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Review

Efficacy and mechanisms of non-invasive brain stimulation to enhance exposure therapy: A review

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HIGHLIGHTS

- Review of extant literature investigating brain stimulation and exposure therapy
- Retrieval inhibition as an important mechanism for exposure
- Future studies and directions proposed

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ABSTRACT

Though cognitive behavioral techniques are generally effective in the treatment of anxiety disorders, some people fail to benefit from exposure therapy or experience a return of fear after terminating exposure therapy. The burgeoning field of non-invasive brain stimulation provides a potential method of augmenting exposure therapy so that it is more effective. Successful exposure therapy is hypothesized to occur due to inhibition, and research suggests that brain stimulation can alter inhibitory learning and related processes. As such, one can reasonably posit that brain stimulation could be used to test the inhibitory learning theory of exposure therapy and to increase the efficacy of exposure therapy by inducing stronger inhibitory learning during exposures. Four known studies that pair brain stimulation with exposure therapy have yielded promising preliminary evidence in support of the therapeutic use of brain stimulation. In this review we describe research illustrating the mechanisms and efficacy of non-invasive brain stimulation to enhance the understanding of and outcomes produced by exposure therapy.

1. Introduction

Anxiety and related disorders often result in serious impairment and distress in those who suffer with them—they are associated with a myriad of negative outcomes, including decreased physical and mental health as well as problems in one's home, work, and social life (Olatunji, Cisler, & Tolin, 2007). People with anxiety are also significantly more likely to fall below the poverty line, and estimates of the overall annual cost to society of anxiety disorders approach 100 billion (Tolin, Gilliam, & Dufresne, 2010). Fortunately, cognitive behavioral therapy (CBT), and especially exposure therapy, is generally an effective method of treating anxiety disorders (e.g., Barlow, 2002). However, exposure therapy is far from perfect—patients sometimes fail to achieve clinically significant benefits from exposure (Barlow, Allen, & Choate, 2004) or experience return of fear (Brown & Barlow, 1995). In addition, many patients and even clinicians struggle to tolerate exposure and adhere to best practices (e.g., Farrell, Deacon, Kemp, Dixon, & Sy, 2013). As such, development of a means to improve upon exposure therapy would certainly be valuable, especially if the method were inexpensive, effective, and easy to administer.

Exposure therapy has been hypothesized to work due to inhibitory learning which leads to retrieval inhibition of original, frightening or anxiety provoking memories, rather than due to forgetting of the original memories (e.g., Craske et al., 2008; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Interestingly, anxiety disorders have been found to be associated with dysregulation in inhibitory processes, and specifically in retrieval inhibition (Kircanski, Johnson, Mateen, Bjork, & Gotlib, 2015; Nuñez, Gregory, & Zinbarg, 2015). That being said, even clients with non-dysregulated inhibitory capabilities might benefit more from exposure therapy if inhibitory learning ability were to be

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enhanced.

The emerging field of brain stimulation research could potentially provide a means of augmenting exposure therapy that is safe and effective. Specifically, non-invasive techniques of neuromodulation now exist which can change the excitability of specific areas of the brain quickly and effectively. Transcranial magnetic stimulation (TMS) has recently been granted FDA approval as a treatment for refractory depression (O'Reardon et al., 2007) and obsessive compulsive disorder (Tendler, Zohar, Carmi, Roth, & Zangen, 2018), and TMS and transcranial direct current stimulation (tDCS) have begun to be evaluated as possible treatments for other presentations of anxiety as well.

However, non-invasive brain stimulation may be beneficial for anxiety disorders separately from directly reducing symptomatology. Intriguingly, limited research suggests that TMS and tDCS can alter inhibitory learning and related processes (e.g., Penolazzi, Stramaccla, Braga, Mondini, & Galfano, 2014), which suggests that these methods could potentially increase the efficacy of exposure therapy by inducing stronger inhibitory learning during exposures. Indeed, as will be argued below, extinction provides a useful model of exposure therapy, and studies on laboratory conditioned fear suggest that TMS and tDCS during extinction can affect the amount of fear exhibited later (e.g., Mungee et al., 2014). Four known studies that pair brain stimulation with exposure therapy have yielded promising preliminary evidence in support of the therapeutic use of brain stimulation. In this review we describe research illustrating the mechanisms and efficacy of non-invasive brain stimulation to enhance exposure therapy outcomes.

2. Mechanisms of exposure therapy

Understanding the mechanisms underlying exposure therapy outcomes should shed light on points in the mechanistic chain that can be improved upon. However, there has been considerable debate in the literature regarding what processes are responsible for the fear reduction that occurs in successful exposure therapy. Exposure therapy as we know it today evolved out of the principles of systematic desensitization therapy pioneered by Wolpe (1968), which, following dismantling studies, (Marks, 1978; Mathews, 1978) has evolved to rely heavily upon in vivo exposures to feared stimuli. Wolpe (1968) conceptualized systematic desensitization as working under the principles of Pavlovian conditioning but acknowledged that research had yet to delineate exactly what mechanism was responsible for reduction of the original conditioned response (CR).

Two distinct processes have been presented as possible explanations for the fear response reduction observed in exposure therapy. Habituation and extinction occur when repeated presentation of an unconditioned stimulus (US) or a conditioned stimulus (CS), respectively, results in a decreased response to the stimulus (e.g., Watts, 1979). The important distinction between the two is that habituation refers to the reduction of unconditioned responses (URs) whereas extinction refers to the reduction of CRs. For instance, habituation would be said to have occurred if repeated exposures to a loud noise results in an individual no longer turning his/her head in the direction of the noise. Alternatively, the process would be called extinction if a loud noise were conditioned to be associated with a shock such that the noise then caused freezing behavior on its own, and that after repeated presentation of the noise without the shock the individual no longer exhibiting freezing behavior to the noise alone.

Watts (1979) argued that habituation explains the fear reduction that occurs due to systematic desensitization and exposure therapy. However, exposure therapy clearly targets conditioned fears, considering, for instance, people are not universally fearful of phobic stimuli, such as needles. Thus, Zinbarg (1993) argued that speaking of the fear reduction that occurs due to exposure therapy in terms of extinction rather than as habituation is more logical and useful. That being said, one should note that the term habituation is often used to describe the reduction of fear that occurs *during* an exposure session, whereas the term extinction is rarely used in this manner.

Wolpe's (1968) systematic desensitization was one of the first therapeutic techniques capable of undergoing scientific scrutiny due to its explicit and controlled procedure. Unexpectedly, the resulting research on systematic desensitization gave rise to new mechanistic theories. Perhaps the most influential of these were emotional processing theory (EPT; Foa & Kozak, 1986) and inhibitory learning theory (Craske et al., 2008). EPT proposed that extinction occurs when something in the environment activates the fear network (a set of propositions about a stimulus, a response, and their meaning that are stored in memory; Lang, 1971) and incompatible information is processed and integrated into the fear network. Incompatible information is programmed into the non-fear structure as evidenced by within-session and between-session habituation, or decrease in fear. Foa and Kozak (1986) proposed that in order for exposure to be successful, the fear network must be adequately activated, as indexed by high self-reports of fear and physiological fear reactions. Consequently, the patient must not avoid processing the fearful stimulus. Continued research, however, has demonstrated that extinction can still occur in the absence of reliable within-session and between session habituation and in subjects without high levels of initial distress (Lang & Craske, 2000; Rowe & Craske, 1998; Tsao & Craske, 2000). Furthermore, while distraction has often been found to result in poorer exposure outcomes (e.g., Mohlman & Zinbarg, 2000), distraction during exposure has also been shown to facilitate extinction in some studies (e.g., Johnstone & Page, 2004).

2.1. Inhibitory learning theory of exposure therapy

In response to the initial problems with emotional processing theory, Craske et al. (2008) proposed a new framework to explain fear extinction in which the most important aspect of exposure was not emotional processing but rather inhibitory learning. Some early theories of learning made the assumption that the original CR was extinguished due to unlearning, or “decay”, of the US-CS association (e.g., Muller & Pilzecker, 1900; Thorndike, 1914). However, there is evidence suggesting that this is not the case, and that the original CS-US association is retained, if perhaps weakened. Rather, the critical process underlying extinction is assumed to be that the CS acquires a second, inhibitory meaning, that of “CS-noUS” or even “CS-something pleasant” (e.g., Bouton, 1993; Bouton & King, 1983).

The idea that the original fearful CS-US association is not destroyed is consistent with the memory and learning literature (e.g., the new theory of disuse; Bjork & Bjork, 1992, 2006) and is further consistent with the phenomena of reinstatement, renewal, spontaneous recovery, and reacquisition (Bouton, 2002; Myers & Davis, 2002). A fear response that reoccurs after extinction when the subject encounters the original US is referred to as reinstatement (Rescorla & Heth, 1975). For example, if a tone-fear association was created by pairing the tone with shock, it would be possible for fear of the tone to return after extinction if the subject is shocked again, even if that shock was not paired again with the tone. Renewal occurs when a change in context results in return of the fear response after extinction when presented with the CS (Bouton, 1993). For example, if an association between dogs and biting is learned in a park and the association of dogs and not biting is learned in a therapist's office, then it would be possible for fear of dogs to return if the subject encountered a dog in a park. Spontaneous recovery occurs when the fear response returns when the subject is presented with the CS simply due to a lengthy amount of time having passed since extinction (Baum, 1988; Brooks, Karamanlian, & Foster, 2001). Finally, reacquisition describes the situation in which learning of the original CS-US association is much quicker in subjects that have previously extinguished the association than in subjects for whom the association is novel (Ricker & Bouton, 1996). These effects suggest that the initial fearful associations are not deleted. Indeed, many researchers now agree that extinction learning inhibits old, fearful associations (McNally, 2007). Notably, however, while reinstatement, renewal,

spontaneous recovery, and reacquisition do an excellent job of confirming that fearful memories are not deleted following extinction, they do not necessitate that inhibition must then be the driving force of extinction—indeed, all four effects could be completely accounted for by intact but weakened associations. Furthermore, while inhibitory learning theory has gathered a large following and has informed additional treatment practices (e.g., Arch & Abramowitz, 2015), there is a relative dearth of empirical evidence directly testing its relevance in actual exposure therapy.

Nonetheless, focusing on inhibitory learning as a key mechanism of extinction addressed some of the original criticisms of EPT. The learning and memory literature suggest that performance during instruction, or whether or not desired associations are recalled during initial learning, is a poor predictor of actual long-term learning and retention (Bjork & Bjork, 2006). As an illustration consider a student who is unable to come up with the correct answer when questioned by their teacher during class but later recalls the correct answer on test several weeks later. Such could reasonably also occur during exposure—a person may not habituate during a session nor verbalize new learning or a decrease in fear, but nevertheless be less fearful at their next session. Thus, the lack of support for EPT's assumption that the amount of within session habituation that occurs is predictive of outcome is unsurprising—inhibitory learning can occur whether or not fear declines during or between sessions. The inhibitory learning theory of exposure moves away from the idea that initial fear activation followed by fear reduction is the driving force behind extinction, and instead proposes that extinction will be facilitated by the learning of new, non-threatening associations and by improving one's ability to access or retrieve these new associations instead of the old, threatening association (e.g., Brewin, 2006; Craske et al., 2008, 2014).

EPT has since been revised to accommodate these and related issues (Foa & McNally, 1996; Foa & McClean, 2016). For instance, within session habituation is no longer viewed as necessary unless a particular person's fear involves the belief that anxiety and fear will not abate over time. Additionally, allowance is made for some distraction as long as it does not result in complete attentional disengagement. Perhaps most notably, however, revised views of EPT accept that extinction involves new learning, and that both the new learning and the original, fear related information continue to exist in one's memory. In this regard, EPT aligns itself both with the learning and memory literature and with the inhibitory learning theory of extinction proposed by Craske et al. (2008).

A notable remaining difference, however, is that while allowing for new learning and old learning to coexist, EPT does not posit that retrieval inhibition is necessary for new learning to be recalled over old learning. Instead, EPT suggests that this could occur solely due to factors such as similarity between learning context and recall context or due to updating of original fear memories during reconsolidation (Schiller et al., 2010; Foa & McClean, 2016). Reconsolidation is the process by which the retrieval of an established memory allows for alteration of the memory (e.g., Alberini & LeDoux, 2013). As such, EPT suggests that retrieval inhibition may not be a necessary mechanism of change as fearful associations could be “rewritten” or combined with the new learning that occurred during an exposure session. This rewriting would only require retrieval of the original memory, and not necessarily later retrieval inhibition of the original memory. There are several other proposed mechanisms through which exposure therapy may augment one's response to previously feared stimuli (for a detailed review see Cooper, Clifton, & Feeny, 2017). For instance, patients who do not necessarily experience a decrease in fear may still build self-efficacy in their ability to tolerate fear and distress, and thus achieve a higher level of life functioning.

As with most psychological phenomena, extinction is likely driven by complex interactions between these and numerous important mechanisms, and both theories allow for this. The primary *difference* between EPT and inhibitory learning theory, then, is whether retrieval inhibition is an important and necessary mechanism underlying extinction and exposure therapy. The question then regarding how to pit these two theories against each other in our efforts to improve exposure therapy becomes a question of improving inhibition for proponents of inhibitory learning theory but not necessarily EPT. As such, if exposure therapy outcomes can be improved by targeting retrieval inhibition we would not only have uncovered a means of enhancing treatment but also our understanding of the mechanisms of exposure therapy. Of course, any method developed to improve exposure therapy should also conform to the necessary profile of a treatment amendment—for instance, it should be inexpensive, effective, and easy to administer (Shoham et al., 2014). The burgeoning area of brain stimulation research presents the possibility for development of such an instrument if brain areas responsible for inhibition and extinction can be adequately pinpointed.

3. Brain structures involved in inhibition and extinction learning

A large number of brain regions have been proposed to play a role in extinction learning, such as the sensory cortex, the periaqueductal gray, the inferior colliculus, the lateral septum, the bed nucleus of the stria terminalis, and the ventral and dorsal striatum (e.g., Myers & Davis, 2007). However, the majority of fear extinction research has focused on the hippocampus, the amygdala, and the prefrontal cortex (PFC; Craske et al., 2008). The PFC in particular is a promising area to investigate as a potential target for brain stimulation as it is much more physically accessible than either the amygdala or the hippocampus. As will be discussed later, one should note that the methods through which non-invasive brain stimulation techniques alter neural activity in different brain regions is not yet well understood. As such, the following review aims only to identify a potential target for brain stimulation. No claims will be made suggesting that changes in exposure therapy outcomes due to brain stimulation are directly a result of altered neural activity in a targeted brain area. The discussion of such relationships will be purely speculative in the interest of encouraging continued research to pinpoint brain areas and demonstrate causality.

The PFC in humans is made up of the lateral PFC, the orbital frontal cortex (OFC), and the medial PFC (mPFC). The lateral PFC, and especially the dorsolateral PFC (DLPFC), seems to be responsible for working memory and emotional control (e.g., Curtis & D'Esposito, 2003). The OFC is involved with reward, motivation, and emotional decision making (e.g., Berns, McClure, Pagnoni, & Montague, 2001). The mPFC loosely refers to several different areas including the anterior cingulate cortex (ACC), the infralimbic (IL) cortex, the prelimbic (PL) cortex, and the medial orbital cortex. The IL, PL, and medial orbital cortex are also sometimes referred to as the ventral medial PFC (vmPFC) either as a group or individually. The vmPFC is believed to be involved in emotion regulation, especially the ability to adjust behavior in response to emotional stimuli (e.g., Bechara, Damasio, & Damasio, 2000; Bush, Luu, & Posner, 2000; Cohen, Botvinick, & Carter, 2000).

Research on fear extinction and inhibition in humans has generally implicated the lateral and medial parts of the PFC. However, most fear extinction research involves rodents, and the lateral PFC is considered a unique primate adaptation (e.g., Povinelli & Preuss, 1995). Research on fear extinction in rodents has generally implicated the medial PFC, which is encouraging as the ventral and medial areas of the PFC tend to be fairly similar in all mammals (Uylings, Groenewegen, & Kolb, 2003).

3.1. Research implicating the PFC

Investigation into the PFC as a structure potentially involved in fear extinction was initiated when Morgan, Romanski, and LeDoux (1993) demonstrated that lesioning of the mPFC in rats resulted in resistance to fear extinction. Continued research suggested that the effects of PFC lesions on fear acquisition and extinction varied depending on what subregion of the PFC was targeted (Morgan & LeDoux, 1995, 1999;

Quirk, Russo, Barron, & Lebron, 2000), and, potentially, whether the lesion was applied before or after fear acquisition. Milad and Quirk (2002) also investigated the role of the mPFC on extinction by using single-unit recording to measure activity in the mPFC in rats who had undergone fear conditioning followed by extinction. They found that the firing of mPFC neurons was associated with less conditioned fear behavior. Another subset of rats received fear conditioning but not extinction. Stimulation of the mPFC in the un-extinguished rats during a test of the CS (a tone) resulted in significantly less freezing at test compared to unextinguished rats that did not receive stimulation during CS presentation. Milad and Quirk (2002) suggested that the stimulation paired with the tone seemed to actually simulate extinction learning in rats who had not encountered the CS alone until retest. Interestingly, in the rats that did receive extinction training, these neurons only fired on their own in response to the CS the day following extinction training and not during fear acquisition or extinction learning itself. Milad and Quirk (2002) concluded that the mPFC may be responsible for storing memories of extinction learning, and that these neurons fire during retrieval of these memories, rather than during learning itself.

Supporting the idea that the mPFC is responsible for extinction learning retrieval, Herry and Garcia (2002) found that inhibitory low frequency stimulation of the mediodorsal thalamic inputs to the mPFC before extinction resulted in resistance to extinction learning, while excitatory high frequency stimulation had no effect on the rate of learning. However, the mice that received high frequency stimulation exhibited less freezing than controls at one-week re-test, suggesting that excitation of the mPFC enhanced consolidation and retrieval of extinction learning memories. Improved retention of extinction learning (as indexed by decreased freezing behavior) has also been achieved by administering methylene blue, a metabolic enhancer, to the PFC for five days *following* extinction learning (Gonzalez-Lima & Bruchey, 2004), and mapping of metabolic neural pathways following retrieval of extinction learning revealed increased uptake of a labeled glucose analog in the mPFC (Barrett, Shumake, Jones, & Gonzalez-Lima, 2003). Additionally, intra-PFC administration of various metabolic inhibiting agents has been shown to impair retention of extinction learning (Hugues, Chessel, Lena, Marsault, & Garcia, 2006; Pfeiffer & Fendt, 2006; Santini, Ge, Ren, Pena de Ortiz, & Quirk, 2004). Lesion studies tend to implicate the vmPFC, specifically, as necessary for retrieval of extinction memories but not for extinction learning itself (e.g., Morgan, Schulkin, & LeDoux, 2003; Quirk et al., 2000). These findings that manipulating PFC activity results in changes at test but not during learning are again in line with the learning and memory literature which would predict that performance during learning is not always an accurate measure of actual learning (Bjork & Bjork, 2006).

Though less research has been done on humans, the work that has been done has suggested that the mechanisms of extinction learning are highly similar in both humans and non-primate animals. fMRI studies have recorded increased activity in frontal regions during extinction learning (e.g, Gottfried & Dolan, 2004), and increased activity specifically in the vmPFC during retrieval of extinction learning (Phelps, Delgado, Nearing, & LeDoux, 2004). Furthermore, Milad et al. (2005) found that extinction learning retention in humans, as assessed by skin conductance response (SCR) when exposed to a CS a day after having been conditioned and extinguished, is correlated with vmPFC thickness as measured by MRI. That is, thicker vmPFC was associated with greater extinction memory.

3.2. Connections between the PFC, hippocampus, and amygdala

Elucidating the relationship between the PFC, the amygdala, and the hippocampus is key for understanding inhibitory processes. Connections between the PFC, the amygdala, and the hippocampus are now believed to represent at least part of the neural basis of fear extinction. As mentioned above, investigation into the PFC as a structure potentially involved in fear extinction was initiated when Morgan et al. (1993) demonstrated that lesioning of the mPFC in rats resulted in resistance to fear extinction. Morgan et al. (1993) believed this resistance was due to emotional perseveration. They noted that the mPFC projects to the amygdala in several distinct regions and that the two structures seem to be functionally coupled (e.g., McDonald, 1991). This coupling and the findings that the amygdala is involved in acquisition and storage of fearful CS-US associations (see Davis & Whalen, 2001 for a review) led Morgan et al. (1993) to propose that connections between the mPFC and the amygdala are responsible for the ability of an organism to control emotional behavior. They further suggested that some defect resulting in loss of prefrontal control of the amygdala might explain the difficulty people with anxiety disorders have in regulating their emotions. Researchers later proposed that the PFC exerts inhibitory control over the amygdala during extinction and retest (presentation of the CS some time after exposure therapy has ended; Maren & Quirk, 2004; Sotres-Bayon, Bush, & LeDoux, 2004).

Sotres-Bayon et al. (2004) expanded this model to include the hippocampus, which has strong projections and excitatory synapses to the PFC (Carr & Sesack, 1996; Conde, Maire Lepoivre, Audinat, & Crepel, 1995; Jay & Witter, 1991), to explain the occurrence of renewal and why context is important for the retrieval of inhibitory learning. They proposed that mPFC control over the amygdala inhibits expression of amygdala-processed conditioned fear responses and that mPFC control over the amygdala is also required for retrieval of prior extinction learning. Whether or not the mPFC will exert this control is hypothesized to be dependent on the hippocampus. If the current environment in which the CS is presented is, for instance, much more similar to the CS-US learning environment than to the CS-noUS learning environment, then the hippocampus would not recognize the context as an inhibitory learning context and thus would not excite the mPFC, which otherwise would have then inhibited the amygdala and subsequent fear expression.

This hypothesized relationship between the PFC, hippocampus, and amygdala is backed by considerable empirical evidence. fMRI studies have shown that as activity in the lateral PFC (which is adjacent to the mPFC) increases, activity in the amygdala decreases (Hariri, Bookheimer, & Mazziotta, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Lieberman et al., 2007; Lieberman, Hariri, Jarcho, Eisenberger, & Bookheimer, 2005; Ochsner, Bunge, Gross, & Gabrieli, 2002). In rats, stimulation of the mPFC differentially inhibits (Quirk, Likhtik, Pelletier, & Paré, 2003; Rosenkranz, 2002; Rosenkranz, Moore, & Grace, 2003) or stimulates (Likhtik, Pelletier, Paz, & Paré, 2005) different sections of the amygdala. Notably, one study found that decreased activity in the amygdala and increased activity in the DLPFC occurred immediately following successful exposure therapy but that at 6-month follow-up only the effect on the amygdala was maintained (Hauner, Mineka, Voss, & Paller, 2012). This finding suggests that successful fear extinction learning requires inhibition of the amygdala by the PFC, but that this control might not always be necessary for later retrieval of extinction memories.

Involvement of the hippocampus is evidenced as deactivation of the dorsal hippocampus with muscimol has been shown to remove contextual constraints on retrieval of extinction learning such that renewal of fear did not occur due to a change in context (Corcoran & Maren, 2001). Lesions to the dorsal hippocampus achieved the same effect (Ji & Maren, 2005). Thus, it is reasonable to infer that prefrontal control of the amygdala, and subsequently of fear expression, is dependent upon stimulation or inhibition of the PFC by regions of the hippocampus, which is determined by the similarity of contextual cues to the extinction environment.

3.3. The PFC and psychopathology

Unsurprisingly, the structures implicated above in extinction learning and inhibition have also been implicated as possible sites of

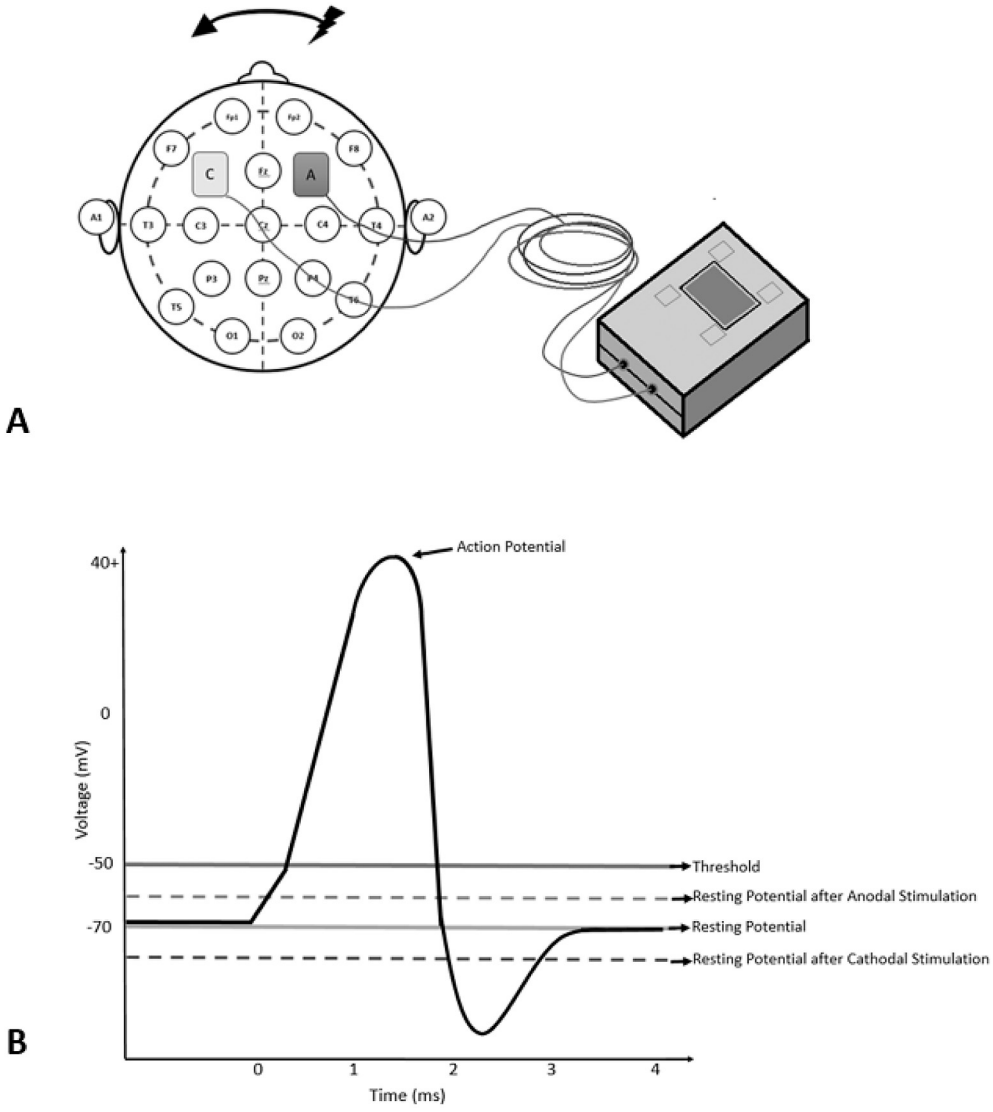

Fig. 1. A. A typical tDCS montage to stimulate the prefrontal cortex. The anodal electrode is placed over f4 and the cathode is placed over f4. The current passes from the anode to the cathode, theoretically exciting the right DLPFC and inhibiting the left DLPFC. B. Resting membrane polarity shift caused by tDCS. Anodal stimulation raises resting state thus making action potentials more likely to occur. Cathodal stimulation lowers resting state thus making action potentials less likely to occur.

dysregulation in psychopathology. Specifically, failure of the mPFC to exert inhibitory control over the amygdala has been proposed to disrupt the ability to adapt to changing situations, leading to maladaptive emotionally related behaviors and development of disorders such as depression (Davidson, 2002b; Drevets, 2003; Siegle, Konecky, Thase, & Carter, 2003), anxiety (Davidson, 2002a), and post-traumatic stress disorder (PTSD; Quirk & Gehlert, 2003; Rothbaum & Davis, 2003). For instance, veterans with PTSD have been shown to exhibit decreased activation in the mPFC when exposed to traumatic vs. neutral stimuli (Shin et al., 2004). Furthermore, this decreased activation in the mPFC was correlated with increased activity in the amygdala, and symptom severity was positively correlated with activation in the amygdala and negatively correlated with activation in the mPFC. A similar pattern has been found to be associated with trait anxiety as well (Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011). One could reasonably expect that a means of increasing mPFC activation in these veterans or trait anxious persons could potentially lead to a decrease in symptom severity and, if they were to undergo exposure therapy, improved retention of extinction learning. Indeed, in considering their findings regarding the role of mPFC activation in retrieval of extinction learning, Milad and Quirk (2002) suggested that stimulation of the mPFC could improve exposure therapy outcomes. Thus, there is reason to believe that the PFC serves as the "neurobiological basis for inhibitory learning" (Craske et al., 2008), and that stimulation of the PFC could be a means of improving exposure therapy by aiding in the inhibition of fear memories and responses.

4. Brain stimulation

The roots of brain stimulation as it is known today can be traced back about a millennium to a time when ancient physicians suggested placing live electric catfish and torpedo fish on the scalp to treat epilepsy and headaches (Brunoni et al., 2012). In the past century, modern techniques of brain stimulation have been developed and utilized to study brain function, and as a treatment for various illnesses, motor disorders, pain disorders, and psychopathology (Andrews, 2010). Methods of brain stimulation have historically been fairly invasive and potentially dangerous—electroconvulsive therapy, for instance, works by inducing seizure through application of an electrical current to the brain between 70 and 150 V (Scovern & Kilmann, 1980). Deep brain stimulation involves surgical implantation of electrodes directly into a selected area of the brain to enable ablation of the area's function when

the current is switched on (Andrews, 2010). Even the more recently developed method of vagus nerve stimulation requires surgical implantation of coils around the vagus nerve which are subcutaneously connected to a generator (Terry, Tarver, & Zabara, 1991). However, a new class of neurostimulation techniques has evolved and opened the door for the possibility of using brain stimulation as a feasible means of treating psychopathology non-invasively.

4.1. Non-invasive brain stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) both project current through the skin and intact skull so that no incision need be made, and both have minimal, low severity side effects (e.g., Brunoni et al., 2012; George, Higgins, & Nahas, 2011). A sufficiently lengthy application of either method results in changes in excitability of the cortex that outlast the period of stimulation (e.g., Priori, Hallett, & Rothwell, 2009), but TMS and tDCS induce these changes through different mechanisms.

TMS uses a pulse generator to create a brief, rapidly alternating, high (5000 amperes or more) electrical current. The current is passed through a large coil which an operator places on a participant's scalp in a predetermined area. The rapidly alternating current creates a focused magnetic field of similar strength to that produced by an MRI (Andrews, 2010). Next, as per Faraday's principle of electromagnetic induction, the rapidly alternating magnetic field becomes an intracranial electric current which initiates action potentials in the targeted neurons. TMS is most effective when the pulses are repeated (rTMS) up to a frequency of 50 hertz (Hz). rTMS at or below 1 Hz has an inhibitory effect on the targeted neurons while frequencies above 1 Hz have an excitatory effect.

tDCS in its most basic form involves passing a weak current between two electrodes connected to a direct current source. The electrodes are generally saline soaked sponges placed on the scalp. While the actual mechanism of action of tDCS is not yet well understood, the current is theorized to cause a polarity-dependent shift of resting membrane potential, or threshold (e.g., Brunoni et al., 2012). Importantly, unlike TMS, tDCS does not cause action potentials but rather changes the probability of action potentials occurring in the targeted areas, although this does change individual neurons' average level of discharge (Fig. 1). tDCS is also believed to augment synaptic plasticity (e.g., Fritsch et al., 2010). In fact, tDCS is technically a neuromodulator rather than a neurostimulator, although the term stimulation will continue to be used for ease of communication. The electrode through which the current enters the brain is referred to as the anode while the electrode through which the current exits is the cathode. The orientation of the two electrodes is referred to as the montage. A unipolar montage refers to a set-up in which one of the electrodes is placed below the neck as a reference electrode while a bipolar montage refers to a set-up with both electrodes placed on the scalp. Again, although the exact mechanism through which it occurs is not completely understood, research supports that generally the neurons under the anode are depolarized (excited) while the neurons under the cathode are hyperpolarized (inhibited, Nitsche et al., 2007). The related method of transcranial *alternating* current stimulation (tACS), is believed to interact with cortical oscillations (Frölich, 2015). The newest iterations of tDCS employ multiple electrodes, generally one of which generates either anodal or cathodal stimulation with the rest of the "return" electrodes generating the opposite current. This method, more accurately referred to as transcranial stimulation (tCS) since the current is no longer direct, seems to allow for more focal stimulation of deeper structures or networks (e.g., Ruffini, Fox, Ripolles, Miranda, & Pascual-Leone, 2014).

TMS and tDCS also differ in more practical ways. TMS has greater spatial resolution, although tDCS is still able to target an area the size of, for instance, the DLPFC, and the sponge electrodes can be cut to be tailored to a specific individual's brain (Priori et al., 2009). Another research-relevant difference is that people are more easily blinded to active vs. sham stimulation condition with tDCS compared to TMS—sham tDCS still provides a tingling scalp sensation, while to achieve this with TMS additional steps would need to be taken to provide a weak current to the scalp from another source. Additionally, participants can move their heads and complete other active tasks while undergoing tDCS, which is not possible with TMS (Priori et al., 2009). tDCS is advantageous in other ways as well—tDCS units cost far less than TMS units, are smaller and much lighter, and do not require a special power supply. As such, unlike TMS machines, they are portable and could potentially even be used in the home (Priori et al., 2009). tDCS is a more promising method for treatment enhancement as per guidelines that any new treatment should aim to be inexpensive and accessible (Shoham et al., 2014). However, studies using both TMS and tDCS will be reviewed below as prolonged application of both methods lead to very similar outcomes—that is, both methods have been shown to quickly alter neuronal function both directly under the stimulated site and in connected brain regions (e.g., George et al., 2009).

It has been proposed that about half of the applied current from tDCS is passed through the brain between the two electrodes while the rest is shunted by the skull (e.g., George et al., 2009). Recent studies applying tDCS to cadavers, however, have suggested that as little as 10% of the applied current passes through the brain, and that 4 mA (milliamperes), a very large amount of current, would be necessary to cause the firing of neurons under the electrodes (Underwood, 2016). While this has caused some doubt in the field surrounding the efficacy of tDCS, studies discussed below provide evidence that tDCS is, indeed, doing something to significantly alter brain activity. Furthermore, as already discussed, while the exact mechanisms of action involved in tDCS are not known, it has been well established that tDCS at typical levels (e.g. 1.5–2 mA) doesn't cause firing of neurons, but rather changes the likelihood that a neuron will fire or even alters connections between neurons. Thus, that a larger amount of current than is typically applied is necessary to cause firing of neurons may not be critical.

5. Brain stimulation in clinical research

The clinical efficacy of non-invasive brain stimulation has been researched most commonly in relation to treatment-resistant depression (TRD; George et al., 2009). Indeed, TMS has been granted FDA approval as a treatment for TRD partly in response to a particular study showing TMS treatment gains with effect sizes similar to those found in clinical trials of antidepressant drugs (O'Reardon et al., 2007). Patients in the study received high frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) five times a week for 4 to 6 weeks. Similar results have also been found using low frequency stimulation of the right DLPFC (e.g, Loo & Mitchell, 2005). tDCS with the anode over the left DLPFC and the cathode over either the right DLPFC or a reference site has also been proven efficacious in the treatment of major depressive disorder (MDD), although less work has been done using this montage (Kekic, Boysen, Campbell, & Schmidt, 2016). Stimulation research has also been conducted with clinical populations that benefit from exposure therapy and experience symptoms that are likely somewhat driven by fear memory and inhibition.

Though not an exhaustive list, the following terms were used to search the literature for relevant studies: "brain stimulation and exposure therapy", "brain stimulation and extinction", "brain stimulation and inhibitory learning", "brain stimulation and conditioned fear", "brain stimulation and psychopathology", "brain stimulation and anxiety", "brain stimulation and fear", and "brain stimulation and OCD". These searches were also repeated using "tDCS" and "TMS" in place of "brain stimulation" and "panic disorder", "generalized anxiety disorder", "social anxiety disorder", "PTSD", and "phobia" in place of "OCD". Additional relevant sources were identified by searching the references of manuscripts found during the initial literature search. Additional details about the following studies can be found in Table 1.

Table 1
Methods and stimulation parameters of selected studies.

Study	Study type	n	Population	Primary outcome measures	Device	Stimulation	Target/montage	Methods	Outcome	Effect size
Berlim et al., 2013	Meta analysis of 10 RCTs	282	OCD	Y-BOCS	rTMS	varied	Varied	5 or more sessions	Significantly greater reduction in Y-BOCS with low freq over SMA and OFC for active as compared to sham	Hedges' g = 0.8 for 1 Hz, 1.37 for SMA/OFC
Modirrousta et al., 2015	Open-label trial	10	OCD	Y-BOCS	Deep rTMS	Low frequency (1 Hz)	mPFC	10 daily sessions	Significant reduction in Y-BOCS post-treatment and at 1 month follow-up	Means and standard deviations not reported
Bation et al., 2016	Open-label trial	8	OCD	Y-BOCS	tDCS	2 mA	Cathode left OFC/anode right cerebellum	10 sessions over 5 days	Significant reduction in Y-BOCS post-treatment and at 3 month follow-up	d = 1.28
Carmi et al., 2018	RCT	30	OCD	Y-BOCS	Deep rTMS	High frequency (20 Hz)	mPFC and ACC	25 sessions over 5 weeks	Near-significant reduction in Y-BOCS for active compared to sham	Means and standard deviations not reported
Tendler et al., 2018	RCT	94	OCD	Y-BOCS	Deep rTMS	High frequency (20 Hz)	mPFC and ACC	29 sessions over 6 weeks	Significant reduction in Y-BOCS	Means and standard deviations not reported
Boggio et al., 2010	RCT	30	PTSD	PCL, HAM-A, HAM-D	rTMS	High frequency (20 Hz)	right DLPFC	10 session over 2 weeks	Significantly greater improvement in PCL compared to left DLPFC and sham, significant improvement in HAM-A	Means and standard deviations not reported
						High frequency (20 Hz)	left DLPFC		Significantly greater improvement in PCL compared to sham, significant improvement in HAM-D	Means and standard deviations not reported
Watts et al., 2012	RCT	20	PTSD	CAPS, PCL, BDI	rTMS	low frequency (1 Hz)	Right DLPFC	10 sessions over 2 weeks	Significantly greater improvement in CAPS, PCL, and BDI compared to sham	CAPS d = 1.40, PCL d = 2.04, BDI d = 0.76
Cohen et al., 2004	RCT	24	PTSD	PCL, TOP-8, HAM-A	rTMS	high frequency (10 Hz)	Right DLPFC	10 sessions over 2 weeks	Significantly more improvement on PCL, TOP-8, and HAM-A compared to sham and low frequency (1 Hz)	PCL d = 2.15, TOP-8 d = 1.74, HAM-A d = 1.65
Philip et al., 2016	Open-label chart review	10	PTSD + MDD	PCL and QIDS	rTMS	Medium frequency (5 hz)	left DLPFC	Up to 36 sessions over 3 weeks with treatment as usual	Significant improvement in PCL and QIDS	PCL d = 1.24, QIDS d = 1.16
Bystritsky et al., 2008, 2009	Open-label trial	10	GAD	HAM-A	rTMS	Low frequency (1 Hz)	Right DLPFC	6 sessions over 3 weeks	Significant improvement on the HAM-A post-treatment and at 6 month follow-up	d = 2.27
Shiowaza et al., 2014	Case study	1	GAD	GAD-7; BAI	tDCS	2 mA	Cathode right DLPFC/anode contralateral deltoid	15 daily sessions	Clinically significant improvement on GAD-7 and BAI post-treatment and at one-month follow-up	N/A
Mantovani et al., 2007	Open-label trial	6	PD + MDD	PDSS	rTMS	Low frequency (1 Hz)	Right DLPFC	14 daily sessions	Significant improvement on PDSS	d = 2.14
Mantovani et al., 2013	RCT	25	PD + MDD	PDSS	rTMS	Low frequency (1 Hz)	Right DLPFC	20 sessions over 4 weeks	Significantly greater improvement on PDSS compared to sham	d = 1.77

Note. RCT = Randomized controlled trial. OCD = Obsessive-Compulsive Disorder. PTSD = Posttrraumatic Stress Disorder. GAD = Generalized Anxiety Disorder. PD = Panic Disorder. MDD = Major Depressive Disorder. Y-BOCS = Yale-Brown Cornell Obsessive-Compulsive Scale. PCL = PTSD Checklist. HAM-A = Hamilton Anxiety Rating Scale. HAM-D = Hamilton Depression Rating Scale. CAPS = Clinician-Administered Post Traumatic Stress Disorder Scale II. BDI = Beck Depression Inventory. TOP-8 = Treatment Outcome PTSD Scale. QIDS = Quick Inventory of Depressive Symptomatology. GAD-7 = Generalized Anxiety 7-Item Scale. BAI = Beck Anxiety Inventory. PDSS = Panic Disorder Severity Scale. rTMS = Repetitive transcranial magnetic stimulation. tDCS = Transcranial direct current stimulation. Hz = Hertz. mA = Milliampere. mPFC = Medial prefrontal cortex. OFC = Orbitofrontal cortex. ACC = Anterior cingulate cortex. DLPFC = Dorsolateral prefrontal cortex. SMA = Supplementary motor area. d = Cohen's d.

5.1. OCD

A fair amount of research has investigated what role stimulation may play in the treatment of obsessive compulsive disorder (OCD). This is perhaps not surprising given that OCD has been observed to be characterized by dysfunction in the DLPFC, the OFC, the mPFC, and the supplementary motor area (SMA), amongst other regions (e.g., Milad & Rauch, 2012). A 2013 meta-analysis of 10 randomized and sham controlled trials suggested that low frequency rTMS over the OFC or the SMA can significantly reduce symptoms of OCD as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Berlim, Neufeld, & Van den Eynde, 2013). Notably, studies targeting the DLPFC did not result in significantly improved scores on the Y-BOCS, even though the DLPFC is commonly targeted to treat other disorders. Modirrousta et al. (2015) instead targeted the mPFC in a small pilot study by using low frequency rTMS with a double-cone coil to enable deeper penetration and found significant improvement in Y-BOCS scores after 10 sessions and at one-month follow-up. Evidence has also been found suggesting tDCS with the cathode over the left OFC and the anode over the right cerebellum significantly reduces Y-BOCS symptoms after 10 sessions and at 3-month follow-up (Bation, Poulet, Haesebaert, Saoud, & Brunelin, 2016).

High frequency deep TMS over the mPFC and ACC has also been used to successfully alleviate OCD symptomatology (Carmi et al., 2018). Most recently, TMS was granted FDA approval for treating OCD in adults due to a randomized control double-blinded multi-site study expanding on the work of Carmi et al. (2018). 94 participants received 29 sessions over 6 weeks of either active or sham deep TMS over the mPFC and ACC. Participants who received active stimulation experienced a significantly greater decrease in Y-BOCS scores compared to those who received sham stimulation (Tendler et al., 2018).

5.2. PTSD

PTSD has also been fairly well represented in the brain stimulation literature. A meta-analysis of 3 randomized and sham-controlled trials found that 10 sessions of low (inhibitory) or high (excitatory) frequency rTMS to the right DLPFC or high frequency rTMS to the left DLPFC resulted in significantly lower clinician and self-reported symptoms of PTSD as compared to control (Berlim & Ven den Eynde, 2014). Interestingly, one study also found that high frequency rTMS to the right DLPFC was associated with greater improvement in PTSD symptoms as compared to left, that right stimulation was associated with significant improvement in anxiety symptoms while the left was not, and that left stimulation was associated with significant improvement in depressive symptoms while the right was not (Boggio et al., 2010). Accordingly, the other studies in the meta-analysis found that low frequency stimulation of the right DLPFC alleviated depressive symptoms (Watts, Landon, Groft, & Young-Xu, 2012) and, again, that high frequency stimulation of the right DLPFC alleviated anxiety symptoms (Cohen et al., 2004). A separate study not included in the meta-analysis found that “medium” frequency (5 Hz; while this would technically be considered excitatory, a minimum of 10 Hz is usually used) rTMS to the left DLPFC led to a decrease in both PTSD and depressive symptoms in 10 veterans with comorbid PTSD and MDD (Philip, Ridout, Albright, Sanchez, & Carpenter, 2016).

The above pattern of results is somewhat troubling. Both low and high frequency stimulation of the right DLPFC and both high and medium frequency stimulation of the left DLPFC has led to improvements in PTSD symptoms. This is troubling because high and low frequency stimulation theoretically should have opposing effects. That being said, only one of the reported studies used an external source of scalp stimulation during sham stimulation (Priori et al., 2009), and none of the studies employed a questionnaire to evaluate differences in sensation and expectations between active and sham groups. As such it is possible that the pattern of results across this set of studies could be due to placebo effects in some or all of the studies. Nevertheless, these findings highlight the importance of continued research delineating the mechanisms of non-invasive stimulation techniques.

5.3. Other anxiety research

Though less research has been done on other anxiety disorders, there is some evidence suggesting that TMS and tDCS could be useful in treating GAD and PD. A pilot study conducted on 10 participants diagnosed with GAD found significantly decreased scores on the Hamilton Rating Scale for Anxiety (HAM-A; Bystritsky et al., 2008) following 6 sessions of low frequency rTMS over the right DLPFC (Bystritsky et al., 2008) and at 6-month follow-up (Bystritsky, Kerwin, & Feusner, 2009). A case study of tDCS with the cathode over the right DLPFC and the anode over the contralateral deltoid in a woman with severe treatment-resistant GAD provides some additional preliminary evidence for the efficacy of tDCS in treating GAD (Shiowaza et al., 2014). This woman was found to be asymptotic as measured by the Generalized Anxiety 7-item scale (GAD-7) and the Beck Anxiety Inventory (BAI) following 15 daily sessions of tDCS and at 30-day follow-up. PD has only been investigated comorbidly with depression, but symptoms of both were found to improve significantly following 14 sessions of daily low frequency rTMS to the right DLPFC in 6 subjects (Mantovani et al., 2007). In a randomized sham-controlled follow-up study, participants in the active TMS group (20 sessions of low frequency rTMS to the right DLPFC) rated significantly lower on the Panic Disorder Severity Scale as compared to the group who received sham stimulation (44% vs. 5% reduction; Mantovani, Aly, Dagan, Allart, & Lisanby, 2013).

Research investigating the effects of stimulation on cognitive biases in non-clinical populations is also promising. Vigilance to threat, which is reliably shown to be hyperactive in many anxiety disorders (e.g., Yiend & Mathews, 2001), has been shown to be reduced following one session of tDCS with the anode over the left DLPFC and the cathode over the right DLPFC (Ironside, O'Shea, Cowen, & Harmer, 2016). Furthermore, attention bias modification training both towards and away from threat was more successful with active vs. sham tDCS with the anode over the left DLPFC and the cathode positioned as a reference electrode (Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014; Heeren, Baeken, Vanderhasselt, Philippot, & de Raedt, 2015).

5.4. Brain stimulation and extinction learning

Whereas research suggests that non-invasive brain stimulation may alleviate symptoms of anxiety and fear related disorders, it is still unclear whether they do so through mechanisms that may also underlie and promote the efficacy of exposure therapy and fear extinction. That is, evidence discussed above suggests that certain brain areas are involved in fear extinction, but as of yet evidence has not been presented suggesting that stimulation of these areas in humans can affect extinction memory consolidation or retrieval. There has been very little research done to evaluate the utility of TMS and tDCS in extinction of phobic fears. However, research on extinguishing laboratory-conditioned fears provide an analogue for exposure therapy studies as the process is likely similar to extinguishing fears that have been acquired naturally.

Guhn et al. (2014) investigated whether stimulation could be used to enhance inhibitory learning following fear conditioning. 85 healthy volunteers underwent fear conditioning in which an aversive scream was paired with neutral male faces (CS) and they then received either high frequency rTMS over a prefrontal cluster thought to influence the mPFC or sham stimulation. Immediately following stimulation subjects underwent extinction learning, and extinction recall was assessed on the following day. Subjects were excluded if they either did not exhibit a significant fear potentiated startle (FPS) response to the aversive scream or did not condition, that is, did not exhibit higher FPS to the CS following fear conditioning and before extinction. The remaining 45

subjects who underwent active rTMS exhibited lower FPS responses to the CS during extinction and at follow-up. Enhanced extinction learning also occurred in a study that used anodal tDCS over AF3 and the cathode on the contralateral mastoid process in an effort to reach the vmPFC (van't Wout et al., 2016). These studies provide evidence that extinction learning can be manipulated by non-invasive brain stimulation, which suggests such stimulation could enhance exposure therapy.

6. Brain stimulation and retrieval inhibition

Further supporting the idea that stimulation of the PFC may be alleviating symptoms of anxiety and fear disorders through mechanisms similar to exposure therapy can be found in studies investigating the effect of stimulation on retrieval inhibition. As discussed above, one theory of exposure therapy and extinction suggests that inhibitory learning is the most important mechanism underlying exposure therapy (e.g., Craske et al., 2008, 2014). That is, fear memories are not forgotten, but rather extinction memories are learned and inhibit the fear memories. Thus, retrieval inhibition, or the inhibition of retrieval of fear memories, should underlie successful extinction and exposure therapy. Two ways that the strength of one's ability to inhibit retrieval of memories can be measured are through retrieval induced forgetting (RIF) and directed forgetting (DF).

6.1. RIF as a measure of inhibition

RIF is the phenomenon in which retrieval of some information from long term memory leads to the subsequent inhibition of un-retrieved but related information in order to decrease competition for recall (e.g., Anderson, Bjork, & Bjork, 1994). Resolution of competition specifically has been hypothesized to be the function of retrieval inhibition and critically important for cognitive-behavioral therapy (Brewin, 2006). In relation to extinction learning and exposure therapy, the RIF process would result in retrieval of extinction memories inhibiting retrieval of the original fear memories such that the original fear memories would become harder to recall. That is, retrieval of CS-noUS should inhibit the recall of CS-US when the CS is presented alone, or the retrieval of memories about friendly dogs should inhibited the recall of memories of dogs biting. Thus, it is reasonable to expect that the amount of RIF (forgetting of unpracticed material when related material *is* practiced) one exhibits should be negatively correlated with return of fear, or recall of the original CS-US association. However, this would only be the case if RIF is, indeed, a measure of retrieval inhibition. There has been some debate over whether RIF is driven by inhibition or interference. That is, RIF could potentially be caused by retrieval practice strengthening the association between practiced exemplars and their category cues, which could "steal activation" from other related unpracticed cues. This would mean that the effect would occur due to strengthening rather than to inhibiting processes. That being said, the evidence in favor of inhibition over interference is very strong. Research has established that RIF is competition-dependent, strength independent, cue-independent, and retrieval success-independent (Storm, Bjork, Bjork, & Nestojko, 2006). Each of these findings, as elaborated below, rules out an interference model and supports the hypothesis that RIF is an inhibitory phenomenon.

The competition-dependent nature of RIF is evidence against the interference model because the stronger association an exemplar has to a cue the more likely it is to be inhibited (Storm, 2010). For example, both the words "guava" and "apple" are exemplars of the category of "Fruit." For most North Americans, however, apple is much more closely associated to the category Fruit than guava is. If another exemplar of the Fruit category is practiced (banana), then apple will be more strongly inhibited than guava will be, because apple was a much more competitive exemplar for retrieval than guava was. That is, if the category-exemplar pair "Fruit: banana" is practiced, inhibitory processes will work to most strongly suppress other exemplars of Fruit that would compete with banana for recall, and apple is a stronger competitor than guava. This wouldn't occur due to interference, because strengthening of banana should interfere equally with recall of apple and guava.

The strength-independent findings provide evidence that RIF cannot solely be a result of increased strengthening of the relationships between practiced exemplars and categories resulting in interference with unpracticed exemplars. If the effect were due to interference, one would expect that the more you practice a given category-exemplar pair, the more forgetting would occur, because the practiced, extra-strengthened exemplar will provide that much more interference to other exemplars. However, the same amount of forgetting occurs whether a study employs the typical 3 practice sessions of certain category-exemplar pairs or an extensive 10 practice sessions (e.g., Storm & Nestojko, 2010).

Cue-independence refers to the pattern of findings in which inhibition of an exemplar due to competition in a given category, A, also results in inhibition of said exemplar in another category, B, that it also belongs to (Anderson & Spellman, 1995). That is, if the category exemplar pair of "Fruit: banana" is practiced, one of the exemplars that will likely be inhibited is strawberry. That is, at test, a participant would likely be unable to recall the exemplar strawberry in response to the cue Fruit: St____. Additionally, however, recall ability would likely also be diminished for the cue Red: St___ even though the category Red was never practiced. This further demonstrates that RIF occurs independent of exemplar and cue association strengthening.

A final argument against exemplar-cue strengthening and interference is that RIF is retrieval-success independent. If a person is cued to practice recall of a word that does not exist (Fruit: Zo__), inhibition of other, real exemplars in the category will still occur. Thus, RIF still occurs even when retrieval practice is unsuccessful or even impossible.

6.2. Directed Forgetting (DF) as a measure of retrieval inhibition

DF occurs when an instruction to forget information that was just presented results in improved recall for subsequently presented information (e.g., Bjork, 1972). As a typical example, a person may be presented with three lists of words. In the middle of one list of words the participant would be cued to forget the preceding words and only remember the following words (F-R list). In the middle of another list the participant would be cued to remember the preceding words in addition to the following words (R-R list). On a third list a participant may see a series of shapes rather than words in the first half of the list, then be cued to forget the preceding shapes and only remember the following words (control list; Fig. 2). In a final recall test of *all* of the words, three phenomena tend to occur: 1. Recall for post-cue items in the F-R list will be better than recall for post-cue items in the R-R list. 2. Recall for post-cue items in the F-R list will not differ significantly from recall for post-cue items in the control list. 3. Recall for pre-cue items in the F-R list will be worse than recall for pre-cue items in the R-R list. Thus, effortful forgetting of to-be-forgotten items is not only successful, but it resolves proactive interference enough that words presented after the forget cue are remembered just as well as those that were preceded by shapes rather than words (and as such should not experience any proactive interference). Additionally, this resolution of proactive interference results in words following the forget cue being remembered better than words presented after a remember cue.

DF, somewhat similarly to RIF, could be related to extinction and exposure therapy in that effortful forgetting of fear memories might also result in enhancement of the retrievability of extinction/exposure memories. That is, purposeful forgetting of the CS-US association would result in inhibition of the CS-US association, which would cause the CS-noUS association to be more easily recalled due to a lack of proactive interference from the CS-US association. In other words, purposeful inhibition of memories of dogs biting would make it easier for one to recall memories of friendly dogs. An important distinction between this process and that proposed for RIF is that inhibition is being induced

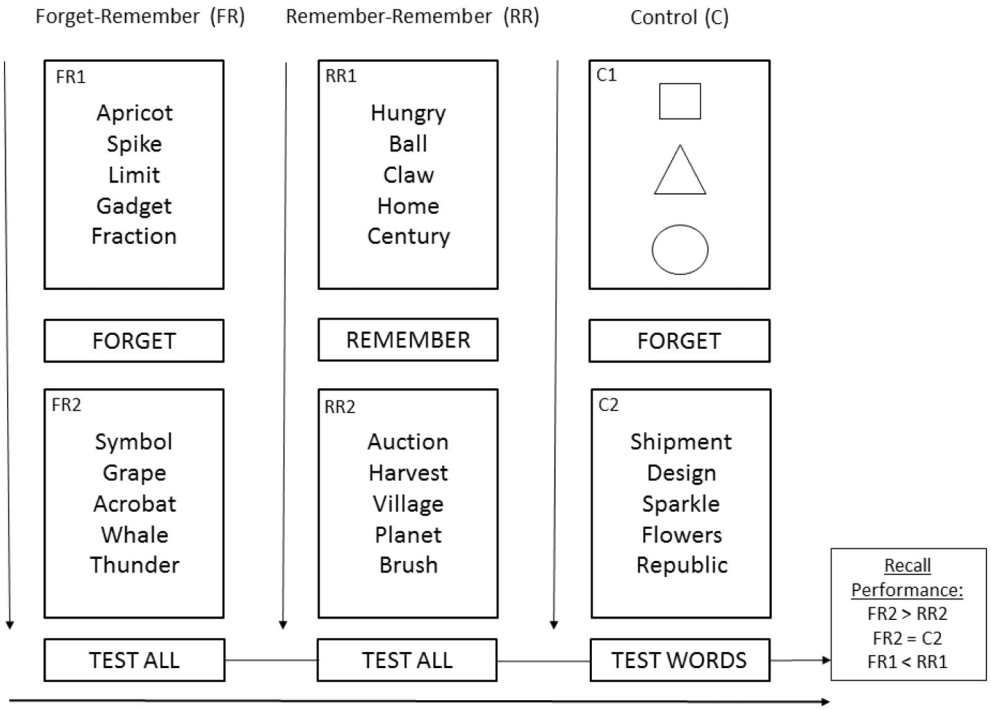

Fig. 2. Typical directed forgetting procedure and outcomes. Forget-remember is the list that includes an instruction to forget the preceding words half way through. Remember-remember is the list that includes an instruction to remember the preceding words half way through. Control is the list that includes a forget instruction but the preceding items were shapes rather than words. Typical recall performance by list type and position is presented in the box on the right, with a 1 indicating words that occur in the first half of a list and a 2 indicating words that occur in the second half of a list.

purposefully rather than occurring due to retrieval competition with the CS-noUS association. With RIF, retrieval competition causes inhibition while with DF retrieval competition does not occur due to active inhibition. Of course, these two processes may differ only in how inhibition is initiated while the inhibitory process itself may be the same.

Thus, like with RIF, it is reasonable to expect that the size of the DF effect one exhibits, indexed either by successful forgetting of words preceding a forget cue (the "cost" of forgetting) or enhanced retrieval of words following a forget cue (the "benefit" of forgetting), or both, should be negatively correlated with return of fear, or recall of the original CS-US association. However, also like with RIF, this would only be the case if DF is, indeed, a measure of retrieval inhibition. While there is likely more than one process underlying DF, evidence supports the idea that retrieval inhibition is a primary mechanism of action (for a review see Bjork, Bjork, & Anderson, 1998). Some evidence for a retrieval inhibition account comes from findings suggesting that the strength in memory of the to-be-forgotten items is ultimately unaffected. That is, in a sense the term directed *forgetting* is a misnomer—items are not forgotten but rather inhibited. This has been demonstrated in several ways. To-be-forgotten items are later relearned just as readily as to-be-remembered items (e.g., Geiselman & Bagheri, 1985; Reed, 1970). Additionally, participants' recognition of to-be-forgotten words has been shown to be no different than recognition for to-be-remembered words (e.g., Block, 1971; Elmes, Adams, & Roediger, 1970; Geiselman, Bjork, & Fishman, 1983; Gross, Baresi, & Smith, 1970). Finally, the proactive interference eliminated by forgetting items can be reinstated by certain manipulations, such as a recognition task administered post-list study and pre-test (e.g., Bjork, Bjork, & Glenberg, 1973). Thus, the behavior of the to-be-forgotten items seems remarkably similar to the extinction-related return-of-fear phenomena of reacquisition and spontaneous recovery. Finally, a study that measured neural activity during a recognition task of to-be-remembered and to-be-forgotten words has provided electrophysiological evidence that to-be-forgotten event related potentials (ERPs) are indicative of retrieval inhibition processes (Ullsperger, Mecklinger, & Müller, 2000).

6.3. Brain stimulation, RIF, and DF

In an attempt to provide further evidence that RIF is driven by inhibition, Penolazzi et al. (2014) administered a test of RIF to 60 students in which tDCS was applied to the right DLPFC during the phase of the experiment in which only some words are practiced, presumably leading to inhibition of the unpracticed related words. Participants either received anodal (excitatory) or cathodal (inhibitory) stimulation through the electrode over the right DLPFC with the other electrode over the left supraorbital region as a reference electrode, or they received sham stimulation. At the final recall test, both the anodal and the sham groups displayed typical amounts of RIF while in the cathodal group the RIF effect was abolished. That is, cathodal stimulation of the right DLPFC seemed to disrupt the process in which retrieval competition is resolved by inhibition of unpracticed information. Thus, it appears that at least in this study excitation of the right DLPFC had no effect on inhibition while inhibition of the right DLPFC decreased inhibition.

Similarly, Anderson, Davis, Fitzgerald, and Hoy (2015) had 14 participants complete a baseline measure of RIF (i.e., while undergoing sham tDCS) as well as a RIF task while undergoing active tDCS to assess whether individual differences in RIF would predict RIF performance following stimulation. Participants received either cathodal (inhibitory) stimulation of the left DLPFC with the anode over the right supraorbital area as a reference electrode, or sham stimulation. Interestingly, Anderson et al. (2015) found that individuals with high baseline RIF levels experienced a significant reduction in RIF following active tDCS, while individuals with low baseline RIF levels experienced significantly improved levels of RIF following active tDCS. Thus, in this study, cathodal (inhibitory) stimulation of the left DLPFC caused more inhibition when baseline inhibition was low and less inhibition when baseline inhibition was high.

The Anderson et al. (2015) findings are surprising, especially considering a positive linear relationship has been established using fMRI between retrieval practice during RIF and DLPFC activation (Wimber, Rutschmann, Greenlee, & Bäuml, 2009). That being said, Wimber et al. (2009) also found that activation in left prefrontal areas correlated *negatively* with forgetting at test in healthy participants. The results of

Anderson et al. (2015) suggest that while inhibition of the left DLPFC might increase inhibition and thus enhance exposure therapy in a person with low baseline levels, it may impair inhibition in someone with high baseline levels of RIF. This pattern of results is certainly puzzling, and cannot be readily explained in a satisfactory way. Moreover, this pattern was not predicted and therefore might represent a type I error. However, looking forward, even if this pattern should prove replicable, individual differences in reactions to tDCS need not preclude use of stimulation to enhance exposure therapy. For instance, clinicians could administer a RIF test before starting exposure therapy. A patient's level of inhibitory dysregulation, as assessed by the RIF test, could then inform the clinician whether or not tDCS would be indicated.

Brain stimulation has also been used in conjunction with DF. Silas and Brandt (2016) paired tDCS with the anodal (excitatory) electrode over the left DLPFC and the cathodal (inhibitory) electrode over the right DLPFC with DF tests in 30 university students and found that active stimulation resulted in a nearly abolished DF effect. That is, the active tDCS group remembered more to-be-forgotten words and fewer to-be-remembered words than the sham tDCS group, which is theoretically consistent with a decrease in inhibition.

The discrepant results of these three studies need not be viewed as discouraging regarding the use of non-invasive brain stimulation to augment retrieval inhibition and exposure therapy. Rather, the power of brain stimulation to have a measurable effect on processes which have been empirically demonstrated to index retrieval inhibition is encouraging. As is the case with most of the non-invasive brain stimulation literature, heterogeneity in methods prevents one from forming clear conclusions about the nature of the relationships between stimulation and variables of interest. Continued investigation using consistent methods will hopefully illuminate this relationship.

Importantly, the studies above used neutral stimuli, while the retrieval inhibition of emotional stimuli that would occur in exposure therapy could function much differently. However, RIF effects have been found in which retrieval of neutral information resulted in inhibition of threatening information (Fig. 3; Nuñez et al., 2015; Kircanski et al., 2015), and directed forgetting effects have been found for both threatening and neutral words (Wessel & Merckelbach, 2006). Evidently stimulation can modulate retrieval inhibition as indexed by RIF and DF and, given that RIF and DF effects have been found for threatening material, perhaps stimulation could increase the likelihood of fear memories being inhibited by extinction memories.

Notably, both the RIF and DF paradigms seem to result in inhibition of associations between the meanings of words (as per the cue-independent nature of RIF). These paradigms do not speak to what facets of the fearful associations might be inhibited due to exposure therapy. Fear-related human memories are more complex than word associations; perhaps the meaning of the memories are inhibited, but perhaps other features such as content, emotions, smells, etc. are also inhibited. If it can be firmly established that inhibition is one of the mechanisms underlying exposure therapy, the question of precisely what is inhibited will be an important one to address in future research.

Of course, it is possible that brain stimulation could increase the efficacy of exposure through channels unrelated to inhibitory learning. For instance, relative left frontal asymmetry, which is induced under conditions of tDCS with a bipolar montage with the anode on the left DLPFC and the cathode on the right DLPFC, has been shown to cause an increase in approach motivation and related emotions (e.g., Harmon-Jones, Gable, & Peterson, 2010). If tDCS enhances approach motivation, patients may approach more closely to the feared stimulus, which might then result in increased inhibitory learning as well as improved exposure therapy outcomes simply due to increased contact with the feared stimulus. Since tDCS has been effective in alleviating psychopathology symptoms in participants not undergoing exposure therapy it is also possible that stimulation could result in improved exposure outcomes by directly improving mood. These alternative explanations will be important to test in future research on brain stimulation and exposure therapy.

7. Brain stimulation and exposure therapy

Finally, a few recent studies have begun to investigate the effects of brain stimulation paired with actual exposure therapy in humans. Two case studies have demonstrated a significant improvement in Y-BOCS in treatment-resistant patients with OCD using exposure and response prevention (ERP) immediately preceded by high frequency rTMS to the

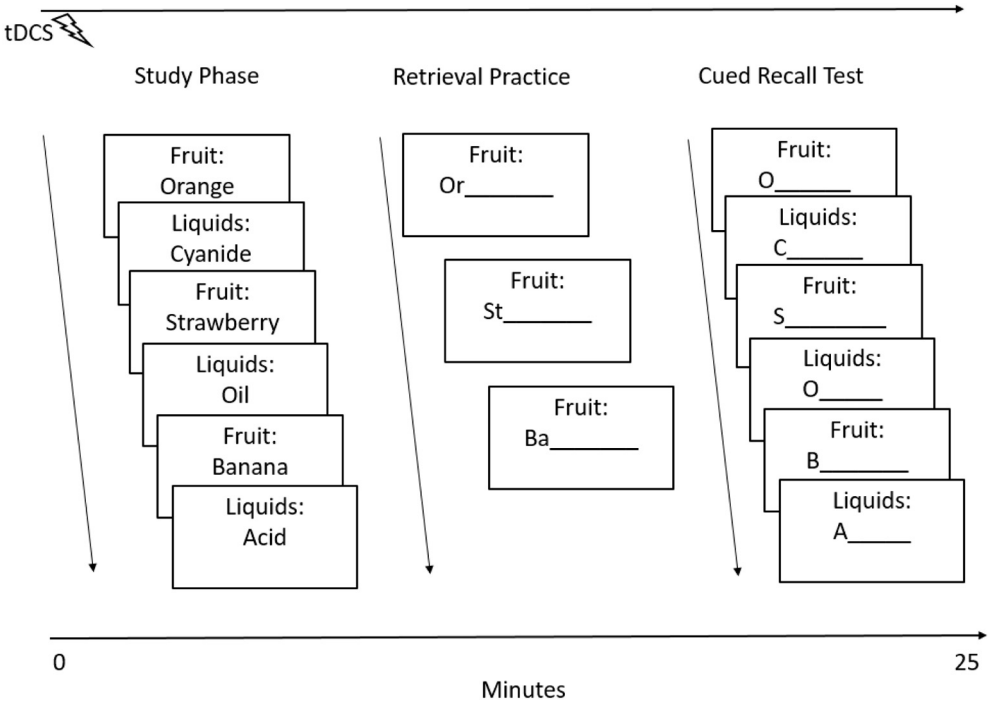

Fig. 3. Threat adapted retrieval induced forgetting procedure with concurrent tDCS administration. tDCS = transcranial direct current stimulation.

left DLPFC (Grassi, Godini, Grippo, Piccagliani, & Pallanti, 2014) and low frequency rTMS to the pre SMA (Adams, Badran, & George, 2014). Both patients had previously failed to benefit from medication and one of them also previously failed to benefit from ERP. The latter feature suggests that the addition of rTMS could have bolstered the efficacy of the ERP treatment.

There have also been four controlled studies conducted that have paired brain stimulation with exposure. The first study combined low frequency rTMS of the right DLPFC with imaginal exposure in 8 participants with treatment-resistant PTSD (Osuch et al., 2009). A crossover design was utilized such that all participants underwent a block of 20 exposure and active rTMS sessions and a block of 20 exposure and sham rTMS sessions. The sham rTMS involved placing the coil at a 45° angle to the head while still maintaining contact with the head so as to mimic the sensation felt during active rTMS. Each participant created a unique 10-item hierarchy of trauma-related events to be used for imaginal exposure during the sessions. Items ranged from neutral to very traumatic and were related to the traumatic experience which had resulted in the person's diagnosis of PTSD. Each session lasted 30 min and began with 5 min of rTMS only after which participants would be prompted to talk about an item of their choosing from their hierarchy. Before and after both treatment blocks participants were assessed using the Clinician Administered PTSD Scale (CAPS), the Impact of Events Scale (IES), and the Hamilton Depression Rating Scale (HAM-D). The results of the study were marginally successful. That is, the CAPS hyperarousal scale suggested that exposure plus active rTMS was superior to exposure plus sham rTMS (d = 0.42), however, none of the other measures yielded significant differences between groups. Osuch et al. (2009) had chosen low frequency rTMS to the right DLPFC hoping to address presumed right frontal hyperactivity associated with PTSD. They concluded that perhaps high frequency stimulation would be more effective in PTSD.

Isserles et al. (2013) recruited 26 participants with PTSD and administered 12 sessions of a similar imaginal exposure task paired with either active high frequency deep rTMS to the mPFC or sham rTMS. A third group imagined positive scenes before receiving active rTMS. Both active and sham rTMS were applied by encasing either a real or a sham coil inside a helmet which resulted in similar acoustics and scalp sensations in both conditions. Participants were assessed weekly over four weeks using the CAPS, the PTSD-symptoms scale—self report (PSS-SR), the HAM-D, and the Beck Depression Inventory-II (BDI-II). Again, results were marginally successful. Thus, only the Intrusion subscale of the CAPS time by group interaction was significant. Planned analyses revealed that participants who received exposure and active rTMS experienced a significant decrease in total CAPS score, as well as in each CAPS subscale whereas the other two groups did not experience a significant difference in scores from pre to post-treatment. Regarding this latter pattern, however, it must be noted that the differences between the groups in changes in total CAPS score over time were not significant. Similarly, the interaction of group and time was also not significant for the other outcome measures with significant change pre- to post-treatment occurring in the exposure plus active stimulation group and not in the other two groups.

A third study investigated whether rTMS could be utilized to enhance exposure therapy for individuals with acrophobia (Herrmann et al., 2017). 39 participants underwent 2 sessions of brief virtual reality exposure therapy (VRET) following 20 min of either active or sham high frequency rTMS over the mPFC. During the VRET sessions participants were instructed to climb a very high winding staircase in a virtual environment. Rather than creating exposure hierarchies, each step of the staircase was conceptualized as a step on the hierarchy with subjective units of distress (SUDs) collected on each step. Participants who received active rTMS reported lower self-reported fear immediately following exposure (d = 0.54), although differences were no longer present at 3 month follow-up. In this study active rTMS seems to have accelerated participant response to exposure.

Finally, Van't Wout-Frank, Shea, Larson, Greenberg, and Philip (2019) administered tDCS paired with VRET to 12 male veterans with PTSD. Six sessions were administered over two weeks. Participants were randomly assigned to receive 25 min of either active or sham 2 mA tDCS with the anode over AF3 and the cathode over PO8 to attempt to target the vmPFC. Each session of VRET consisted of three eight minute driving scenarios in which the participants would navigate through warzones. The VRET was made more realistic by including olfactory cues such as the smell of gunfire and a vibrating steering wheel. Again, results were promising—participants in the active group exhibited a quicker decline in SCR across sessions than participants in the sham group. Additionally, while decrease in self-report scores on the PTSD checklist for DSM-5 did not differ between groups, there was a small effect found such that participants in the active group appeared to show minor continued improvement at one month follow-up while participants in the sham group did not (d = 0.37).

Notably, nearly every study in this review utilized a unique set of stimulation parameters, which results in a somewhat muddied picture in the literature. Indeed, this has been identified as an important area for further development by the NIMH (Bikson et al., 2018). Nevertheless, there is some evidence suggesting that pursuing non-invasive brain stimulation as a means of augmenting exposure therapy and shedding light on potential mechanisms is a promising undertaking.

8. Conclusion

Exposure therapy as it is utilized today has grown out of half a century of theorizing, practice, and empiricism. The remarkable and lasting effects the treatment can have on the lives of those with anxiety disorders is well documented; nevertheless, due to the strengths of exposure therapy it is still worthwhile to address its weaknesses so that more patients can benefit. This review summarizes literature suggesting that exposure therapy may be augmented by targeting retrieval inhibition with non-invasive brain stimulation. However, no known studies have directly investigated this possibility.

The evidence discussed in this review suggests the following two hypotheses. First, non-invasive brain stimulation, and particularly stimulation that targets the vmPFC either directly or through the DLPFC, may be a useful adjunct to exposure based therapy. Second, retrieval inhibition may mediate the relationship between stimulation and enhanced outcomes. The current state of the literature generates several practical suggestions for future studies testing these and related hypotheses.

Future research will yield more clinically relevant results by using randomized controlled methods and systematically and consistently investigating specific stimulation parameters such as montage, voltage, and timing. Of course, researchers should regularly investigate mechanisms of change in addition to outcomes to provide insight into the neural and cognitive underpinnings of successful exposure therapy and to identify targets for intervention. Specifically, due to the existence of empirical evidence supporting their validity as measures of retrieval inhibition, RIF and DF tasks with emotionally relevant content should be utilized when investigating retrieval inhibition. In order to generalize findings, future studies should also pair brain stimulation with in vivo exposure, exposure and response prevention, with both single-session treatment and higher levels of care, and with a variety of populations, including more complex cases. This must be accomplished with large sample sizes and again in a systematic and consistent manner.

Meeting these research needs will certainly be a tremendous undertaking for a literature still in its infancy. Taking this on could be well worth the effort, however. In addition to improving treatment outcomes, studies that successfully pair brain stimulation and exposure therapy while measuring retrieval inhibition can provide a more direct test of the hypothesis that inhibition is a mechanism underlying exposure therapy than has been conducted to date.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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