., Ohman, A., 2009. Genetic gating of human fear learning and extinction: Possible implications for gene-environment interaction in anxiety disorder. *Psychological Science* 20 (2), 198–206.
- Lonsdorf, T.B., Menz, M.M., Andrea, M., Fullana, M.A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Romer, S., Shiban, Y., Schmitz, A., Straube, B., Vervliet, B., Wendt, J., Baas, J.M.P., Merz, C.J., 2017. Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neurosci Biobehav Rev* 77, 247–285.
- Lopresto, D., Schipper, P., Homberg, J.R., 2016. Neural circuits and mechanisms involved in fear generalization: Implications for the pathophysiology and treatment of post-traumatic stress disorder. *Neurosci Biobehav Rev* 60, 31–42.
- Lovibond, P.F., 2006. Fear and Avoidance: An Integrated Expectancy Model. In: Craske, M.G., Hermans, D., Vansteenwegen, D. (Eds.), *Fear and Learning: From Basic Processes to Clinical Implications*. American Psychological Association, Washington

- DC, pp. 117–132.
- Lovibond, P.F., Mitchell, C.J., Minard, E., Brady, A., Menzies, R.G., 2009. Safety behaviours preserve threat beliefs: Protection from extinction of human fear conditioning by an avoidance response. *Behaviour Research and Therapy* 47 (8), 716–720.
- Maddox, S.A., Schafe, G.E., Ressler, K.J., 2013. Exploring epigenetic regulation of fear memory and biomarkers associated with post-traumatic stress disorder. *Frontiers in Psychiatry* 4, 62.
- Maren, S., Phan, K.L., Liberzon, I., 2013. The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience* 14 (6), 417–428.
- Matsuoka, Y., Nishi, D., Noguchi, H., Kim, Y., Hashimoto, K., 2013. Longitudinal changes in serum brain-derived neurotrophic factor in accident survivors with posttraumatic stress disorder. *Neuropsychobiology* 68 (1), 44–50.
- McHugh, T., Forbes, D., Bates, G., Hopwood, M., Creamer, M., 2012. Anger in PTSD: is there a need for a concept of PTSD-related posttraumatic anger? *Clin Psychol Rev* 32 (2), 93–104.
- McLean, C.P., Foa, E.B., 2011. Prolonged exposure therapy for post-traumatic stress disorder: a review of evidence and dissemination. *Expert review of neurotherapeutics* 11 (8), 1151–1163.
- McNally, R.J., 2006. Cognitive abnormalities in post-traumatic stress disorder. *Trends in Cognitive Sciences* 10 (6), 271–277.
- Milad, M.R., Quirk, G.J., 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 420 (6911), 70–74.
- Milad, M.R., Vidal-Gonzalez, I., Quirk, G.J., 2004. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behavioural Brain Research* 118 (2), 389–394.
- Milad, M.R., Rauch, S.L., Pitman, R.K., Quirk, G.J., 2006. Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biological Psychology* 73 (1), 61–71.
- Milad, M.R., Quirk, G.J., Pitman, R.K., Orr, S.P., Fischl, B., Rauch, S.L., 2007a. A role for the human dorsal anterior cingulate cortex in fear expression. *Biological Psychiatry* 62 (10), 1191–1194.
- Milad, M.R., Wright, C.I., Orr, S.P., Pitman, R.K., Quirk, G.J., Rauch, S.L., 2007b. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry* 62 (5), 446–454.
- Milad, M.R., Orr, S.P., Lasko, N.B., Chang, Y., Rauch, S.L., Pitman, R.K., 2008. Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study. *Journal of Psychiatric Research* 42 (7), 515–520.
- Milad, M.R., Pitman, R.K., Ellis, C.B., Gold, A.L., Shin, L.M., Lasko, N.B., Zeidan, M.A., Handwerker, K., Orr, S.P., Rauch, S.L., 2009. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological Psychiatry* 66 (12), 1075–1082.
- Milad, M.R., Zeidan, M.A., Contero, A., Pitman, R.K., Klibanski, A., Rauch, S.L., Goldstein, J.M., 2010. The influence of gonadal hormones on conditioned fear extinction in healthy humans. *Neuroscience* 168 (3), 652–658.
- Milad, M.R., Furtak, S.C., Greenberg, J.L., Keshaviah, A., Im, J.J., Falkenstein, M.J., Jenike, M., Rauch, S.L., Wilhelm, S., 2013. Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit. *JAMA Psychiatr* 70 (6), 608–618 quiz 554.
- Mineka, S., 1979. The role of fear in theories of avoidance learning, flooding, and extinction. *Psychological Bulletin* 86, 985–1010.
- Mineka, S., Oehlberg, K., 2008. The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta Psychologica* 127 (3), 567–580.
- Morey, R.A., Dunsmoor, J.E., Haswell, C.C., Brown, V.M., Vora, A., Weiner, J., Stjepanovic, D., Wagner 3rd, H.R., LaBar, K.S., 2015. Fear learning circuitry is biased toward generalization of fear associations in posttraumatic stress disorder. *Transl Psychiatry* 5, e700.
- Morris, R.W., Bouton, M.E., 2007. The effect of yohimbine on the extinction of conditioned fear: a role for context. *Behav. Neurosci.* 121 (3), 501–514 (Jun).
- Morris, J.S., Dolan, R.J., 2004. Dissociable amygdala and orbitofrontal responses during reversal fear conditioning. *Neuroimage* 22 (1), 372–380.
- Morris, M.C., Compas, B.E., Garber, J., 2012. Relations among posttraumatic stress disorder, comorbid major depression, and HPA function: a systematic review and meta-analysis. *Clin Psychol Rev* 32 (4), 301–315.
- Motzkin, J.C., Philipp, C.L., Wolf, R.C., Baskaya, M.K., Koenigs, M., 2015. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry* 77 (3), 276–284.
- Mueller, D., Cahill, S.P., 2010. Noradrenergic modulation of extinction learning and exposure therapy. *Behavioural Brain Research* 208 (1), 1–11.
- Myers, K.M., Davis, M., 2002. Behavioral and Neural Analysis of Extinction. *Neuron* 36 (4), 567–584.
- Myers, K.M., Davis, M., 2007. Mechanisms of fear extinction. *Molecular Psychiatry* 12 (2), 120–150.
- National Institute of Mental Health, 2016. Behavioral assessment methods for RDoC constructs, Rockville, MD. In: USA.
- Norrholm, S.D., 2012. Clinical implications of impaired fear extinction in posttraumatic stress disorder (PTSD). In: Flach, A., Powell, S.M., Gallub, R. (Eds.), *Directions in Psychiatry*. The Hatherleigh Company, Ltd, Hobart, NY.
- Norrholm, S.D., Jovanovic, T., 2018. Fear Processing, Psychophysiology, and PTSD. *Harvard Review of Psychiatry* 26 (3), 129–141.
- Norrholm, S.D., Jovanovic, T., Vervliet, B., Myers, K.M., Davis, M., Rothbaum, B.O., Duncan, E.J., 2006. Conditioned fear extinction and reinstatement in a human fear-potentiated startle paradigm. *Learning & memory* 13 (6), 681–685.
- Norrholm, S.D., Vervliet, B., Jovanovic, T., Boshoven, W., Myers, K.M., Davis, M., Rothbaum, B., Duncan, E.J., 2008. Timing of extinction relative to acquisition: a parametric analysis of fear extinction in humans. *Behav Neurosci* 122 (5), 1016–1030.
- Norrholm, S.D., Jovanovic, T., Olin, I.W., Sands, L.A., Karapanou, I., Bradley, B., Ressler, K.J., 2011. Fear extinction in traumatized civilians with posttraumatic stress disorder: Relation to symptom severity. *Biological Psychiatry* 69 (6), 556–563.
- Norrholm, S.D., Jovanovic, T., Smith, A.K., Binder, E., Klengel, T., Conneely, K., Mercer, K.B., Davis, J.S., Kerley, K., Winkler, J., Gillespie, C.F., Bradley, B., Ressler, K.J., 2013. Differential genetic and epigenetic regulation of catechol-O-methyltransferase is associated with impaired fear inhibition in posttraumatic stress disorder. *Frontiers in Behavioral Neuroscience* 7, 10.
- Norrholm, S.D., Glover, E.M., Stevens, J.S., Fani, N., Galatzer-Levy, I.R., Bradley, B., Ressler, K.J., Jovanovic, T., 2015. Fear load: The psychophysiological over-expression of fear as an intermediate phenotype associated with trauma reactions. *International Journal of Psychophysiology* 98 (2), 270–275 Pt 2.
- Orr, S.P., Metzger, L.J., Lasko, N.B., Macklin, M.L., Peri, T., Pitman, R.K., 2000. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology* 109 (2), 290–298.
- Pace-Schott, E.F., Milad, M.R., Orr, S.P., Rauch, S.L., Stickgold, R., Pitman, R.K., 2009. Sleep promotes generalization of extinction of conditioned fear. *Sleep* 32 (1), 19–26.
- Pace-Schott, E.F., Spencer, R.M.C., Vijayakumar, S., Ahmed, N.A.K., Verga, P.W., Orr, S.P., Pitman, R.K., Milad, M.R., 2013. Extinction of conditioned fear is better learned and recalled in the morning than in the evening. *Journal of Psychiatric Research* 47 (11), 1776–1784.
- Pace-Schott, E.F., Germain, A., Milad, M.R., 2015a. Effects of sleep on memory for conditioned fear and fear extinction. *Psychological Bulletin* 141 (4), 835–857.
- Pace-Schott, E.F., Germain, A., Milad, M.R., 2015b. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. *Biology of Mood & Anxiety Disorders* 5, 3.
- Pare, D., Duvarci, S., 2012. Amygdala microcircuits mediating fear expression and extinction. *Current Opinion in Neurobiology* 22 (4), 717–723.
- Pavlov, I.P., 1927. *Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex*. Oxford University Press, London.
- Peri, T., Ben-Shakhar, G., Orr, S.P., Shalev, A.Y., 2000. Psychophysiological assessment of aversive conditioning in posttraumatic stress disorder. *Biological Psychiatry* 47 (6), 512–519.
- Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E., 2004. Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron* 43 (6), 897–905.
- Pietrzak, R.H., Gallezot, J.D., Ding, Y.S., Henry, S., Potenza, M.N., Southwick, S.M., Krystal, J.H., Carson, R.E., Neumeister, A., 2013. Association of posttraumatic stress disorder with reduced in vivo norepinephrine transporter availability in the locus coeruleus. *JAMA psychiatry* 70 (11), 1199–1205.
- Pineles, S.L., Nilni, Y.I., King, M.W., Patton, S.C., Bauer, M.R., Mostoufi, S.M., Gerber, M.R., Hauger, R., Resick, P.A., Rasmusson, A.M., Orr, S.P., 2016. Extinction retention and the menstrual cycle: Different associations for women with posttraumatic stress disorder. *J Abnorm Psychol* 125 (3), 349–355.
- Pitman, R.K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., Milad, M.R., Liberzon, I., 2012. Biological studies of post-traumatic stress disorder. *Nature* 13, 769–787.
- Pittig, A., Treanor, M., LeBeau, R.T., Craske, M.G., 2018. The role of associative fear and avoidance learning in anxiety disorders: Gaps and directions for future research. *Neurosci Biobehav Rev* 88, 117–140.
- Possemato, K., Maisto, S.A., Wade, M., Barrie, K., McKenzie, S., Lantinga, L.J., Ouimette, P., 2015. Ecological momentary assessment of PTSD symptoms and alcohol use in combat veterans. *Psychology of Addictive Behaviors* 29 (4), 894–905.
- Quirk, G.J., Russo, G.K., Barron, J.L., Lebron, K., 2000. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *The Journal of Neuroscience* 20 (16), 6225–6231.
- Raes, A.K., De Raedt, R., Verschuere, B., De Houwer, J., 2009. Failure to loose fear: The impact of cognitive load and trait anxiety on extinction. *Behaviour Research and Therapy* 47 (12), 1096–1101.
- Raij, T., Nummenmaa, A., Marin, M.F., Porter, D., Furtak, S., Setsompop, K., Milad, M.R., 2017. Prefrontal Cortex Stimulation Enhances Fear Extinction Memory in Humans. *Biol Psychiatry*. S0006-3223 (17), 32144–32153.
- Rakofsky, J.J., Ressler, K.J., Dunlop, B.W., 2012. BDNF function as a potential mediator of bipolar disorder and post-traumatic stress disorder comorbidity. *Molecular Psychiatry* 17, 22–35.
- Ramchand, R., Schell, T.L., Karney, B.R., Osilla, K.C., Burns, R.M., Caldarone, L.B., 2010. Disparate prevalence estimates of PTSD among service members who served in Iraq and Afghanistan: possible explanations. *Journal of Traumatic Stress* 23 (1), 59–68.
- Rauch, S.A., Eftekhari, A., Ruzek, J.I., 2012. Review of exposure therapy: a gold standard for PTSD treatment. *J Rehabil Res Dev* 49 (5), 679–687.
- Rescorla, R.A., Heth, C.D., 1975. Reinstatement of fear to an extinguished conditioned stimulus. *Journal of Experimental Psychology. Animal behavior processes* 1 (1), 88–96.
- Resnick, H.S., Kilpatrick, D.G., Dansky, B.S., Saunders, B.E., Best, C.L., 1993. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J Consult Clin Psychol* 61 (6), 984–991.
- Rothbaum, B.O., Davis, M., 2003. Applying learning principles to the treatment of post-trauma reactions. *Annals of the New York Academy of Sciences* 1008, 112–121.
- Rougémont-Bücking, A., Linnman, C., Zeffiro, T.A., Zeidan, M.A., Lebron-Milad, K., Rodríguez-Romaguera, J., Rauch, S.L., Pitman, R.K., Milad, M.R., 2011. Altered processing of contextual information during fear extinction in PTSD: An fMRI study. *Cns Neuroscience & Therapeutics* 17 (4), 227–236.
- Sawamura, T., Klengel, T., Armario, A., Jovanovic, T., Norrholm, S.D., Ressler, K.J., Anderson, R., 2016. Dexamethasone Treatment Leads to Enhanced Fear Extinction and Dynamic Fkbp5 Regulation in Amygdala. *Neuropsychopharmacology* 41 (3),

- 832–846.
- Schnurr, P.P., Friedman, M.J., Engel, C.C., Foa, E.B., Shea, M.T., Chow, B.K., Resick, P.A., Thurston, V., Orsillo, S.M., Haug, R., Turner, C., Bernardy, N., 2007. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *Journal of the American Medical Association* 297 (8), 820–830.
- Sehlmeyer, C., Dannlowski, U., Schoning, S., Kugel, H., Pyka, M., Pfleiderer, B., Zwieterlood, P., Schifflbauer, H., Heindel, W., Arolt, V., Konrad, C., 2011. Neural correlates of trait anxiety in fear extinction. *Psychological medicine* 41 (4), 789–798.
- Sevenster, D., Beckers, T., Kindt, M., 2014. Fear conditioning of SCR but not the startle reflex requires conscious discrimination of threat and safety. *Frontiers in behavioral neuroscience* 8, 32.
- Shalev, A.Y., Sahar, T., Freedman, S., Peri, T., Glick, N., Brandes, D., Orr, S.P., Pitman, R.K., 1998. A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder. *Arch Gen Psychiatry* 55 (6), 553–559.
- Shalev, A.Y., Vidolock, E.J., Peleg, T., Segman, R., Pitman, R.K., Yehuda, R., 2008. Stress hormones and post-traumatic stress disorder in civilian trauma victims: a longitudinal study. Part I: HPA axis responses. *Int. J. Neuropsychopharmacol.* 11 (3), 365–372.
- Shvil, E., Sullivan, G.M., Schafer, S., Markowitz, J.C., Campeas, M., Wager, T.D., Milad, M.R., Neria, Y., 2014. Sex differences in extinction recall in posttraumatic stress disorder: A pilot fMRI study. *Neurobiology of Learning and Memory*. 113, 101–108.
- Sierra-Mercado, D., Padilla-Coreano, N., Quirk, G.J., 2011. Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. *Neuropsychopharmacology* 36 (2), 529–538.
- Simmons, A.N., Norman, S.B., Spadoni, A.D., Strigo, I.A., 2013. Neurosubstrates of remission following prolonged exposure therapy in veterans with posttraumatic stress disorder. *Psychotherapy and psychosomatics* 82 (6), 382–389.
- Soeter, M., Kindt, M., 2012. Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. *Neuropsychopharmacology* 37 (5), 1204–1215.
- Soliman, F., Glatt, C.E., Bath, K.G., Levita, L., Jones, R.M., Pattwell, S.S., Jing, D.Q., Tottenham, N., Amso, D., Somerville, L.H., Voss, H.U., Glover, G., Ballon, D.J., Liston, C., Teslovich, T., Van Kempen, T., Lee, F.S., Casey, B.J., 2010. A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science* 327 (5967), 863–866.
- Sripada, R.K., Garfinkel, S.N., Liberzon, I., 2013. Avoidant symptoms in PTSD predict fear circuit activation during multimodal fear extinction. *Frontiers in Human Neuroscience* 7, 672.
- Stickgold, R., 2005. Sleep-dependent memory consolidation. *Nature* 437 (7063), 1272–1278.
- Szeszko, P.R., Lehrner, A., Yehuda, R., 2018. Glucocorticoids and Hippocampal Structure and Function in PTSD. *Harvard review of psychiatry* 26 (3), 142–157.
- Taylor, J.H., Jakubowski, E., Bloch, M.H., 2015. Predictors of anxiety recurrence in the Coordinated Anxiety Learning and Management (CALM) trial. *J Psychiatr Res* 65, 154–165.
- Tunbridge, E.M., Harrison, P.J., Weinberger, D.R., 2006. Catechol-O-methyltransferase, cognition, and psychosis: Val158Met and beyond. *Biological Psychiatry* 60 (2), 141–151.
- Valente, N.L., Vallada, H., Cordeiro, Q., Bressan, R.A., Andreoli, S.B., Mari, J.J., Mello, M.F., 2011. Catechol-O-methyltransferase (COMT) val158met polymorphism as a risk factor for PTSD after urban violence. *Journal of Molecular Neuroscience* 43 (3), 516–523.
- VanElzakker, M.B., Kathryn Dahlgren, M., Caroline Davis, F., Dubois, S., Shin, L.M., 2014. From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and anxiety disorders. *Neurobiology of Learning and Memory*. 113, 3–18.
- Vervliet, B., Vansteenwegen, D., Hermans, D., Eelen, P., 2007. Concurrent exciters limit the extinction of conditioned fear in humans. *Behaviour Research and Therapy* 45 (2), 375–383.
- Wahbeh, H., Oken, B.S., 2013. Salivary cortisol lower in posttraumatic stress disorder. *Journal of Traumatic Stress* 26 (2), 241–248.
- Wald, I., Degnan, K.A., Gorodetsky, E., Charney, D.S., Fox, N.A., Fruchter, E., Goldman, D., Lubin, G., Pine, D.S., Bar-Haim, Y., 2013. Attention to threats and combat-related posttraumatic stress symptoms: prospective associations and moderation by the serotonin transporter gene. *JAMA psychiatry* 70 (4), 401–408.
- Waters, A.M., Pine, D.S., 2016. Evaluating differences in Pavlovian fear acquisition and extinction as predictors of outcome from cognitive behavioural therapy for anxious children. *Journal of Child Psychology and Psychiatry, and allied Disciplines* 57 (7), 869–876.
- Wegerer, M., Kerschbaum, H., Blechert, J., Wilhelm, F.H., 2014. Low levels of estradiol are associated with elevated conditioned responding during fear extinction and with intrusive memories in daily life. *Neurobiology of Learning and Memory* 116, 145–154.
- Wendt, J., Neubert, J., Lindner, K., Ernst, F.D., Homuth, G., Weike, A.I., Hamm, A.O., 2015. Genetic influences on the acquisition and inhibition of fear. *International Journal of Psychophysiology*. 98 (3 Pt 2), 499–505.
- Wingenfeld, K., Whooley, M.A., Neylan, T.C., Otte, C., Cohen, B.E., 2015. Effect of current and lifetime posttraumatic stress disorder on 24-h urinary catecholamines and cortisol: results from the Mind Your Heart Study. *Psychoneuroendocrinology* 52, 83–91.
- Xia, W., Dymond, S., Lloyd, K., Vervliet, B., 2017. Partial reinforcement of avoidance and resistance to extinction in humans. *Behav Res Ther* 96, 79–89.
- Xie, P., Kranzler, H.R., Poling, J., Stein, M.B., Anton, R.F., Farrer, L.A., Gelernter, J., 2010. Interaction of FKBP5 with childhood adversity on risk for post-traumatic stress disorder. *Neuropsychopharmacology* 35 (8), 1684–1692.
- Yang, Y.L., Chao, P.K., Lu, K.T., 2006. Systemic and intra-amygdala administration of glucocorticoid agonist and antagonist modulate extinction of conditioned fear. *Neuropsychopharmacology* 31 (5), 912–924.
- Yehuda, R., Southwick, S., Giller, E.L., Ma, X., Mason, J.W., 1992. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. *The Journal of Nervous and Mental Disease* 180 (5), 321–325.
- Yehuda, R., Siever, L.J., Teicher, M.H., Levengood, R.A., Gerber, D.K., Schmeidler, J., Yang, R.K., 1998. Plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol concentrations and severity of depression in combat posttraumatic stress disorder and major depressive disorder. *Biological Psychiatry* 44 (1), 56–63.
- Yehuda, R., Tischler, L., Golier, J.A., Grossman, R., Brand, S.R., Kaufman, S., Harvey, P.D., 2006. Longitudinal assessment of cognitive performance in Holocaust survivors with and without PTSD. *Biological Psychiatry* 60 (7), 714–721.
- Yehuda, R., Golier, J.A., Tischler, L., Harvey, P.D., Newmark, R., Yang, R.K., Buchsbaum, M.S., 2007a. Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: Relation to risk and resilience factors. *Journal of Psychiatric Research* 41, 435–445.
- Yehuda, R., Morris, A., Labinsky, E., Zelman, S., Schmeidler, J., 2007b. Ten-year follow-up study of cortisol levels in aging holocaust survivors with and without PTSD. *Journal of Traumatic Stress* 20 (5), 757–761.
- Yehuda, R., Bierer, L.M., Sarapas, C., Makotkine, I., Andrew, R., Seckl, J.R., 2009. Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001. *Psychoneuroendocrinology* 34 (9), 1304–1313.
- Yehuda, R., Bierer, L.M., Pratchett, L.C., Lehrner, A., Koch, E.C., Van Manen, J.A., Flory, J.D., Makotkine, I., Hildebrandt, T., 2015a. Cortisol augmentation of a psychological treatment for warfighters with posttraumatic stress disorder: Randomized trial showing improved treatment retention and outcome. *Psychoneuroendocrinology* 51, 589–597.
- Yehuda, R., Hoge, C.W., McFarlane, A.C., Vermetten, E., Lanius, R.A., Nievergelt, C.M., Hobfoll, S.E., Koenen, K.C., Neylan, T.C., Hyman, S.E., 2015b. Post-traumatic stress disorder. *Nature reviews. Disease primers* 1, 15057.
- Zannas, A.S., Binder, E.B., 2014. Gene-environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes, Brain and Behavior* 13 (1), 25–37.
- Zeidan, M.A., Igoe, S.A., Linnman, C., Vitalo, A., Levine, J.B., Klibanski, A., Goldstein, J.M., Milad, M.R., 2011. Estradiol modulates medial prefrontal cortex and amygdala activity during fear extinction in women and female rats. *Biological Psychiatry* 70 (10), 920–927.
- Zeidan, M.A., Lebron-Milad, K., Thompson-Hollands, J., Im, J.J.Y., Dougherty, D.D., Holt, D.J., Orr, S.P., Milad, M.R., 2012. Test-retest reliability during fear acquisition and fear extinction in humans. *Cns Neuroscience & Therapeutics* 18 (4), 313–317.
- Zoladz, P.R., Diamond, D.M., 2013. Current status on behavioral and biological markers of PTSD: A search for clarity in a conflicting literature. *Neuroscience and Biobehavioral Reviews* 37 (5), 860–895.
- Zuj, D.V., Palmer, M.A., Hsu, C.K., Nicholson, E.L., Cushing, P.J., Gray, K.E., Felmingham, K.L., 2016a. Impaired fear extinction associated with PTSD increases with hours-since-waking. *Depression and Anxiety* 33 (3), 203–210.
- Zuj, D.V., Palmer, M.A., Lommen, M.J.J., Felmingham, K.L., 2016b. The centrality of fear extinction in linking risk factors to PTSD: A narrative review. *Neuroscience & Biobehavioral Reviews* 69, 15–35.
- Zuj, D.V., Felmingham, K.L., Palmer, M.A., Lawrence-Wood, E., Van Hooff, M., Lawrence, A.J., Bryant, R.A., McFarlane, A.C., 2017a. Neural activity and emotional processing following military deployment: Effects of mild traumatic brain injury and posttraumatic stress disorder. *Brain Cogn* 118, 19–26.
- Zuj, D.V., Palmer, M.A., Gray, K.E., Hsu, C.K., Nicholson, E.L., Malhi, G.S., Bryant, R.A., Felmingham, K.L., 2017b. Negative appraisals and fear extinction are independently related to PTSD symptoms. *Journal of Affective Disorders* 217, 246–251.
- Zuj, D.V., Palmer, M.A., Malhi, G.S., Bryant, R.A., Felmingham, K.L., 2017c. Endogenous cortisol reactivity moderates the relationship between fear inhibition to safety signals and posttraumatic stress disorder symptoms. *Psychoneuroendocrinology* 78, 14–21.
- Zuj, D.V., Palmer, M.A., Malhi, G.S., Bryant, R.A., Felmingham, K.L., 2018. Endogenous salivary alpha-amylase does not interact with skin conductance response during fear extinction in posttraumatic stress disorder. *Psychiatry Res* 262, 316–322.