Review

Behavioral and neural mechanisms of latent inhibition

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Fear is an adaptive emotion that serves to protect an organism against potential dangers. It is often studied using classical conditioning paradigms where a conditioned stimulus is paired with an aversive unconditioned stimulus to induce a threat response. Less commonly studied is a phenomenon that is related to this form of conditioning, known as latent inhibition. Latent inhibition (LI) is a paradigm in which a neutral cue is repeatedly presented in the absence of any aversive associations. Subsequent pairing of this pre-exposed cue with an aversive stimulus typically leads to reduced expression of a conditioned fear/threat response. In this article, we review some of the theoretical basis for LI and its behavioral and neural mechanisms. We compare and contrast LI and fear/threat extinction—a process in which a previously conditioned cue is repeatedly presented in the absence of aversive outcomes. We end with highlighting the potential clinical utility of LI. Particularly, we focus on how LI application could be useful for enhancing resilience, especially for individuals who are more prone to continuous exposure to trauma and stressful environments, such as healthcare workers and first responders. The knowledge to be gained from advancing our understanding of neural mechanisms in latent inhibition could be applicable across psychiatric disorders characterized by exaggerated fear responses and impaired emotion regulation.

Threat conditioning is a phenomenon in which a conditioned stimulus is paired with an aversive unconditioned stimulus to induce a threat response. The behavioral and neurobiological mechanisms of this process have been studied extensively (Maren 2001; Kim and Jung 2006), as has its clinical relevance given that excessive fear is a key feature of fear-based psychiatric disorders such as post-traumatic stress disorder (PTSD) (Blechert et al. 2007; Amstadter et al. 2009; Rabinak et al. 2017). Threat extinction, in which a previously conditioned cue is repeatedly presented in the absence of aversive outcomes, has therefore been an important area of research (Milad and Quirk 2012). Threat extinction research has formed the basis of widely implemented clinical treatments for fear-based disorders (Hofmann 2008; Scheveneels et al. 2016). However, current evidence-based treatments for PTSD (e.g., exposure therapy, cognitive therapy, eye movement desensitization and reprocessing, and medication management) are administered after-the-fact (Cusack et al. 2016). Despite receiving first-line treatments available for PTSD, a substantial minority of patients do not achieve remission (Hamner et al. 2004; Stein et al. 2009; Rodriguez et al. 2012; Dunlop et al. 2014). Consequently, calls for preventative interventions to promote healthy recovery from traumatic events have emerged (Feldner et al. 2007). Latent inhibition (LI) research provides theoretical and empirical evidence to suggest it may be possible to enhance resilience in anticipation of potential future traumatic exposures. Here, we review some of the theoretical bases for LI, and its behavioral and neural mechanisms. We compare and contrast LI and fear/threat extinction, and we end with highlighting the potential clinical utility of LI. Particularly, we focus on how LI application could be useful for enhancing resilience, especially for individuals who are more prone to continuous exposure to trauma and stressful environments, such as healthcare workers and first responders. Our method for gathering articles used in this review was guided by a PubMed search for studies on the behavioral and neural mechanisms of LI, LI and fear extinction, and LI and clinical disorders including PTSD. This method was used in order to find articles that would inform the potential clinical value of LI and the need for further research.

What is latent inhibition?

Latent inhibition, a term coined ~60 yr ago by Lubow and Moore (1959), describes the phenomenon in which the learning or retrieving of an association between a conditioned stimulus (CS) and another innately rewarding or threatening stimulus (unconditioned stimulus; US) is impaired by previous exposure to the to-be-CS in the absence of the unconditioned stimulus (i.e., nonreinforced stimulus) (see Fig. 1 for a legend of LI-related terms; Lubow and Moore 1959).

This pre-exposure delays and weakens the formation or expression of a future conditioned conscious fear response in humans (CR), or nonconscious conditioned threat response in animals (see Fig. 2A,B; LeDoux 2014). Most explanations of latent inhibition can be classified within either the attentional or retrieval/competition theories (Schmajuk et al. 1996; Lubow 2010). The attentional theories contend that pre-exposure reduces the salience and novelty of the to-be-conditioned stimulus, and therefore inhibits acquisition of an association with the unconditioned stimulus (Mackintosh 1975; Pearce and Hall 1980; Lubow 1989; Weiner and Feldon 1997; McLaren and Mackintosh 2000). Due to the loss of novelty of the to-be-conditioned stimulus as a result of pre-exposure, less attention is given to the CS during conditioning, reducing the effectiveness of the CS–US relationship (Schmajuk et al. 1996). The conditioned attention theory (Lubow 1989), for instance, postulates that LI occurs because the subject learns during pre-exposure not to attend to the neutral stimulus (to-be-CS),

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Article is online at http://www.learnmem.org/cgi/doi/10.1101/lm.053439.121.

Acronym	Term	Definition	Example
NS	Neutral Stimulus	A cue that does not evoke an evolutionarily conserved emotional response	Bell
	Pre-Exposure	Experience with an inherently neutral stimulus prior to its pairing with an unconditioned stimulus in conditioning	Bell exposure before shock introduction
US	Unconditioned Stimulus	A stimulus that provokes an innate emotional response (fear)	Shock
UR	Unconditioned Response	The innate emotional response (fear) to the unconditioned stimulus	Fear response to the shock
	Conditioning	The process during which an inherently neutral stimulus is repeatedly paired with an unconditioned stimulus. With effective conditioning, the neutral stimulus becomes the conditioned stimulus	Repeated bell/shock pairing
CS	Conditioned Stimulus	An inherently neutral stimulus that provokes an emotional response after it is repeatedly paired with an unconditioned stimulus and the association of the two is learned	Bell after fear conditioning, now with an associated fear response
CR	Conditioned Response	The learned emotional response to what was previously the neutral stimulus and has become the conditioned stimulus through conditioning	Learned fear response to the bell
	Extinction	The process during which a conditioned stimulus is repeatedly presented by itself without the unconditioned stimulus. With effective extinction, the conditioned stimulus and the conditioned response will become unlearned, and the conditioned stimulus becomes the neutral stimulus	Repeated bell exposure alone after conditioning
LI	Latent Inhibition	When exposure to the neutral stimulus before conditioning (pre-exposure) slows the learning of the association with the unconditioned stimulus and lessens the intensity of the conditioned response	Slowing/lessening of the development of the learned fear response to the bell during the bell/shock pairing after pre-exposure to the bell alone

Figure 1. Latent inhibition in fear learning: vocabulary and illustrative examples. This figure provides definitions and examples for the relevant latent inhibition, conditioning, and extinction related terms and acronyms used here.

recognizing it as inconsequential and making a CS–no consequence association. This association interferes with later learning involving the to-be-CS. The retrieval/competition theories argue, in contrast, that LI is not a failure of acquisition, but a product of competing retrieval of associations (Miller et al. 1986; Weiner 1990; Bouton 1993). Proponents of the retrieval/competition theories propose that two competing associative memories are retrieved during the testing stage: the CS–no consequence association (from pre-exposure) and the CS–US association (from conditioning). Given that the CS–no consequence association was presented first and did not contradict any earlier learning, this response dominates, assuming all other factors affecting the stimuli presentations are equal (e.g., context, timing, number of presentations) (Miller et al. 1986; Bouton 1993). Debate continues over which theoretical framework is most accurate (e.g., Escobar et al. 2002; Lubow 2005; Kaplan and Lubow 2011; Miller et al. 2015; Rodriguez et al. 2019) with some models incorporating both (Schmajuk et al. 1996). Indeed attentional and retrieval/competition theories may not contradict each other, but rather describe different parts of the same learning and performance process that is LI (Lubow 2010). These theoretical considerations point to the adaptive significance of LI (Lubow and Gewirtz 1995; Kraemer and Golding 1997). The ability to ignore irrelevant/inconsequential stimuli in favor of attending to newer, more consequential or threatening environmental inputs allows for conservation of attentional resources for important stimuli (Lubow 2005; Mitchell et al. 2011; Gonzalo et al. 2013; Piantadosi and Floresco 2014).

Variables impacting LI

There is substantial variance in currently existing experimental protocols of LI. As with any experiment, the protocol designs are driven by the specific scientific inquiry of the investigative teams. This experimental variance has led to the identification of a number of variables that influence the expression of LI. As expected, the number of pre-exposures to the to-be-CS appears to be a critical variable; the more pre-exposures, the stronger the observed LI effect (Vaitl and Lipp 1997; De la Casa and Lubow 2001; Lipina et al. 2013). On the other hand, the number of CS–US pairings and US intensity have a negative correlation with the expression of LI (Ruob et al. 1998; Lipina et al. 2013).

Studies in animals suggest that LI is context-dependent. Specifically, the LI effect is attenuated or abolished when the context in which the CS was presented changes between pre-exposure and conditioning (Hall and Channell 1985; Escobar et al. 2002; Quintero et al. 2011a,b; Miguez et al. 2015, 2018; Miller et al. 2015). Shifts in temporal contexts have also been shown to modulate the magnitude of LI (Manrique et al. 2004; Molero et al. 2005). It has been theorized that when pre-exposure and conditioning occur at different times of day, they are associated with different internal contextual cues, resulting in reduced LI (Molero-Chamizo 2017, 2018; Molero-Chamizo and Rivera-Urbina 2017). Time-induced attenuation of LI appears to occur when the retention interval takes place in the same context as the pre-exposure, conditioning, and test phases (Bakner et al. 1991; Aguado et al. 1994). Enhanced LI (super-LI), however, occurs when a longer retention interval takes place in a different context from that of the other phases (De La Casa and Lubow 2000, 2005; Lubow and De la Casa 2005), and when it occurs between the conditioning and test phase, but not between the pre-exposure and conditioning phase (De la Casa and Lubow 2002).

Human studies also support the finding that LI is context-dependent (De la Casa and Lubow 2001; Gray et al. 2001; Byron Nelson and del Carmen Sanjuan 2006). Research indicates that when the test context differs from the context in which pre-exposure took place, LI is abolished in human subjects (De la Casa and Lubow 2001; Gray et al. 2001). Human studies have also shown that a disruption between pre-exposure and conditioning, or between conditioning and testing, by the interpolation of an irrelevant novel stimulus or a time interval, can modulate LI (De la Casa and Lubow 2001; Díaz and De la Casa 2002; Pineño

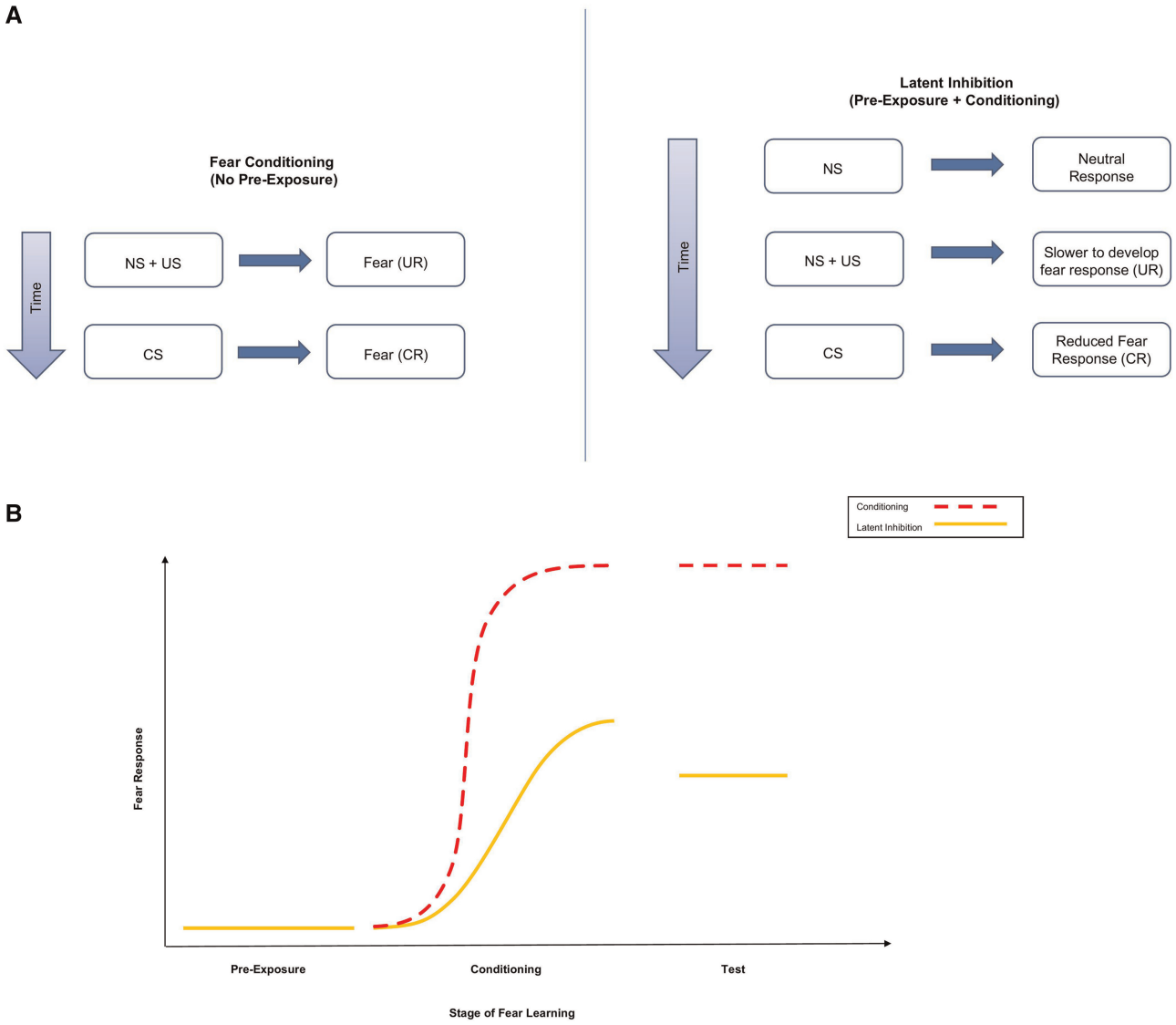

Figure 2. (*A*) Fear conditioning versus latent inhibition. This figure compares the fear response to a stimulus without (*left*) and with (*right*) pre-exposure (i.e., latent inhibition). CS refers to the conditioned stimulus, US refers to the unconditioned stimulus, and CR refers to the conditioned fear response. (*B*) The effect of pre-exposure on fear response. This graph compares the difference in fear response magnitudes during fear conditioning and test with and without pre-exposure. The red line represents fear conditioning, while the yellow line indicates latent inhibition.

et al. 2006). Specifically, the LI effect is suppressed when a delay is introduced between the pre-exposure and test phases (De la Casa and Lubow 2001; Escobar et al. 2003), especially when this delay incorporates material that demands attention (Escobar et al. 2003). The concept that a time delay and context change have parallel effects on LI in humans suggests that they may be based on a similar process (De la Casa and Lubow 2001). The animal and human studies described above highlight the key experimental variables that modulate LI and show the sensitivity of LI expression to subtle manipulations. As such, much more research is needed to better understand how these key variables affect LI during the conditioning phase, and impact the durability and longevity of LI.

LI neurocircuitry

The LI circuit involves the nucleus accumbens (NAc), hippocampus, amygdala, and ventromedial prefrontal cortex (vmPFC). Animal studies have shown that the NAc shell and core have a functional differentiation in their expression of LI. Lesions to the NAc shell before pre-exposure disrupt LI (Weiner and Feldon 1997; Schmajuk et al. 2001), and dopamine blockade in the same region restores it (Schmajuk et al. 2001; Weiner 2003; Quintero et al. 2011a). In fact, initial studies demonstrated that antipsychotic drug administration during pre-exposure enhances LI in animals (Weiner and Feldon 1987; Christison et al. 1988; Dunn et al. 1993). In contrast, lesions to the NAc core before pre-exposure generate abnormally persistent LI even under conditions that typically disrupt LI (Weiner 2003). These and other animal studies confirm the critical role of the NAc in the neural network of LI (Weiner and Feldon 1997; Schmajuk et al. 2001; Weiner 2003; Puga et al. 2007; Quintero et al. 2011a). Another important region in the fear/threat extinction network, the subiculum/hippocampus, is also involved in LI via its input to the NAc (Weiner and Feldon 1997; Schmajuk et al. 2001). Quintero et al. (2011a) further specified the ventral subiculum as a modulator of LI expression because

of its influence on dopamine activity in the NAc and involvement in contextual processing. Another study found that the contextual dependence of LI was attenuated by hippocampal lesions (Talk et al. 2005; but see Weiner 2003).

Mirroring the observed effect of hippocampal and NAc core lesions, electrolytic and excitotoxic lesions to the basolateral amygdala (BLA) prior to pre-exposure cause potentiated and persistent LI in rats (Weiner 2003; Schiller and Weiner 2005). Finally, while not as well explored as in the threat detection extinction network, the critical role of the prefrontal cortex (PFC) in LI was recently demonstrated in a study in which PFC–GABA blockade abolished LI (Piantadosi and Floresco 2014). Overall, animal studies have supported the involvement of the NAc, hippocampal region, amygdala, and PFC in LI. Other regions implicated in animal LI studies include the entorhinal cortex (Schmajuk et al. 2001; Weiner 2003; Quintero et al. 2011a), parabrachial nuclei (Lopez et al. 2010; Gasalla et al. 2016), anterior dorsal striatum (Murphy et al. 2000), anterior thalamic nuclei (Talk et al. 2005; Nelson et al. 2018), and posterior cingulate cortex (Talk et al. 2005).

A large gap exists in human studies on the neurocircuitry of LI, possibly due to a lack of functional magnetic resonance imaging (fMRI)-compatible LI paradigms (Young et al. 2005). Nevertheless, a few human studies have begun to provide evidence for the involvement of brain regions in LI. Koolschijn et al. (2019) recently used blood oxygen level-dependent (BOLD) fMRI to reveal hippocampal participation in the selective recall of individual memories from a group of memories with a shared context, without interruption from interfering memories (Koolschijn et al. 2019). Similarly, an fMRI study by Young et al. (2005) demonstrated the important role of the hippocampus in a study of learned irrelevance, a concept closely related to LI. While great strides have been made in the study of the neural mechanisms of LI in animals, additional fMRI studies of LI are necessary to further our understanding of its underlying neural mechanisms within the human brain. Figure 3 provides a visual representation of the brain regions involved in latent inhibition.

Threat extinction neurocircuitry

The LI circuit considerably resembles that of threat extinction, involving the NAc, hippocampus, amygdala, and vmPFC. Threat response extinction research in rats shows that the infralimbic cortex (IL) has an inhibitory effect on the amygdala, suppressing the expression of amygdala-dependent threat memories (Milad and Quirk 2012; Marek and Sah 2018). Recent dopamine and β-catenin manipulation studies in animals suggest the NAc is also important in learning to inhibit threat detection responses (Storozheva et al. 2003; Holtzman-Assif et al. 2010; Korem et al. 2017). One rodent study examining the related mechanisms of the LI and fear extinction networks found that the initial inhibitory memory established by either latent inhibition or threat detection extinction was reactivated in the IL during additional extinction. Furthermore, in both LI and fear extinction, the inhibitory memory was enhanced by GABA antagonist-induced pharmacological stimulation of the IL and weakened by blockade of NMDA receptors in the IL (Lingawi et al. 2017).

In humans, the BLA receives projections from the vmPFC, a functional homolog to the IL in rats, and the inhibition of this projection impairs fear extinction recall (Milad and Quirk 2012; Cho et al. 2013; Bloodgood et al. 2018). In addition to the amygdala and the vmPFC, the hippocampus is responsible for contextual gating of extinction to a specific CS and is activated along with the vmPFC during extinction recall (Milad and Quirk 2012; Maren et al. 2013; Singewald and Holmes 2019). Both animal and human studies support the hypothesis that latent inhibition and fear/threat extinction involve similar forms of inhibitory learning with common neural substrates and molecular requirements (Barad et al. 2004; Lingawi et al. 2017).

Latent inhibition versus fear extinction

One could conceptualize LI as conducting fear extinction training before fear conditioning even begins. This raises the possibility that LI might share some mechanisms with fear extinction, a widely used method of conditioned fear reduction. During fear extinction training, the conditioned stimulus is repeatedly presented in the absence of the aversive unconditioned stimulus. Thus, both LI and fear extinction involve the repeated presentation of a cue without any aversive consequences (Kraemer and Golding 1997; Lingawi et al. 2017). Additionally, studies have shown that context manipulations that affect LI have an identical effect on extinction learning, with both LI and extinction exhibiting context specificity (Kraemer and Golding 1997; Miller et al. 2015). Moreover, LI can expedite later extinction of the conditioned fear (Vervliet 2013; but see Jordan et al. 2015). In Figure 4, we briefly compare and contrast the mechanisms of fear extinction and latent inhibition.

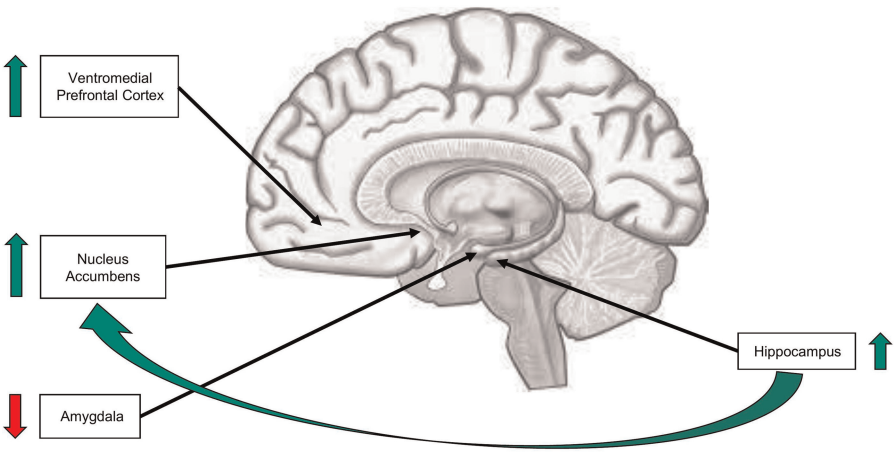

Figure 3. Latent inhibition brain regions. This figure represents the neural substrates primarily engaged in latent inhibition. From *left* to *right*, the vmPFC, NAc, amygdala, and hippocampus are highlighted, with a green upward arrow indicating increased activation, and a red downward arrow indicating decreased activation for successful latent inhibition to occur. Additionally, the green arrow connecting the hippocampus to the NAc indicated that hippocampus provides input to the NAc during latent inhibition expression.

Clinical applications of LI

Schizophrenia

Scientists studying schizophrenia were the first to explore the potential clinical relevance of LI. Hypothesizing that a failure to filter irrelevant stimuli mediates psychotic symptoms, they conceptualized LI as a test of a subject's capacity to gate attention (Feldon and Weiner 1991). Research finding LI deficits only in acute schizophrenic patients (prior to chronic treatment with medication) (Baruch et al. 1988) prompted extensive investigation of LI as a model of attentional deficits in psychosis (Yogev et al.

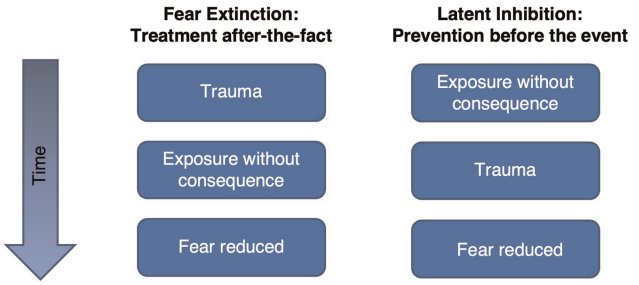

Figure 4. Fear extinction versus latent inhibition. This figure compares the time lines and sequence of events of fear extinction and latent inhibition, highlighting that the primary difference is the timing of exposure without consequence—either before or after the trauma.

2004; Granger et al. 2012; Schmidt-Hansen and Le Pelley 2012). Interestingly, similar to in PTSD, patients with schizophrenia demonstrate deficits in extinction recall, but intact extinction learning, showing an overlap between how these disorders process fear learning and memories (Holt et al. 2009).

Eventually, the LI model of schizophrenia was elaborated and applied to probe the biology of other psychopathology, such as attention deficit/hyperactivity disorder (ADHD) (Lubow et al. 2014) and obsessive–compulsive disorder (OCD) (Kaplan et al. 2006). Specifically, individuals with ADHD endorse deficits in LI (Lubow et al. 2005, 2014), while individuals with OCD display enhanced LI (Swerdlow et al. 1999; Kaplan et al. 2006; Lee and Telch 2010). However, an important yet understudied area of LI research is how it may potentially serve to reduce the incidence of developing aversive conditioned associations in populations at risk for fear- and trauma-related disorders (Mineka and Zinbarg 2006; Feldner et al. 2007).

Anxiety and fear-related disorders

A few human studies have provided preliminary evidence supporting the possible prophylactic effects of latent inhibition-based pre-exposure on human affective learning (e.g., Díaz and De la Casa 2002). For example, a history of neutral or positive dentist office experiences appears to defend against the later development of traumatic associations with the dentist, and subsequently against dental-related phobias or extreme fears (ten Berg 2008). Indeed, LI-based interventions have shown to be efficacious in preventing dental phobias (Davey 1989; de Jongh et al. 1995; Ten Berge et al. 2002). Such results buttress the idea of extending this area of clinical research to other areas of fear learning. LI also appears to play an important role in the inhibition of disgust learning, a concept closely linked to fear learning (Cisler et al. 2009; Klucken et al. 2012; Askew et al. 2014). In a study of LI in rotation chair-induced nausea in healthy humans, Klosterhalfen et al. (2005) found repeated pre-exposures in the chair (without rotation) reduced anticipatory nausea. Other work has similarly demonstrated LI of taste aversion in the context of motion-induced, or Galvanic Vestibular Stimulation-induced nausea (Arwas et al. 1989; Stockhorst et al. 1993; Hall et al. 2016; Quinn et al. 2017; Quinn and Colagiuri 2018).

Researchers have also begun to explore the effects of anxiety, negative affect, and stress on LI. For example, some studies have linked high levels of anxiety with reduced LI (Braunstein-Bercovitz 2000; Braunstein-Bercovitz et al. 2002). It has been hypothesized that anxiety impedes a person's ability to discern irrelevant information, which results in high distractibility and difficulty focusing attention on the relevant aspects of a situation, thereby causing LI attenuation (Braunstein-Bercovitz et al. 2002). Lazar and colleagues revealed that inducing negative affect prior to pre-exposure reduced the LI effect, while positive affect increased it. Additionally, in the positive affect group, increased LI was associated with a lower score on the depression scale, and in the negative affect group, decreased LI was associated with a higher score (Lazar et al. 2012). The impact of anxiety and negative affect on LI suggest that populations suffering from anxiety or persistent negative emotions may be more vulnerable to developing attentional issues or excessive fear-related learning in their daily lives and reinforces the need for further exploration of this area (Braunstein-Bercovitz 2000; Braunstein-Bercovitz et al. 2002; Lazar et al. 2012). This is of particular relevance given that individuals suffering from anxiety or depression tend to be at greater risk for developing PTSD after experiencing a traumatic event (Breslau 2009). Research on the relationship between stress and LI has been little explored, with a few human studies demonstrating a negative relationship between stress and LI (Braunstein-Bercovitz et al. 2001, 2002). Further research is warranted to clarify the impact of stress on LI, as this is especially critical to understand LI's applicability to pre-exposure to innately stressful/fearful stimuli.

PTSD

Post-traumatic stress disorder is a chronic and debilitating mental health condition characterized by intrusive reexperiencing of the trauma, avoidance of related cues, negative affect or cognitions, and altered reactivity and arousal caused by conditioned fear following a traumatic event (American Psychiatric Association 2013). A few studies have demonstrated the promise of LI-based paradigms as a prophylactic intervention for combat-related PTSD (Feldner et al. 2007). Virtual reality (VR) tools that replicate combat situations have been successfully used in post-traumatic exposure therapy for veterans with PTSD (Rothbaum et al. 2001, 2003; Norr et al. 2018; Loucks et al. 2019), but rarely have such techniques been applied for prevention. Rizzo et al. (2013) began to explore this approach by developing and evaluating a VR tool for predeployment stress resilience training. The goal of this "Stress Resilience In Virtual Environments" (STRIVE) project was to expose users to an interactive experience involving a series of combat simulations (from their existing Iraq/Afghanistan virtual PTSD exposure therapy system) prior to deployment (Rizzo et al. 2013). They predicted exposing military personnel to simulated combat contexts with no real-life consequences may reduce the likelihood of future fear learning in actual combat situations (Sones et al. 2011; Rizzo et al. 2013). Pilot STRIVE studies have shown initial support for the feasibility of using virtual reality episodes to build resilience, as indicated by heart rate monitoring and positive ratings of STRIVE's utility for preparing for a combat environment by service members (Rizzo and Shilling 2017). A systematic review of nine VR-based stress management studies concluded that VR is a promising approach for increasing soldiers' resilience to stress, as demonstrated by subjects' reduced emotional stress in response to negative stimuli, even at later times (Pallavicini et al. 2016). In a similar vein, Essar et al. (2010) developed a PreTraumatic Vaccination (PTV) intervention in an effort to prevent trauma- and stress-related mental health problems among emergency military rescue personnel. It aims to help military rescue trainees with anticipated disasters or distressing situations associated with this line of work. Results of a preliminary study of PTV suggest the intervention reduced dissociation, thereby increasing detail awareness, and lessening suffering and probability of mistakes (Essar et al. 2010). Given that dissociative symptoms are a strong predictor for the development of PTSD (Ozer et al. 2003), this suggests a lower likelihood of a PTSD diagnosis in rescue personnel (Essar et al. 2010).

These examples of clinically applicable fear inoculation are not necessarily perfect representations of latent inhibition because the pre-exposed stimuli or contexts are not always neutral, but rather may be innately fear-inducing. Because of this, an argument could be made that the reduced fear in these studies is not necessarily due to latent inhibition, but possibly to fear extinction learning or habituation. However, we are not aware of any evidence to suggest that LI would not be effective to nonneutral stimuli or contexts. The goal of the above-reviewed studies is to expose personnel to relevant stimuli in a safe setting with no real-life consequences, so as to reduce the likelihood of developing a maladaptive and excessive fear reaction, rather than expect to eliminate fear completely. This aims to build resilience so they are able to respond appropriately to threatening situations, rather than freezing or developing traumatic responses. Future research on preventive LI interventions using virtual pre-exposure may be key to bolstering resilience among individuals in the military (Feldner et al. 2007; Johnson et al. 2012). Given the overlap between LI and fear extinction, it may be difficult to distinguish which is in effect in an experimental design. However, given their clinical applicability, we believe that this may not be important as long as the pre-exposure is effective in prospectively reducing clinical symptoms of fear and anxiety.

Future directions and conclusions

In order to advance the potential clinical utility of LI-based inoculation, it is imperative to reflect on the many understudied areas of LI research. Firstly, research on the neural mechanisms of LI is particularly lacking in humans, as the majority of studies investigating LI neurocircuitry have been conducted in animals (for reviews, see Weiner and Feldon 1997; Schmajuk et al. 2001). In a similar fashion to the translation of fear extinction neurocircuitry research from animals to humans (Milad and Quirk 2012), the expansion of LI neuroimaging studies in humans is necessary for the advancement of the field. Furthermore, a number of criticisms have been made about the methodology of human behavioral LI studies. Specifically, many human studies involve complicated methods, some including confounding variables other than pre-exposure, which limit the ability to simply identify and assess the effects of LI in humans. The development of well-designed studies is necessary to form a more comprehensive and concrete understanding of latent inhibition in humans (Byrom et al. 2018). Most studies conclude once LI is demonstrated in fear conditioning, leaving unanswered questions about the possibility of spontaneous recovery of fear, renewal, or reinstatement. Future studies should explore whether these occur following latent inhibition. Finally, more experimentation evaluating the effects of context(s), the number of pre-exposures, time intervals between phases, and other variables on LI is crucial to produce the most accurate and strongest LI effect—a necessary precursor to designing effective LI-based clinical interventions. See Figure 5 for a summary of suggested future directions.

Now more than ever, frontline healthcare workers are facing unprecedented challenges and traumatic experiences in dealing with the COVID-19 pandemic, leaving them highly vulnerable to developing mental health problems including anxiety and trauma-related disorders (Greenberg et al. 2020; Huang et al. 2020a,b; Liang et al. 2020). Experts recommend that medical institutions better prepare healthcare staff for the stressors they will face and provide stronger psychological skills training (Huang et al. 2020b). The development of a standardized LI protocol that is applicable to all stimuli and individuals is highly unlikely. Research to date indicates that LI does not generalize across contexts (De la Casa and Lubow 2001; Gray et al. 2001; Escobar et al.

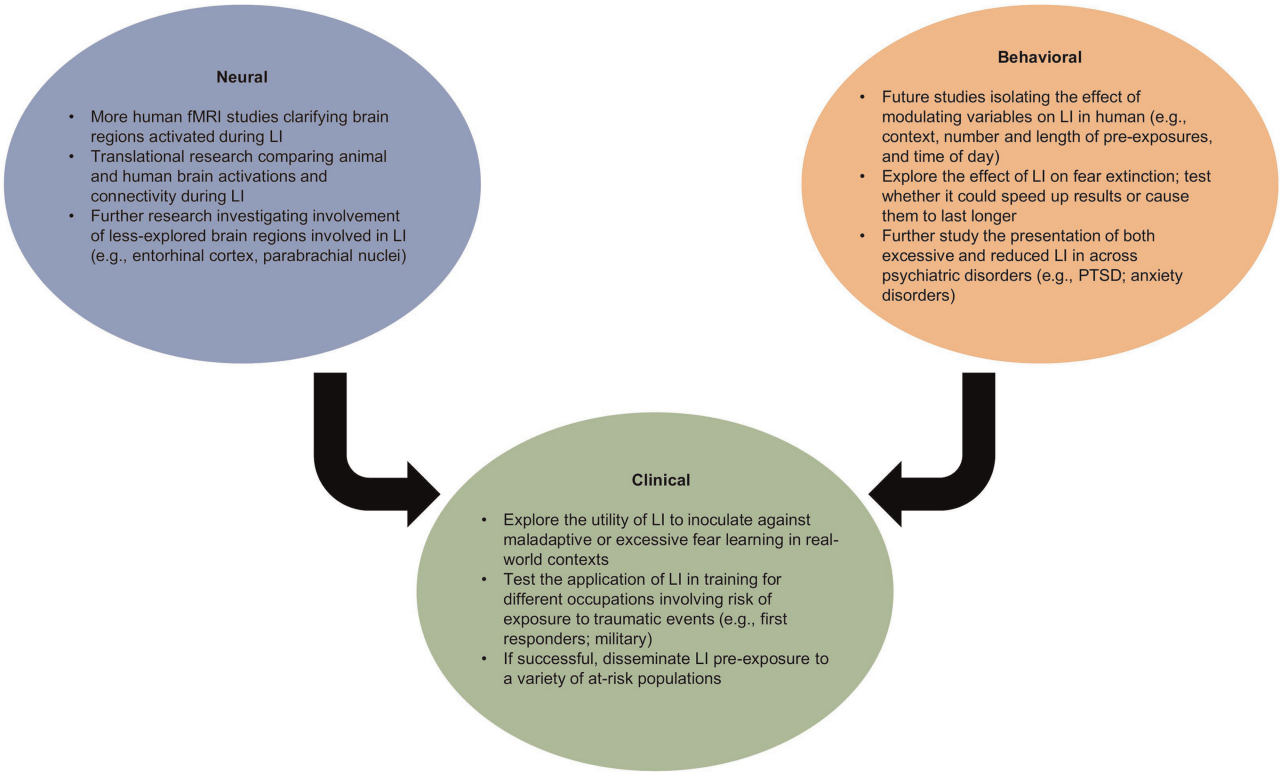

Figure 5. Future directions in latent inhibition research. This figure describes the suggested areas for future latent inhibition research, starting with further exploration of neural and behavioral aspects of LI, leading to clinical research and applications.

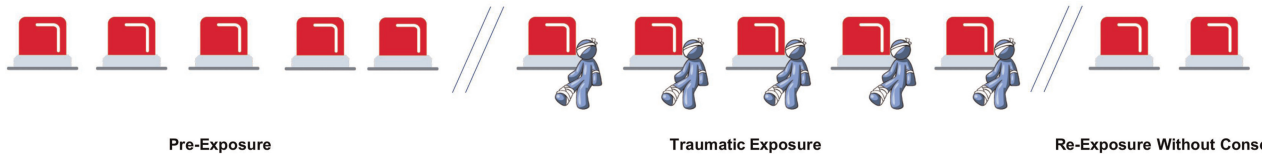

Figure 6. Latent inhibition-based fear prevention example. This figure displays a simplified potential clinical application of latent inhibition-based training that could be used to prevent the development of a conditioned fear response to a siren for first responders.

2002; Byron Nelson and del Carmen Sanjuan 2006; Quintero et al. 2011a; Miller et al. 2015; Miguez et al. 2018), and may not generalize between stimuli (Byron Nelson and del Carmen Sanjuan 2006). Due to this, each institution would need to incorporate pre-exposures to the specific stimuli (e.g., sirens and ventilators) and contexts (e.g., ER, ICU, and ambulance) their workers might face in a crisis (such as COVID-19) to potentially protect these high-risk individuals from developing long-lasting mental health consequences. This development would most likely require the testing of multiple contexts, timing, and number of pre-exposures for effective traumatic fear inoculation. See Figure 6 for a simplified example of pre-exposure training procedures. Although institutions cannot predict and address every possible stimulus that could be present at the time of a traumatic event, with adequate research and preparation, the most salient stimuli in potentially traumatizing occupational situations could be targeted.

While we recognize that clinically applicable LI research is in its early stages, and much work is needed before LI-based protocols can be effectively applied, we believe this could be an important area of future research. Although traumatic experiences are often unavoidable, and a universal LI protocol might not be possible, the development and implementation of LI-based interventions may reduce the incidence of PTSD symptomology. A precision medicine approach to latent inhibition-based preventative measures may lead to the attenuation of future maladaptive fear-based learning.

Competing interest statement

K.A.C. has worked as a rater for MedAvante-ProPhase. M.R.M., D.B.M., and M.M.R. report no biomedical financial interests or potential competing interests.

Acknowledgments

This work was supported by National Institutes of Mental Health grant number R33MH111907. We thank Dr. Sarah Boukezzi for helpful comments on prior versions of the manuscript.

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Received May 18, 2021; accepted in revised form December 1, 2021.