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Review

Eternal sunshine of the neuromodulated mind: Altering fear memories through neuromodulation

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ABSTRACT

Anxiety disorders pose one of the greatest threats to mental health. Modern treatment methods exist but are hindered by relapse, toxicity, and low efficacy. The use of neuromodulation to treat anxiety disorders has shown promising results, yet its underpinning mechanisms remain poorly understood. In this review, we make the case for further development of neuromodulation techniques to alter fear memories, with particular regard to future clinical applications in treating anxiety disorders. We start by briefly summarizing the neural circuitry of fear while identifying the pros and cons of possible neuromodulation targets. We then highlight recent advances in neuromodulation techniques that have been used to alter fear memories. Next, we apply a novel network-based approach to elucidate possible mechanisms of neuromodulation which may disrupt the consolidation of fear memory. Finally, we emphasize the need for more systematic neuromodulation studies on animal models and the developing brain. Overall, we aim to provide an integrated framework for future action, identifying key research priorities that must be addressed before effective neuromodulation-based treatments can be developed for practical use.

1. Introduction

From the mythological rivers of Lethe to the pen-shaped “standard issue” neuralyzer of Men In Black fame, the idea of erasing memories has long captured our imaginations. However, beyond obviating traumatic alien encounters, these fictional concepts are now getting closer to reality in neuroscience; neuromodulation techniques hold enormous potential for effective treatment of many forms of anxiety disorders by decoupling maladaptive fear responses.

Fear learning and memory are crucial for the continuity of any species. These adaptive fear responses promote the avoidance of danger and prevent detrimental actions that threaten survival (Roy, 2010). However, fear learning and memory can also become maladaptive and manifest as anxiety disorders, interfering with daily functioning. Anxiety disorders pose one of the greatest and most prevalent global threats to mental health (World Health Organization, 2017) with over 1 in 10 people likely to suffer from a ‘disabling anxiety disorder’ at some stage in their lives (Ehlers, 1997).

1.1. Current treatments and their limitations

Learned fear as a basis of anxiety disorder is not a novel concept; Breuer & Freud (1893) suggested that these disorders (previously known as hysteria) were caused by previously experienced fearful events that triggered anxious thoughts and maladaptive behavior. While this is not the only model of anxiety - and cannot by any means explain all forms of anxiety disorders, nor can it arguably even fully explain any form of anxiety (LeDoux, 2015) - it is one of the oldest and well-established models (Ganella and Kim, 2014). In accordance with this concept, treatment of anxiety disorder is often conducted through exposure therapy, a form of cognitive-behavior therapy (CBT) which involves repeatedly exposing a patient to feared stimulus in the absence of danger until it no longer elicits a fear response. It has long been believed that exposure therapy does not erase fear memory, but rather creates a new learning pathway that merely inhibits the previous maladaptive learning. Recent findings have however suggest that reconsolidation (during extinction) updates the fear memory trace rather than inhibiting it (Khalaf et al., 2018), furthermore, the ability of extinction to erase memories has also been suggested (Barad, 2006). Regardless, relapse is a common occurrence in patients (Barad, 2006;

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Baum, 1988; Bouton, 2002; Bouton and Bolles, 1979; Rescorla and Heth, 1975) and many who undergo CBT are unable to maintain long-term benefits of therapy (McNally, 2007), suggesting that extinction (exposure therapy) alone is ineffective.

In order to increase the effectiveness of CBT, researchers have investigated a variety of methods including co-treatments and procedure modifications. Firstly, co-treatment with pharmacological manipulations has been explored (de Kleine et al., 2013; Farach et al., 2012), the most notable being the *N*-methyl-D-aspartate (NMDA) partial agonist d-cycloserine, which has been shown to facilitate the consolidation of memory and extinction (Handford et al., 2014; Norberg et al., 2008; Ressler et al., 2004). Another prominent approach is by blocking the reconsolidation of fear memories when they are in a "fragile" protein-synthesis dependent state – a state in which they are susceptible to change (Nader et al., 2000). For example, administration of the β-adrenergic receptor antagonist propranolol before or after memory re-activation has been shown to disrupt reconsolidation of the fear memory, thereby reducing behavioral expression of fear (Brunet et al., 2008; Kindt et al., 2009).

An alternative to using pharmacological methods to disrupt reconsolidation of memory is the modification of behavioral therapy protocols. Extinction (laboratory-based exposure therapy) carried out during a reconsolidation period (during which the memory is more susceptible to alterations) has shown to be effective in removing fear response and preventing relapse in both rodents and human models (Monfils et al., 2009; Schiller et al., 2010). While these methods begin to address the pitfalls of standard CBT, pharmacological methods come with many complications (Farach et al., 2012), and behavioral approaches walk the tricky line between the dissociable processes of extinction and reconsolidation (Torregrossa and Taylor, 2013). Importantly, if these techniques are not properly handled, they can conversely lead to exacerbation of the problem (Eisenberg et al., 2003; Merlo et al., 2014; Pedreira and Maldonado, 2003). Furthermore, efficacy of the method put out by Monfils et al. (2009) has also been recently questioned (Klucken et al., 2016).

1.2. A new hope: neuromodulation

With advances in technology, modern techniques of altering brain activity and connectivity have emerged. These brain stimulation and neuromodulation techniques, while varied in methodology, share the commonality of delivering controlled electrical charges to specific parts of the brain. It was thought that this "pacemaker" for the brain imposed an artificial rhythm/pattern of firing to modify maladaptive patterns of activity and connectivity, resetting a new balance which resulted in healthy cognitive and behavioral states (Marin et al., 2014). This is however overly simplistic, and more recent studies have started to highlight different mechanisms in which these techniques exert their effects such as neurogenesis (Liu et al., 2015; Stone et al., 2011), neurotransmitter release (Van Dijk et al., 2012), or alterations to synaptic plasticity (Sui et al., 2014). These neuromodulation techniques have since been explored in the treatment of psychiatric diseases (Temel et al., 2012), including maladaptive learning disorders such as anxiety disorder (Hu et al., 2015), and have shown promising results. In this review, we will highlight recent research looking at the effects of neuromodulation on fear learning and memory.

1.3. Learned fear in a laboratory setting

In the laboratory, learned fear is modeled by a Pavlovian fear conditioning paradigm, in which an initially neutral conditioned stimulus (CS) is associated with an aversive stimulus unconditioned stimulus (US). After pairing, presentation of the CS would elicit an autonomic fear behavior termed conditioned response (CR), regardless of US presentation. This model has been successfully carried out in both human and animal models.

In rodents, a typical procedure involves an auditory CS (such as a tone that lasts 2–30s) that co-terminates with a US (such as a footshock of 1–2 s). Repeated CS-US pairings would then lead to the expression of fear to the CS alone. Additionally, the context in which the rodent received fear conditioning will also elicit fear due to a context-US association. Expression of fear can be assessed using a species-specific fear defense response, such as freezing and absence of all movement other than that required for respiration (Blanchard and Blanchard, 1969). In humans, similar paradigms are used, e.g. visual cues can be associated with an aversive stimulus such as a light electric shock, and skin conductance responses can be used to measure expression of fear (Delgado et al., 2006; Hygge and Öhman, 1978; LaBar et al., 1998).

Similar to learned fear, exposure therapy can also be modeled in the lab through a process known as extinction. This is a situation whereby the subject is presented with the US without CS, and learns that the US is no longer associated with the CS. Extinction is a complex process involving multiple steps that interacts with previously acquired fear memories. When animals are first re-exposed to unreinforced CS, the original CS-fear memory is retrieved and goes into a state that is sensitive to disruption by protein synthesis inhibitors. This destabilized memory then requires reconsolidation to persist (Nader et al., 2000). With repeated and extensive unreinforced CS exposures, a "new" extinction memory is acquired (or rather the original fear memory trace is updated) (Bouton, 2002; Khalaf et al., 2018). Unfortunately, this "new" updated memory seems to be fragile, and relapse in the form of reinstatement, spontaneous recovery, and renewal of the fear memory is common (Bouton, 2002; Bouton and Bolles, 1979; Johnson and Casey, 2015). Moreover, while it has long been believed that extinction does not involve erasure of memory, this well-established notion has recently been challenged, with strong experimental data that suggests extinction does indeed involve erasure (Barad, 2006; Myers et al., 2006).

Retrieval of memory, destabilization of memory, and re-stabilization of memory are dissociable steps (Milton et al., 2013), all of which have impact on the extinction process and ultimate outcome. Researchers have hence started to study these steps individually in an attempt to increase the erasure of memory (rather than just depending on inhibition). Monfils et al. (2009) demonstrated that extinction carried out during a destabilized reconsolidation period (10 min and 60 min after activation) prevents renewal, reinstatement, and spontaneous recovery of fear memory compared to extinction carried out outside the reconsolidation window (6 h and 24 h after activation). Nader et al. (2000) showed that administrating the protein synthesis inhibitor anisomycin to the amygdala after retrieval prevents reconsolidation of the memory, thereby, effectively erasing it. Understanding and specifically targeting each dissociable step might therefore hold the key to effective treatment of the memory aspects of anxiety disorder.

2. Neural circuitry of fear

Understanding the neurocircuitry of fear is critical in effective targeting of neuromodulation. Advances in modern neuroscience have enabled more rigorous study of the neural circuitry of fear memory and extinction. While these circuitries have been extensively described by numerous researchers (Herry et al., 2010; Maren, 2001; Tovote et al., 2015), it is important that we briefly highlight three major structures involved in fear memory (the amygdala, hippocampus, and prefrontal cortex) in order to ascertain that the prefrontal cortex is an ideal target. While the sections below cover work done on rodents (the ability to do more intricate manipulations, and the ability to conduct terminal studies allow for more precise dissection of functional anatomy), similar works with these 3 structures has been done using functional imaging studies in humans (reviewed by Hughes and Shin, 2011).

2.1. Amygdala

The amygdala is probably the most well-studied structure in the fear circuitry due to its central role (Ledoux, 1995), lesions of which have caused deficits in both short and long term fear memory (Kim et al., 1993). For the purposes of fear conditioning and extinction, two of the most relevant regions are the basolateral amygdala (BLA) and the central amygdala (CeA), which can be considered as the input and output, respectively of this nucleus(Ledoux, 1995; Maren, 2001). During fear conditioning, the BLA is the major interface for sensory information; lesion of the BLA has been shown to cause deficits in both acquisition and expression of conditioned fear (Cousens and Otto, 1998; LeDoux et al., 1990; Maren, 1996; Maren et al., 1996; Sevelinges et al., 2009). It receives input from (but not only from) the sensory thalamus, sensory cortex, perirhinal cortex, and hippocampus (Ledoux, 1995), allowing different aspects of fear memory to converge. The CeA is thought to be the output - the interface for fear response. Similar to the BLA, lesion of the CeA has also been shown to cause deficits in fear acquisition and expression (Zimmerman et al., 2007). Further studies using electrophysiological, pharmacological and optogenetic methods show involvement of the lateral subdivision of the CeA in acquisition of fear, while the medial subdivision of the CeA is required for conditioned fear response (Ciocchi et al., 2010). The amygdala also plays a major role in the acquisition of extinction (Herry et al., 2010). NMDAR antagonist infusion into the amygdala has been shown to prevent fear extinction in both fear-potentiated startle and auditory fear conditioning paradigms (Falls et al., 1992; Sotres-Bayon et al., 2007). Similarly, administration of NMDA receptor agonist d-cycloserine to the amygdala facilitates fear extinction (Ledgerwood et al., 2003; Walker et al., 2002). Lastly, the amygdala also plays a major role in consolidation and reconsolidation of fear memory; Schafe & LeDoux (2000) and Nader et al., (2000) showed that consolidation and reconsolidation requires protein synthesis in the amygdala. Milton et al., (2013) further demonstrated the role of specific subunits of NMDA receptors (in the amygdala) in destabilizing and restabilizing memories during reconsolidation of fear memories. Overall, the amygdala plays a key role in the fear circuitry and is a crucial component to study in the neuromodulation of fear memories. However, the various roles, close proximity of subdivisions, relatively small size, and depth of the amygdala within the brain make it a tricky target for neuromodulation.

2.2. Hippocampus

This hippocampus is another key structure in the fear circuitry with bidirectional connections to the amygdala (Ledoux, 1995). It is therefore not surprising that connections from the hippocampus to the BLA are crucial for contextual information of fear memories (Maren, 2001). Bechara et al. (1995) showed a double dissociation of fear conditioning and declarative knowledge in patients with either bilateral amygdala or hippocampus damage respectively. They showed that a patient with bilateral amygdala lesions was unable to acquire fear conditioning, but could acquire information about the stimuli. Conversely, a patient with bilateral hippocampal lesion was able to acquire fear conditioning, but was unable to acquire the information about the stimuli. Similarly in animals, lesions of the hippocampus affect contextual (polymodal sensory stimuli) fear conditioning but not tonal (unimodal sensory stimuli) fear conditioning (Kim and Fanselow, 1992). Ramirez et al. (2013) further showed that contextual fear memory can be activated through optogenetically stimulating hippocampal neurons that are involved in contextual encoding of the fear memory, directly demonstrating the involvement of the hippocampus in contextual fear memory. The hippocampus functionality is thought to be split through the dorso-ventral axis. The dorsal hippocampus (dHPC) is thought to be involved in spatial encoding while the ventral hippocampus (vHPC) is thought to be involved in anxiety-like behavior (Bannerman et al., 1999; Fanselow and Dong, 2010; Kjelstrup et al., 2002; Moser et al., 1995). Recent optogenetic methods have further shown that modulating the activity of dentate gyrus granule cells in the dHPC controls contextual encoding but not retrieval of memory, while modulating the activity of dentate gyrus granule cells in the vHPC has no effect on contextual encoding, but rather modulates innate anxiety (Kheirbek et al., 2013). In associative fear memory, the hippocampus seems to have a time-limited role; lesions made in the hippocampus one day after contextual fear conditioning caused amnesia of fear, while lesions made later (7, 14, or 28 days) did not affect fear response (Kim and Fanselow, 1992). While this time-limited role has been repudiated by Goshen et al. (2011) who showed that optogenetic inhibition of CA1 can abolish contextual fear memory recall weeks after encoding, more recent research using optogenetic manipulations of engram has shown that only encoding, recent recall, and maturation involve the hippocampus, while remote recall goes through the PFC, independent of the hippocampus (Kitamura et al., 2017). Furthermore, they showed that while engrams in the hippocampus persist, they can only be optogenetically retrieved, but not through natural means. This is also in line with the results by Goshen et al. (2011) which suggested that “long-term memory retrieval normally depends on the hippocampus but can adaptively shift to alternate structures”. Overall, it seems that while the memory technically persists in the hippocampus weeks after encoding, the role that the hippocampus plays in the remote recall is limited. Given the strong role of the dHPC in contextual encoding for fear memories, it is perhaps not surprising that inactivation of the hippocampus disrupts acquisition and contextual encoding of extinction memory (Corcoran et al., 2005). Overall, the hippocampus plays an important role in contextual aspects of fear memory. Could the hippocampus then be a good target for neuromodulation? Unfortunately, a few issues emerge that might prove problematic. The critical role of the hippocampus in declarative memory could be tricky to handle practically in that disrupting declarative memory might result in unwanted side effects. Furthermore, the time-limited role and specific effect towards contextual but not tone fear might be difficult to resolve. Lastly, the hippocampus, while closer to the brain surface than the amygdala, is still relatively a deep structure to access in the brain.

2.3. Prefrontal cortex

The last structure in the trifecta of learned fear regions is the prefrontal cortex (PFC) which has bidirectional connections with both the hippocampus and the amygdala (Jin and Maren, 2015; Marek et al., 2013), particularly, the medial PFC (mPFC). However, it is noteworthy that the dorsal PFC has also been implicated in fear, but it is yet to be thoroughly studied (Giustino and Maren, 2015). In the rodent brain, the mPFC has four subsections: the medial precentral cortex, anterior cingulate cortex (ACC), prelimbic (PrL), and infralimbic (IL) prefrontal cortex (Heidbreder and Groenewegen, 2003). The PrL and IL tend to be the focus of fear conditioning studies (likely due to the ‘limbic’ inputs) as compared to sensorimotor inputs (Hoover and Vertes, 2007). Furthermore, microstimulation of the dorsal anterior cingulate and medial precentral cortex have no effect on conditioned fear (Vidal-Gonzalez et al., 2006). While the ACC is also involved in fear conditioning and storage of memories (Bero et al., 2014; Frankland and Bontempi, 2005; Rozeske et al., 2015), it will not be covered here due to insufficient information in literature. Interestingly however, microstimulation on the PrL and IL have been shown to have opposing effects on the expression of conditioned fear; PrL stimulation increased expression of conditioned fear, while IL stimulation reduced expression of conditioned fear (Vidal-Gonzalez et al., 2006). This bidirectional function of the IL and PrL has been thought of as a division of labour in which the structures carry out functionally opposing actions, yet functional overlap cannot be ruled out (Giustino and Maren, 2015) Unsuprisingly, the mPFC is also involved in extinction as evident from lesioning, electrophysiological, and stimulation studies (Quirk et al., 2006). Similar to the bidirectional nature of expression of conditioned fear in the

PrL and IL, PrL prevented extinction while IL stimulation increased extinction learning (Vidal-Gonzalez et al., 2006). The authors subsequently suggested the mechanism of this bidirectional modulation of fear wherein PrL excites the amygdala output, while the IL inhibits it. While the role of mPFC in fear conditioning has been studied in detail, less is known about specific neuronal populations which might hold the key to explaining observed contradictory results (Giustino and Maren, 2015). The "executive" nature of the mPFC on the fear circuitry makes it an ideal target for modulation. However, the proximity and bidirectional nature of the PrL and IL make it an extremely difficult stucture to target in terms of specificity. Aside from the mPFC, structures in the ventral frontal cortex such as the orbital frontal cortex (OFC) and ventrolateral PFC (vlPFC) have been reported to be involved in anxiety diorders (Etkin and Wager, 2007; Milad and Rauch, 2007). These similarly have connections to fear-associated structures (such as the amygdala) and have been implicated in anxietylike behaviours and disorders (Hughes and Shin, 2011; Morgan and Ledoux, 1999). Given these connections to the amygdala, it is perhaps unsurprising that lesion studies of more ventrolateral parts of the frontal cortex have also shown effects on fear - lesion of the vlPFC disrupts contextual fear acquisition, although interestingly it has no effects on extinction (Morgan and Ledoux, 1999). Lesions of non-human primates in the anterior OFC or vlPFC were also shown to heighten innate fear (Izquierdo, 2005; Shiba et al., 2015). Simlar to the mPFC, the multitude of functions and proximity of structures (Izquierdo, 2017) make it problematic to accurately target.

2.4. Targeting

Comparing the three major structures in the fear circuitry, targeting the PFC would arguably be the most logical solution given its "executive" nature, bidirectional connections to the other two structures, and relative ease of access. The difficulty of differentiating structures and functions remains a problem; however, limitations in targetting the amygdala or hippocampus seem to outweigh that of the PFC. While other targets have been explored in modulating fear, this review will focus on the effects of neuromodulation on memories rather than covering the extended circuitry of fear memories.

3. Neuromodulation techniques

3.1. Transcranial magnetic stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive method that uses magnetic induction to alter electric fields in targeted regions of the brain (Rossi et al., 2012). Through repetitive application of TMS (rTMS), cortical excitability can be modulated, ideally creating long lasting changes in the brain. rTMS can lead to bi-directional changes in cortical excitability depending on stimulation parameters – low frequency (< 1 Hz) has inhibitory effects, while high frequency (> 5 Hz) has excitatory effects (Klomjai et al., 2015). However, this technique has a major limitation in that it is unable to directly reach subcortical structures in the brain. Deeper cortical structures can be accessed through transynaptic spreading of the initial action potential – changes in excitability of one region of the brain can lead to changes in its downstream targets. It is therefore possible to access deeper structures and networks if the right "surface cortical window" is found and altered (Marin et al., 2014). As such, it is hypothetically feasible to target a structure like the PFC as a window to deeper structures involved in fear memory, like the hippocampus and amygdala.

Multiple human studies have shown that rTMS treatment over the dorsolateral prefrontal cortex (dlPFC) (particularly the right hemisphere) is effective in the treatment of anxiety disorders, with the most successful treatments being on post-traumatic stress disorder (PTSD) (Boggio et al., 2010; Cohen et al., 2004; Osuch et al., 2010). Boggio et al. (2010) showed that high frequency (20 Hz) rTMS over both left and right dlPFC had a beneficial effect on PTSD patients, with right dlPFC stimulation being more effective. Cohen et al. (2004) similarly showed beneficial effects of high frequency (10 Hz) rTMS over right dlPFC on PTSD patients, while having no effect on low frequency rTMS (1 Hz). Interestingly enough, low frequency rTMS (1 Hz) over the dlPFC have shown to be effective when combined with exposure therapy (Osuch et al., 2010). The differences in these studies highlight the importance of the period during which rTMS is carried out, and hints at the difference in effects on memory depending on what processes it is undergoing (already consolidated memory without exposure therapy, and retrieval and extinction during exposure therapy). However, more studies are needed to draw concrete conclusions. While these methods look promising as means of treatment, they are mostly preliminary with small sample sizes. Overall, the data are too preliminary, and the mechanism behind how rTMS works in anxiety is still very much unknown, with many contradictory studies and theories (Pigot et al., 2008). Given the higher success rate in PTSD, a disease that is well modeled by fear conditioning, it is likely that rTMS, alters fear memory at least in part. Animal studies present a means of understanding the mechanisms by which rTMS exerts its effects on the brain in fear conditioning. Nevertheless, little work has been done on the effect of rTMS on fear memory of an animal model. Baek et al. (2012) showed that pairing 10 Hz rTMS on the ventromedial prefrontal cortex (vmPFC) with CS presentations during extinction lowered freezing, and increased retention of extinction memory in retention test, though possibilities of its effects on the prelimbic region cannot be excluded due to the limitations on spatial accuracy of TMS. While this study shows a beneficial effect of using rTMS on extinction, the underlying mechanisms are still very much unknown. Furthermore, the inability to assess freezing during rTMS administration, due to the need for restraint, makes the results difficult to analyze. Lastly, the effects of rTMS on specific dissociable parts of memory is still unknown.

3.2. Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is also a non-invasive neuromodulation technique that uses a low current through the scalp and skull in order to modulate excitability within the brain. Although the exact mechanism of tDCS is only partially understood (Marin et al., 2014), it is thought to exert its effects through modification of membrane polarization. Anodal stimulation depolarizes neurons, increasing chances of action potentials occurring, while cathodal stimulation hyperpolarizes neurons, decreasing the chances of action potentials occurring (Nitsche et al., 2000; Purpura and Mcmurtry, 1965), hence altering the firing probability instead of directly causing action potentials (Kuo et al., 2014; Marin et al., 2014). This implies that the effects of tDCS are highly dependent on many factors, and the summation of each of these would contribute to the overall effects of tDCS, be it excitation or inhibition of neurons. Similar to rTMS, tDCS has limitations in its capability to reach deeper structures. Regardless, tDCS has been explored for therapeutic purposes in a range of psychiatric diseases such as depression, addiction,schizophrenia, and importantly for this paper, anxiety disorders (reviewed by Kuo et al., 2014). Penolzaai et al. (2010) showed that right anodal/left cathodal stimulation (1 mA, 20mins) of the fronto-temporal cortical areas during acquisition of images with affective valence enhanced the recall of pleasant images, while left anodal/right cathodal stimulation enhanced the recall of unpleasant images. This indicates that tDCS is indeed capable of modulating emotional memory. Given its potential, multiple studies have attempted to use this method to modulate fear memories. Firstly, Asthana et al. (2013) showed that cathodal, but not anodal, tDCS over the left DLPFC during consolidation (10–20 min after fear conditioning), reduced fear expression 24 h later. Secondly, Mungee et al. (2013) showed that anodal stimulation of the right DLPFC together with cathodal stimulation of the contralateral supraorbital area (aimed to inhibit the left vmPFC) after retrieval of memory, enhanced fear expression the next day.

Overall, it would seem that inhibiting the left vmPFC through cathodal stimulation is an effective strategy for disrupting consolidation of fear memories. The obvious flaw in these two experiments is that it lacks direct relevance to treatments, as these experiments only show effects on recently acquired memories rather than pre-existing ones. Recent studies showed that stimulation of the vmPFC (2 mA anodal tDCS) during extinction increases its efficacy. However, little was concluded about how it affected the actual fear memory (van't Wout et al., 2016). The authors further suggest that tDCS is a promising therapeutic approach, but more research looking into multiple aspects -including timing of tDCS and mechanism of action - is necessary before we can effectively put this into practice. However, a clinical trial recently showed that tDCS over the mPFC led to over-generalization of fear response to non-reinforced stimuli (Abend et al., 2016), which highlights the complex nature of such a technique. Vicario et al. (2017) critiqued the paper above, stating that the protocol did not allow separation of consolidation and encoding of memory, further highlighting the need for studies on how tDCS affects each individual stage of the memory/extinction process. Overall, these studies highlight the complexity of using tDCS on fear memories and argue for more nuanced studies in order to understand how or whether tDCS is appropriate for use in the clinic.

3.3. Deep brain stimulation

Deep Brain Stimulation (DBS), unlike the other two methods above, is an invasive technique in which electrodes are implanted in the desired region of the brain. The principle of DBS is to modulate the firing of neurons through electrical stimulation supplied via electrodes. Despite the long history of using direct electrical stimulation (like DBS), and the highly successful therapies that emerge from it, the mechanisms behind DBS are still unclear (Kringelbach et al., 2007). Researchers have started investigating the use of DBS to treat depression and anxiety related disorders (Denys et al., 2010; Mayberg et al., 2005; Mian et al., 2010; Puigdemont et al., 2012). Given its success in anxiety-related disorders like Obsessive Compulsive Disorder (OCD), it is not surprising that researchers have also began an attempt to manipulate fear memories using DBS (Reznikov et al., 2016). Rodriguez-Romaguera et al. (2012) showed that high frequency DBS (120 Hz) of the ventral striatum, a structure which has connections with the amygdala and has been implicated in reinforced learning including fear learning (Correia et al., 2016; Costa et al., 2016), for 3 h (1 h before, 1 h during, 1 h after) enhances extinction training, though it should be noted that the ventrality/dorsality of electrode placement showed opposing effects on extinction. They further showed that if DBS was given 3 h before or 3 h after extinction, there was no effect on extinction, suggesting that DBS of the ventral striatum directly interacts with extinction, and does not affect reconsolidation, nor does it have a lasting effect once turned off. In a follow up paper, Do-Monte et al. (2013) argued that the augmentation of extinction was due to increased BDNF expression in the PL and IL. Brief stimulations (300 ms, 100 Hz) of IL during extinction have also been shown to enhance extinction training (Milad & Quirk, 2002). Milad et al. (2004) also showed with higher temporal specificity that stimulation of the IL inhibited freezing if given 0.1 s after tone (in extinction), but not when given 1 s before or 1 s after. DBS of the amygdala has also been shown to have therapeutic effects; chronic DBS (daily for 7 days) of the amygdala post-fear-conditioning reduced freezing in a long-term recall test (Mokhtari Hashtjin et al., 2017; Sui et al., 2014). Langevin et al. (2010) showed similar results using a similar fear paradigm (pairing inescapable shocks to a conspicuous object). Overall, DBS seems to be a promising therapeutic strategy. Nonetheless, the biggest downfall is the invasive nature of DBS, making it a difficult "sell" as a treatment. DBS does however allow us to more precisely study the mechanisms of neuromodulation (due to its ability to precisely place electrodes), and may act as a first step in uncovering the key to harnessing neuromodulation techniques for clinical use.

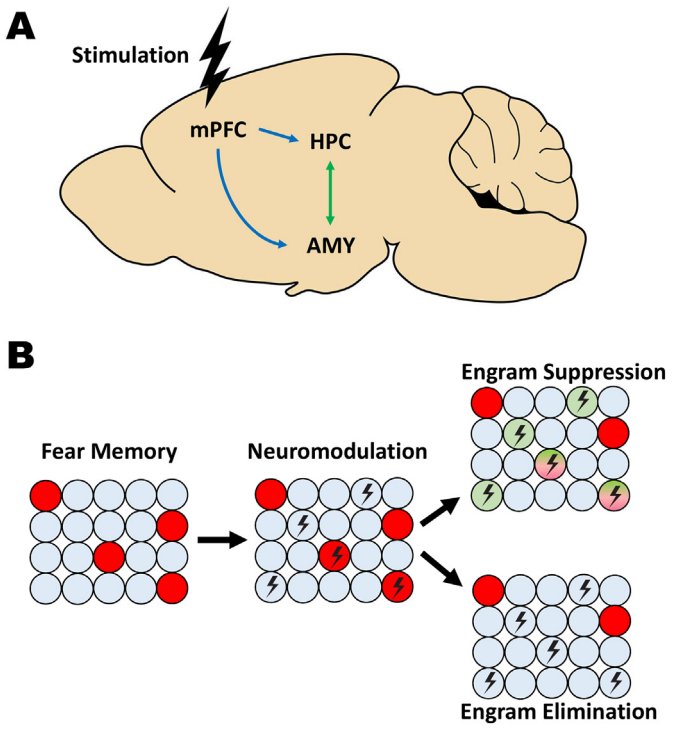

Fig. 1. Hypothetical mechanism of how neuromodulation (alteration of nerve activity through a device eg. DBS, rTMS, or tDCS) of the medial prefrontal cortex could erase/disrupt a fear memory engram. (A) A proposed mechanism in which stimulation of the PFC is able to propagate signals towards the hippocampus and amygdala (blue arrows). Bidirectional connections between the hippocampus and amygdala can further propagate signals to each other (green arrow). (B) shows a diagrammatic representation of how stimulation (represented by in electric symbols) could hypothetically erase/disrupt a fear memory engram (red) by adding more information into the engram (green) or suppressing the fear engram. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Modelling neuromodulation on memory

4.1. Engram

Multiple studies have demonstrated the ability of neuromodulation techniques to manipulate fear memories. However, the mechanism by which this occurs remain very much unknown. In this section, we propose that neuromodulation is capable of affecting fear memory through alterations on the engram.

The engram is a hypothetical representation of the physical/biochemical storage of memories. The engram is encoded in a sparse population of neurons, activation of which is thought to retrieve the memory (Ramirez et al., 2015, 2013). Through optogenetic means, parts of fear memory engrams was found to be present in both the hippocampus and the amygdala (Nabavi et al., 2014; Ramirez et al., 2013). Given that much of the success in manipulating fear memory through neuromodulation has been achieved on the PFC, we propose a mechanism in which stimulation of the PFC is able to propagate signals towards the hippocampus and amygdala (directly or indirectly) and in turn is able to manipulate the fear engram (Fig. 1a). Furthermore, given the bidirectional connectivity between the amygdala and hippocampus (Ledoux, 1995), changing an engram in one would also affect the other, further manipulating the overall fear engram. We hypothesize that signals propagated down to the amygdala and hippocampus can subsequently affect the engram in two ways. Firstly, it could add more information into the engram that might in turn be able to partially disrupt it. Secondly, stimulation could suppress or abolish the engram or nodes in it (Fig. 1b). It is worthy of note that these hypotheses are not

mutually exclusive and a combination of both could contribute to the mechanisms of how neuromodulation affects fear memories. However, these mechanisms remain hypothetical, and more research is needed to substantiate them.

4.2. Networks

Networks underpin the robustness of many dynamic processes and have been used to describe both structural and functional connections in the brain. Neurons and neuron clusters can be represented as nodes, while linkages can represent synaptic connections at cellular or regional resolutions. Previous studies suggest that the neural circuitry for fear is based on distributed network interactions spanning the hippocampus, amygdala and prefrontal cortex (see above). In particular, densely connected "hub" nodes have been implicated as being particularly critical in maintaining network function (Vetere et al., 2017) and the removal and redistribution/chemogenetic silencing of these nodes have been shown to result in memory deficits. Based on the current literature, we propose that electrical stimulation of relevant brain regions perturb global signalling cascades of the neural network, and is able to impair memory consolidation/reconsolidation within critical temporal windows. Depending on the network topology of these network connections, as well as how and which nodes are targeted, this disruption can modulate signal transmission of fear memory and hence disrupt memory consolidation/reconsolidation. In order to further conceptualise this, we applied these concepts to a network-based approach in an attempt to elucidate the mechanisms of neuromodulation in disrupting consolidation of fear memory. For simplification, we modeled the processes of memory onto the concept of an artificial neural network. We propose a system whereby the US serves as an input into the network (in the case of our current example, we will use a standard footshock protocol, in which the US is a footshock hence a binary input), while the CS serves as another input (in the case of tone-footshock association, a tone which could be considered as a continuous input in which a specific frequency and decibel is the associated tone). Lastly, we placed another input being environmental factors that are not associated with the conditioning protocol (i.e. time of day, temperature, random movements, etc.). These inputs would pass through 2 layers – acquisition and consolidation, processes which has been shown to each have their unique molecular mechanisms dissociable from each other (Johansen et al., 2011). Using this model, when a tone and footshock are simultaneously input, the output would associate the tone to a footshock, or an output of 1 (compared to 0 in which tone is not associated to footshock). However, due to the third input of environmental factors which acts as noise, the output would not always be 1 but rather falling somewhere higher than 0 but lower than 1. With increasing inputs of tone to footshock association, the network would learn to more accurately predict the output of 1 (Fig. 2). The following represents a simplified formula for this; where w represents the weight of synaptic input (dependent on a multitude of factors including network architecture, connectivity, excitatory/inhibitory inputs/outputs etc.) and x represents the neural processes of memory:

$$\sum_{1}^{n} w_1 x_1 + \ldots w_n x_n$$

Rather than simply exciting or inhibiting local neurons or affecting input, we have proposed above that neuromodulation can effectively "manipulate" or "remove" key nodes in network structure; this dissociates inputs and outputs, and (depending on network topology) can result in disrupted signal propagation and transmission.

In terms of manipulating key nodes in the network structure, we can adjust the formula above by adding an extra element that we denote as error (ε), thus, changing the formula to:

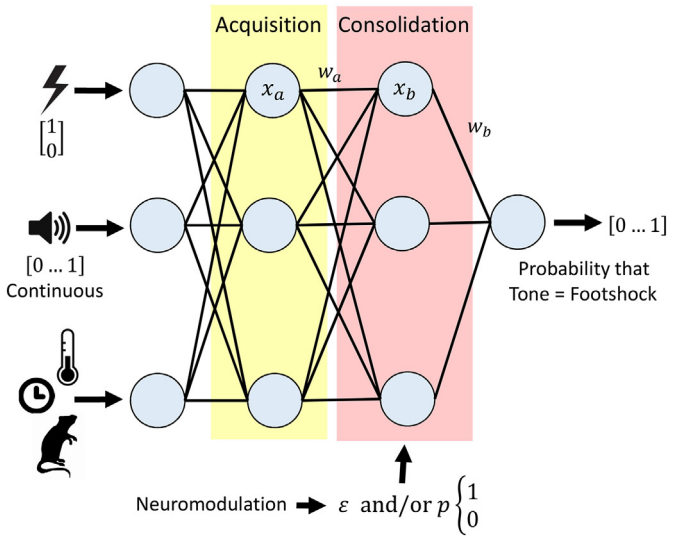

Fig. 2. Artificial neural network as a representation of how neuromodulation (alteration of nerve activity through a device, e.g. DBS, rTMS, or tDCS) is able to disrupt fear memory in a tone-footshock paradigm. Footshock (lightning bolt symbol), tone (tone symbol), and environmental factors (thermometer/clock/rat symbol) are inputs to the network, with the output being Tone = footshock. Neuromodulation during consolidation period can disrupt by introducing extra information denoted as error (ε), or suppress or abolish the engram or nodes in it, denoted by (p) which represents a probability of switching nodes off.

$$\left(\sum_{1}^{n} w_1 x_1 + \ldots w_n x_n\right) + \varepsilon$$

Within the above formula, adding ε would muddle the output, giving a less accurate prediction outcome, hence disrupting the memory.

Alternatively, the second hypothesis of "removing" key nodes, in which stimulation could function to suppress or abolish the engram or nodes in it, adding an extra element (p) that due to simulation can either remain on or turn the node off, would model this well. This would change the formula to:

$$\sum_{1}^{n} p_1 w_1 x_1 + \ldots p_n w_n x_n;\ p\{1, 0$$

Within the above formula, the addition of p would by "random" nature knock some nodes out, which in turn reduces the accuracy of the output, similarly disrupting memory. Similar to the hypotheses laid out in Fig. 1, these models are not mutually exclusive and a combination of both could be in play with regards to how neuromodulation can erase memories.

Robustness (a network's ability to withstand perturbance without failure) and error tolerance in networks are often attributed to redundant wiring, as the removal of one pathway can be replaced by another, such that end-to-end signal transmission is ultimately not affected. However, despite its redundancy, a network's tolerance to different types of disturbance also greatly depends on emergent properties of its network architecture. In exponential networks for example, all nodes have approximately the same average number of links. On the other hand, as with many networks in nature, brain networks have been suggested to demonstrate small world (Watts and Strogatz, 1998) and scale-free properties (Barabási, 2014) at certain resolutions, which are characterized by greater network clustering and the importance of "hubs" in a fully connected system. These non-Gaussian distributions are characterized by a few high-degree nodes (more connected) and more abundant low-degree nodes (less connected), which allow for more efficient information processing and rapid transmission within the network. While robust to random failures of low-degree nodes, a more

targeted disruption of the highly connected hub regions (ie neuromodulation on targeted structures of the fear circuitry) disrupts path structure and node communication (Barabási, 2014), which could therefore alter coordinated global activity and effectively disrupt consolidation of memory. While interference or weakening of these connections could impair fear memory, repeated trials involving continued formation of fear memory (more tone/footshocks) help to strengthen the redundancy of synaptic connections. This highlights a significant limitation in using neuromodulation to disrupt memory – increasing the quantity and strength of linkages (in terms of the above formula, that would mean a greater *n*) over time contributes to robustness of that fear memory. What this means is that if a memory were strongly encoded, the likelihood of disturbance for consolidation would be low due to the robust nature of the network. Similarly, older memories seem to be more resistant to post-retrieval disruption (Milekic and Alberini, 2002), and implicit reactivations that cause increased reconsolidation (which in turn strengthens the memory) have been suggested as a mechanism (Alberini, 2011). Taking that into consideration, older memories would have more complex and interconnected networks, which would also have a correspondingly lower likelihood of disturbance. This novel approach provides a quantitative mapping/framework to explain and predict treatment efficacy limitations from functional network properties.

4.3. Enhancing vs. disrupting fear memories

Although this review has mainly focused on using neuromodulation to disrupt fear memories, there is need to briefly discuss the ability of neuromodulation to both enhance (Fell et al., 2013; Miller et al., 2015; Suthana et al., 2012; Titiz et al., 2017), and disrupt (Coleshill, 2004; Halgren et al., 1985; Halgren and Wilson, 1985; Jacobs et al., 2016; Lacruz et al., 2010; Merkow et al., 2017) memory. This paradoxical effect of neuromodulation has confounded researchers, and remains largely unresolved. Regardless, the ability of neuromodulation to enhance memory has led researchers to approach modulation of fear memory by increasing the strength of extinction memories, studies of which have been mentioned above (Baek et al., 2012; Rodriguez-Romaguera et al., 2012; van't Wout et al., 2016). Despite these advances, little is known about the actual fear memory/extinction memory, and if these methods, similar to standard extinction protocols, would face issues with relapse. More work needs to be done to understand this seemingly paradoxical effect of neuromodulation if we are to effectively harness it for treatment of memory-related anxiety disorders, and to ensure that it does not lead to exacerbation of the problems.

5. Future

Neuromodulation holds considerable potential for the treatment of anxiety disorders, but obstacles with consistency in studies and lack of mechanistic understanding in the tools available have drastically hindered progress in this area. What is required for practical deployment of these tools in a clinical setting? In this section, we highlight potential directions that should be studied in order to use neuromodulation effectively in clinical contexts.

5.1. Animal models

While human studies give us a direct translational means of understanding the effects of neuromodulation on fear memory, we argue that there is a need to re-visit this in a more controlled environment using animal models. This is particularly useful in fear studies as the neural circuitry of fear is very much preserved cross-species, lending high translational credibility to animal fear studies (Gottfried and Dolan, 2004; LeDoux, 2000). The use of animal models would allow us to specifically study the effect of neuromodulation on the dissociable steps of memory with minimal confounding variables. Given that memory and extinction processes involve multiple dissociable steps which impacts the outcome of the memory (Johansen et al., 2011; Merlo et al., 2014; Milton et al., 2013), it is likely that neuromodulation exerts an effect on at least one of these processes. Elucidating what neuromodulation does in each of these dissociable steps not only allows us to better understand how it exerts its therapeutic effects, but more importantly also gives us a chance to more precisely target neuromodulation for therapeutic effects. This precision is only available to us in animal models due to the need for intricate manipulation in which surgical implants and molecular techniques can be applied to dissociate the steps of memory. These precision studies could indeed hold the key to effective use of neuromodulation in the treatment of memory-related anxiety disorders. Another benefit of animal models is the ability to conduct terminal studies (studies in which the subject can be sacrificed after experimentation) in order to study the molecular mechanisms involved in neuromodulations effect on fear memories. While much work has been done in understanding the various neuromodulation techniques, the exact mechanisms of each are still very much unknown. Understanding the molecular basis of the effects is crucial if we are to fully utilize these techniques, allowing for new strategies and higher efficacy in research. Overall, we argue that there is a strong case to be made by focusing research efforts on animal studies before investing in human studies.

5.2. Developmental stage of test subjects

Currently, fear memory studies are primarily focused on adult subjects. This poses a huge problem in anxiety disorders research, as anxiety tends to manifest early in life with the median age of onset being 7–14 years old (Kessler et al., 2007) and approximately 50% of adolescents experiencing onset by age 6 (Merikangas et al., 2011). This neglect and disconnect of fear research has not gone unnoticed by researchers, prompting some (though still a minority) to start studying fear memories in developmental models (Ganella and Kim, 2014). Stark differences have been found in how fear memory is processed in the developing brain as compared to adult brains; Unlike adult rats, preweanling rats (P17) seem to erase fear memory through extinction (instead of creating a new inhibitory memory), without showing renewal, reinstatement, or spontaneous recovery of previously acquired fear memory (Kim and Richardson, 2010, 2007). Adolescent/young adult rats (P35), however, show impaired retention of extinction training (Kim et al., 2011). Similarly, molecular changes such as differences in perineuronal nets has been link to differences in memory processing in developmental models (Gogolla et al., 2009). Understanding this has since led to novel strategies in the treatment of learning and memory disorders such as reversing chemical changes that underlie differences in memory processing in the adolescent brain (Zbukvic et al., 2017, 2016), or calling for earlier detection and treatment of anxiety disorders (Ganella and Kim, 2014). These strategies in turn are paving the way for more effective age appropriate therapies. Given the age demographic of anxiety disorder, it is imperative that we study how neuromodulation affects the developing brain. Unfortunately, work conducted on the effects of neuromodulation on the developing brain is minimal and the field is only now starting to emerge (Croarkin and Rotenberg, 2016). While researchers have started looking into the use of neuromodulation techniques as therapeutics in child and adolescent psychiatric disorders such as depression, attention-deficit/hyper-activity disorder (ADHD), autism and schizophrenia (Croarkin et al., 2011), no studies to the best of our knowledge have looked at the effects of neuromodulation on fear memory in the developing brain. Given the ethical concerns of studying potential therapeutics on the developing brain in humans (Fost, 2001), studying neuromodulation on developing models of animals presents a better proxy to explore effective treatments for anxiety disorders.

5.3. Transitioning to humans

As we continue to refine animal models (as mentioned above), neuromodulation-based therapeutics for anxiety disorders will soon start transitioning into clinical studies with humans. This transition to human subjects has to be handled with great care as many more factors come into play, i.e. effects on other more complex conscious aspects of humans, effects of declarative memory due to effects on the hippocampus (mentioned above), and difference in efficacy due to the limitations of fear conditioning as a model of anxiety (LeDoux, 2015). Furthermore, as we are able to more precisely target and modulate memory, it is imperative that ethical considerations for the use of such memory altering technology - such as the threat to authenticity or the ability of misuse (ie. to absolve guilt) (Erler, 2011) - be extensively discussed.

6. Conclusion

With rapid innovations in science and technology, concepts once thought to exist only in the realm of science fiction, like the erasure or modulation of memories, are slowly becoming a reality. While the use of neuromodulation in anxiety disorders is not a novel concept, there is a lack of systematic studies aiming to understand how neuromodulation affects fear memories, which are a key component of anxiety disorders. In this review, we highlighted a few of the research advances in studying the use of neuromodulation to modulate fear memories, and discussed some of the shortfalls and gaps in the literature. We then argued for the need to rigorously study the effects of neuromodulation using animal models, contending that it is a key step before we can effectively translate it to clinical applications. Lastly, we argued for the need to understand the effects of neuromodulation on the developing brain given the demography of anxiety disorders. The research landscape is primed for breakthroughs in the treatment of anxiety disorders. For this to succeed, however, systematic studies integrating expertise from psychology and neuroscience are needed to fully understand and apply this technology effectively. We believe that as we start to understand the mechanisms and study the models behind how neuromodulation can affect memories, these insights will shape how we harness neuromodulation techniques to their best potential.

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Statement of disclosure and conflict of interest

The authors declare no conflict of interest to disclose and no financial assistance that may bias the data interpretation and presentation of this work.

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