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Memories are not written in stone: Re-writing fear memories by means of non-invasive brain stimulation and optogenetic manipulations

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3 **Memories are not written in stone:**
4 **re-writing fear memories by means of non-invasive brain stimulation and**
5 **optogenetic manipulations**
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57 **Keywords:** Fear Conditioning, Memory Consolidation, Reconsolidation, Noninvasive Brain
58 Stimulation, Optogenetic Manipulations
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Abstract

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2 The acquisition of fear associative memory requires brain processes of coordinated neural activity
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4 within the amygdala, prefrontal cortex (PFC), hippocampus, thalamus and brainstem. After fear
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6 consolidation, a suppression of fear memory in the absence of danger is crucial to permit adaptive
7
8 coping behavior. Acquisition and maintenance of fear extinction critically depend on amygdala-
9
10 PFC projections. The robust correspondence between the brain networks encompassed cortical and
11
12 subcortical hubs involved into fear processing in humans and in other species underscores the
13
14 potential utility of comparing the modulation of brain circuitry in humans and animals, as a crucial
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16 step to inform the comprehension of fear mechanisms and the development of treatments for fear-
17
18 related disorders. The present review is aimed at providing a comprehensive description of the
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20 literature on recent clinical and experimental researches regarding the noninvasive brain stimulation
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22 and optogenetics. These innovative manipulations applied over specific hubs of fear matrix during
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24 fear acquisition, consolidation, reconsolidation and extinction allow an accurate characterization of
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26 specific brain circuits and their peculiar interaction within the specific fear processing.
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1. Introduction

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2 An aberrant fear learning process and its persistence may lead to the development of anxiety
3 disorders, such as posttraumatic stress disorder (PTSD) (Indovina et al., 2011; Parsons and Ressler,
4 2013; Tortella-Feliu et al., 2019), which represents a highly debilitating psychiatric disorder
5 affecting more than 4% of the population with genetic susceptibility (Duncan et al., 2018).
6
7 Therefore, understanding how neural circuits are involved in the acquisition and consolidation of
8 fear memories is fundamental for the development of new therapeutic protocols. To date,
9 mechanisms of fear conditioning (FC) have been extensively investigated across different species
10 (Haaker et al., 2019; Kim et al., 2016; Milad and Quirk, 2012; Vidal-Gonzalez et al., 2006), with
11 the challenge of disclosing new ways to modify maladaptive fear memories. To this aim, many
12 different methods have been explored (e.g., pharmacological or behavioral treatments) (Schiller and
13 Phelps, 2011). However, findings from controlled laboratory studies using pharmacological
14 manipulations of memory in humans have demonstrated that, although potentially effective, they
15 present several limitations. They may induce side effects, or they may affect other aspects of
16 memory, or, as in the case of direct β -adrenergic receptor agonists, they do not easily cross the
17 blood-brain barrier. Furthermore, given that not every patient responds to pharmacological
18 treatment, a pharmacological agent safe for human use has not been identified (Davis et al., 2010;
19 Farach et al., 2012). On the other hand, about 28 percent of replication attempts in humans fail to
20 demonstrate the retrieval-extinction effect (Chalkia et al., 2020; Golkar et al., 2012; Schiller et al.,
21 2020; Soeter and Kindt, 2011). Given these premises, it is not surprising that in the last few
22 decades, an incredible surge in interest in the neurobiology of FC has emerged (Fullana et al., 2020;
23 Lonsdorf et al., 2019). Neural circuits underlying FC have been mapped, plastic properties of these
24 circuits have been identified, and biochemical and genetic approaches are beginning to disentangle
25 the molecular machinery responsible for the storage and retrieval of fear memories (Kim and Jung,
26 2006; Maren, 2001; Maren and Quirk, 2004). FC experiments commonly consist of a series of
27 different experimental phases (e.g., habituation, acquisition, and extinction), and various protocols

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can be applied to investigate the return of fear (e.g., reinstatement of fear; Haaker et al., 2014; Lonsdorf et al., 2017). The habituation or familiarization process is a preliminary phase before conditioned fear acquisition takes place. Habituation or familiarization phase to cue or contextual information in human FC precedes all the experimental manipulation and it may have various roles: (1) it establishing a baseline of responses, which allows the determination and correction for possible pre-conditioning differences in each participant, (2) allowing to assess a decline in responding over the first number of trials (i.e. orienting responses), (3) ensuring that participants understood the task (Lonsdorf et al., 2017). The acquisition of conditioned fear is achieved by presenting a neutral stimulus (NS) paired with an aversive event (unconditioned stimulus, US), a procedure referred to as FC. As a result of these pairings, fear learning is evidenced by an increasing conditioned response (CR) to the NS as it becomes a conditioned stimulus (CS+). While the CS+ response reflects the acquisition of conditioned fear, an additional NS, which is never paired with the US, is presented as a control stimulus (CS-). In human studies, CRs are commonly assessed as the differential response to the CS+ and CS-. This difference represents the most critical statistical index across acquisition and extinction training, as well as a measure of the return of fear (Battaglia et al., 2018; Borgomaneri et al., 2020a; Lonsdorf et al., 2017; Lonsdorf and Merz, 2017). Importantly, there are differences in the neural circuitry supporting discriminative and non-discriminative FC. For example, in the case of very simple auditory stimuli (undiscriminated tones), the CS is transmitted through the auditory system to the thalamus and from there directly to the amygdala. In contrast, if an auditory discrimination is required, then the CS is transmitted from the thalamus to the auditory cortex and then to the amygdala (Phillips and LeDoux, 1992). This general scheme for auditory stimuli may be also applied to other sensory systems, especially the visual system.

Extinction learning is a well-known behavioral phenomenon that allows the organism to adapt their own behavior to a changing environment (Bouton, 2004). Extinction refers to the decrease in fear CRs that occur with repeated presentations of the CS+ that is no longer reinforced with the US. In

1 the past, extinction was described as a process of unlearning (i.e., the CS+ and US association is
2 erased), but a substantial amount of evidence suggests that extinction does not destroy the original
3 learning but instead generates new learning (for a review see Bouton, 2004). Much of the original
4 learning has been shown to survive extinction (Battaglia et al., 2018; Borgomaneri et al., 2020a;
5 Bouton, 2002; Delamater, 2004; Myers and Davis, 2002), thus extinction is widely thought to be a
6 new form of inhibitory learning (Bouton, 2004). In fact, the return of fear is common following the
7 passage of time (spontaneous recovery), when extinguished stimuli previously associated with
8 aversive events are encountered outside the extinction context (contextual renewal) or when the US
9 is presented in absence of the CS+ (reinstatement) (Bouton, 2004; Bouton and King, 1983; Vervliet
10 et al., 2013). These effects provide support for the widely held view that extinction may be a new
11 form of learning and that conditioning and extinction memories may coexist in distinct neural
12 circuits and be independently reactivated based on environmental or situational factors (Dunsmoor
13 et al., 2015; Kalisch et al., 2006; Milad and Quirk, 2012). Procedures that induce the return of fear
14 in the laboratory may therefore be a fundamental control condition relevant to clinical relapse,
15 which affects a substantial percentage of patients subjected to traumatic events (Craske, 1999).
16 Indeed, from an evolutionary perspective, it is functional to never forget the most important life
17 events, especially the negative ones, weakening emotional memories could be crucial to extirpate
18 the root of many psychiatric disorders.

19 Many studies have demonstrated that even the most effective manipulations only eliminate fearful
20 behavioral/psychophysiological responses (e.g., freezing in rodents and skin conductance response -
21 SCR- changes in humans), while leaving the original fear memory trace (i.e., CS-US) intact, as
22 demonstrated by recurrent relapse after successful extinction (Bouton, 2002). However, other
23 studies have shown that fear memories can change when recalled, a phenomenon referred to as
24 reconsolidation (Besnard et al., 2012; Elsey et al., 2018; Kindt et al., 2009). Reconsolidation is a
25 process whereby previously consolidated memories can be reactivated and again made sensitive to
26 alterations (Nader et al., 2000). Reconsolidated memories can be influenced by neurobiological

1 manipulations during or shortly after the memory reactivation period (Kindt et al., 2009; Tronson
2 and Taylor, 2007).

3
4 In both animals and humans, considerable evidence indicates that blockade of the process of
5 reconsolidation by using pharmacological manipulations produces amnesia for the original fear
6 learning (Nader and Hardt, 2009; Sevenster et al., 2013). Among the most important studies in
7 humans, for the first time, Kindt and colleagues (2009) tested the hypothesis that fear CRs can be
8 weakened by disrupting the reconsolidation process of such memories and that such a disruption
9 should permanently prevent the return of fear. Long-lasting disruptions in the reconsolidation were
10 obtained by the administration of a β -adrenergic receptor antagonist (propranolol) prior to memory
11 reactivation (Soeter and Kindt, 2011). Such suppression of the fear responses is in line with the idea
12 that noradrenaline neurotransmission plays a critical role in learning and memory processes and that
13 β -adrenergic receptor activation is important for post-retrieval stabilization of memories, as
14 systemic injections with the β -adrenoceptor antagonist propranolol impair expression of aversive
15 memories in rats that received reactivation (Przybylski et al., 1999).

16
17 The suppression of the fear responses could result from a more diffuse effect of propranolol
18 administration by reducing the aspects of fear triggered by the aversive stimulus itself (i.e., the US
19 rather than the CS-US association). However, the authors argued that propranolol injection
20 specifically targeted the emotional expression of the memory (as suggested by the lack of effect of
21 propranolol in the group without the reactivation of the fear memory to trigger the reconsolidation)
22 and left declarative memory unchanged (Kindt et al., 2009; Soeter and Kindt, 2011).
23 Pharmacological manipulations affect the reconsolidation process, leading to an incapacity to
24 retrieve fear-conditioned memories, suggesting that they are erased or persistently weakened.
25 However, these effects have not been consistently replicated (Wood et al., 2015). Cortisol has been
26 shown to influence fear reconsolidation in men, but this effect has yet to be replicated in women
27 (Meir Drexler et al., 2016). Unfortunately, the use of pharmacological manipulations in humans can
28 be problematic (Schiller et al., 2010).

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Currently, identifying new flexible and safe techniques in humans to target the fear memory process is of interest in the neuroscientific field (Schiller et al., 2010). On the one hand, some studies have aimed to modify fear memories by acting on the memory trace during the consolidation stage related to fear acquisition or extinction (Asthana et al., 2013; Guhn et al., 2012; Rajj et al., 2018; Van 't Wout et al., 2016; Vicario et al., 2019). On the other hand, other studies have investigated the possibility of rewriting the emotional content of a memory by targeting the memory reconsolidation process (Borgomaneri et al., 2020a; Kindt et al., 2009; Mungee et al., 2016, 2014; Schiller et al., 2010). In recent years, noninvasive brain stimulation (NIBS) has established itself as an important form of therapy for neurological and psychiatric diseases (Fitzgerald et al., 2002; Kim et al., 2009; Lisanby et al., 2002) and as a crucial tool to investigate emotional processing in general (Borgomaneri et al., 2020b, 2015a; Paracampo et al., 2018, 2017; Vicario et al., 2017) and fear in particular (Borgomaneri et al., 2020b, 2017, 2015b, 2015c). Indeed, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been used to reveal the mechanisms underlying consolidation and reconsolidation of fear memories (Asthana et al., 2013; Borgomaneri et al., 2020a; Herrmann et al., 2019; Mungee et al., 2014). Based on the ability of NIBS to selectively interfere with activity in target brain regions, such techniques have been used to modulate cerebral activity during the consolidation and reconsolidation processes (Tan et al., 2019), with the ultimate goal of modulating these processes. The aim of this review is to integrate human and animal studies that have investigated the possibility of modulating fear memories by using NIBS (Table 1, Figure 1) and optogenetics to interfere with consolidation, reconsolidation, and extinction processes (Figure 2).

2. Neural bases of FC

To survive in a dynamic and challenging environment, individuals who encounter various contextual situations face imminent dangers. Prior knowledge of potential threats allows the detection of future dangers, the selection of appropriate and safe actions, and the development of

1 fear responses to threatening situations. In fact, during dangerous situations the associative learning
2 increases the chances of survival by allowing individuals to anticipate a threatening event and
3
4 respond preemptively, expressing species-specific fear behaviors (Blanchard and Blanchard, 1969).
5
6 For example, freezing (an expression of fear, when the subject ceases all non-homeostatic motion),
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8 fleeing and fighting are common fear unconditioned responses (UR) in rodents (De Franceschi et
9
10 al., 2016). For these adaptive fear responses to be developed, the brain must discriminate different
11
12 sensory cues and associate relevant stimuli with aversive events (Maren and Fanselow, 1996). As
13
14 previously reported, learned fear has been extensively studied using the classic FC paradigm, which
15
16 has perhaps provided the most useful window for analyzing the neural and molecular basis of fear
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18 associative learning and memory formation (Davis, 2000; LeDoux, 2000). In auditory or contextual
19
20 FC, a tone or a specific context (representing the CS) is associated with one or more shocks
21
22 (representing the US) (Fanselow and Gale, 2003; LeDoux, 2000). The acquisition of CS-US
23
24 associative memory requires brain processes of coordinated and distributed neural activity within
25
26 the amygdala, medial prefrontal cortex (mPFC, encompassing in mice the anterior cingulate cortex
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28 and the rostral and ventral parts of the prefrontal pole, and in humans areas 24, 25, and 32 labelled
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30 with Brodmann's numbers), and hippocampus (Corcoran and Quirk, 2007; Etkin et al., 2011;
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32 Goshen et al., 2011; Quirk and Mueller, 2008; Zhu et al., 2014). As regard the amygdala, this
33
34 almond-shape area is composed of functionally and morphologically heterogeneous subnuclei with
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36 complex interconnectivity. Specifically, the basolateral amygdala (BLA) is primarily glutamatergic
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38 (Carlsen, 1988), conversely the central amygdala (CeA), encompassing the centrolateral (CeL) and
39
40 centromedial (CeM) nuclei, is mainly GABAergic (McDonald, 1982). Thus, BLA neurons could
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42 excite GABAergic CeL neurons that provide feed-forward inhibition onto CeM neurons that, in
43
44 turn, contributes to mediate autonomic and behavioral fear responses via projections to the
45
46 brainstem (Ressler and Maren, 2019; Tye et al., 2011). In turn, inhibitory networks within the BLA
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48 appear to play a crucial role in shaping and magnifying the difference in excitability between
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50 glutamatergic projection neurons (Krabbe et al., 2018).
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1 Direct activation of principal neurons within the BLA is a putative mechanism by which stimuli are
2 associated during learning (Johansen et al., 2010; Tye et al., 2011).
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4 In animals, after conditioning, the tone alone can induce freezing in previously conditioned
5 subjects. In humans, the crucial role of the amygdala and hippocampus has been demonstrated in
6 brain-lesioned patients, showing that selective bilateral damage to the amygdala impeded the
7 acquisition of CRs but not declarative memory, while selective bilateral damage to the hippocampus
8 prevented the acquisition of declarative memory but preserves fear learning (Bechara et al., 1995).
9 Similarly, lesions of the ventral part of the mPFC –ventromedial prefrontal cortex (vmPFC)–
10 prevented the acquisition of fear memories (Battaglia et al., 2020).
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21 Furthermore, FC establishes the CS as secondary incentive that can motivate avoidance behaviors.

22 In fact, individuals can also learn instrumental responses and avoidance CR when responding to a
23 CS to avoid a threatening event (Crawford and Masterson, 1982; Maia, 2010; Wendler et al., 2013).
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28 To know when to act in order to avoid an aversive event signaled by a cue, the subject must first
29 learn that the specific cue predicts the aversive event and then choose the instrumental action to
30 avoid the announced aversive event. In other words, CS can serve as a motivating factor to initiate
31 active responses that reduce exposure to the fear arousing stimulus. There is compelling evidence
32 that the striatum and other regions of the basal ganglia play a role in learning how to select actions
33 that result in rewarding outcomes (Laricchiuta et al., 2020) as well as in instrumental responses to
34 avoid aversive stimuli (Wendler et al., 2013).
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45 As already mentioned, the fear CR to a CS+ may be gradually weakened by repeated exposure to
46 unreinforced CS+, that is, presentation without the US (i.e., extinction procedure) (Pavlov, 1927).
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50 Extinction creates a new CS–noUS memory trace, competing with the initial fear (CS–US) memory
51 and the recall of extinction memory (i.e., CR inhibition at later CS encounters) is facilitated by
52 contextual cues present during extinction training (Kalisch et al., 2006). In fact, context appears to
53 be a critical regulatory factor in the expression of this putative competition (Bouton, 2004).
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60 Additionally, the acquisition and maintenance of extinction memories critically depend on
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1 amygdala-mPFC projections (Lacagnina et al., 2019; Tovote et al., 2015; Trouche et al., 2013).
2 Interestingly, within the BLA populations of neurons distinct on the basis of electrophysiological or
3 neurotransmission properties were identified to manage fear extinction responses (Herry et al.,
4 2008; Sotres-Bayon et al., 2007). Specifically, Zimmerman and Maren (2010) showed that infusions
5 of an N-methyl-D-aspartate (NMDA) receptor antagonist into the BLA impaired the acquisition of
6 long-term extinction memory. Cooperating with the amygdala, the mPFC integrates information
7 from multiple inputs to exert top-down control, allowing for appropriate responses. In fact, a widely
8 validated mouse model suggests that the balance between expression and suppression of learned
9 fear responses is modulated by inputs from/to the amygdala to/from two subregions of the mPFC:
10 the prelimbic cortex (PrL), the rostral part of the mPFC considered to be a core component of the
11 anterior cingulate cortex, which supports fear expression, and the infralimbic cortex (IL), the ventral
12 part of the mPFC, which contributes to fear extinction (Klavir et al., 2017; Sierra-Mercado et al.,
13 2011). Together with these areas, the hippocampus has been found to play an important role in
14 explicit recalling extinction in humans, showing a vmPFC–hippocampal network that provides for
15 context-dependent recall of extinction memories (Kalisch et al., 2006). In support of these findings,
16 lesions of the hippocampus have been found to interfere with FC situations involving complex
17 polymodal events particularly those for which spatial organization is important and involving more
18 than one processing modality (Phillips and LeDoux, 1992). During the reconsolidation process, the
19 same amygdala-mPFC-hippocampus brain network seems to be recruited and contributes to
20 maintaining the delicate equilibrium between fear and safety representations. The crucial role of the
21 amygdala during reconsolidation has been demonstrated by the administration of anisomycin, a
22 drug that inhibits protein synthesis and activates stress-activated protein kinases and other signal
23 transduction pathways. Anisomycin administration during the fear reactivation period resulted in
24 intact short-term post-reactivation and impaired long-term postreactivation fear memories,
25 suggesting a successful blockade of the reconsolidation process (Nader et al., 2000). In parallel,
26 intrahippocampal anisomycin infusions caused amnesia for consolidated hippocampal-dependent
27

1 contextual fear memory, but only if the memory was reactivated prior to infusions, thus inducing
2 **systems-level** reconsolidation (Debiec et al., 2002). Such an effect was consistently replicated even
3
4 if the reactivation delay was 45 days, a time point at which contextual memory should be
5
6 independent of hippocampal activation.
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8
9 Finally, while previous human neuroimaging and patient studies have primarily implicated the
10 dorsolateral part of the prefrontal cortex (dlPFC **Brodmann's areas 9 and 46**) in the cognitive
11 regulation of emotional processes (Fullana et al., 2016; Ochsner et al., 2012), other studies have
12 suggested that this brain region is also involved in some aspects of threat response reduction and
13 fear memory modulation (Asthana et al., 2013; Mungee et al., 2014; Van 't Wout et al., 2016).
14
15 Namely, the dlPFC seems crucially involved in the control of retrieval and reactivation of memory
16 traces and their gradual consolidation (Cabeza and Nyberg, 2000; Eichenbaum, 2017; Moscovitch
17 and Winocur, 2002; Sandrini et al., 2013; Simons and Spiers, 2003). Therefore, the neural
18 modulation of the activity of both the vmPFC and dlPFC has been the focus of several NIBS
19 studies.
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36 **3. NIBS to modulate fear memories**

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38 **NIBS with TMS or transcranial electrical stimulation (tES) (Dayan et al., 2013; Reed and Cohen**
39 **Kadosh, 2018; Rossi et al., 2009; Rossini et al., 1994) is valuable in research and has potential**
40 **therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry, and neurology.**
41 **TMS allows neurostimulation and neuromodulation, while tES is a purely neuromodulatory**
42 **application. TMS and tES allow diagnostic and interventional neurophysiology applications, and**
43 **focal neuropharmacology delivery. NIBS provides a valuable tool for interventional**
44 **neurophysiology applications, modulating brain activity in a specific, distributed, cortico-**
45 **cortical/subcortical network (Chiappini et al., 2020; Fiori et al., 2017, 2016; Zanon et al., 2018).**
46 **Thus, NIBS is considered to be a promising treatment for a variety of medical conditions (Wagner**
47 **et al., 2007).**
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1 tES alters brain functions by passing an electric current through the cerebral cortex. Part of the
2 current is absorbed by the skull, while another part penetrates the scalp and modulates cortical
3 excitability (Reed and Cohen Kadosh, 2018). tES includes several techniques, such as tDCS and
4 transcranial alternating current stimulation (tACS). In the tDCS technique, direct current is applied
5 over the scalp to modulate human brain activity (George and Aston-Jones, 2010). Through this type
6 of stimulation, feeble electric currents (1-2 mA) are conducted through two electrodes (anode and
7 cathode), which increase or decrease neuronal activity by changing the membrane potential
8 (Nitsche and Paulus, 2000). Although the exact functioning of tDCS is not entirely clear, it is well
9 established that several minutes of anodic stimulation excite neurons in the stimulated area,
10 allowing their depolarization. Conversely, cathodic stimulation has an inhibitory effect (Nitsche et
11 al., 2008). This suggests that tDCS allows the modulation of cortical excitability (Arul-Anandam
12 and Loo, 2009). In contrast, during tACS stimulation, a direct current is not applied, but it oscillates
13 between the electrodes in sinusoidal waves (Reed and Cohen Kadosh, 2018). Finally, TMS is a
14 neurostimulation and neuromodulation technique based on the principle of electromagnetic
15 induction of an electric field in the brain. This field can be of sufficient magnitude and density to
16 depolarize neurons, and when TMS pulses are repetitively applied, they can modulate cortical
17 excitability. In particular, it has been shown that repetitive TMS (rTMS) can temporarily modify
18 brain function for minutes to hours (Huang et al., 2005; Iyer et al., 2003; Jung et al., 2008).
19 Stimulation at low (≤ 1 Hz) or high (≥ 5 Hz) frequencies can decrease or increase neuronal
20 excitability, respectively (Klomjai et al., 2015).

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3.1 Changing fear memories by interfering with the consolidation process

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2 Consolidation theory assumes that during acquisition, the memory trace is unstable and labile (i.e.,
3 susceptible to interference) for a limited time window after encoding. After this time period,
4 memory traces become robust and resistant to interference (Alberini and LeDoux, 2013). In light of
5 this, studies have investigated the possibility of modulating fear memories by interfering with the
6 consolidation process by using NIBS, which is applied while memories are still in a labile state
7 (immediately after the acquisition phase). One of the first studies investigated tDCS effectiveness
8 on the consolidation process of fear memories (Asthana et al., 2013). The experimental design
9 consisted of two days: in the first session (day 1), healthy participants underwent an auditory FC
10 paradigm, in which a CS (i.e., colored square) was paired with an aversive auditory stimulus (i.e.,
11 **loud auditory tone**; US). Participants were randomly divided into three groups based on the tDCS
12 protocol: anodal, cathodal and sham stimulation. On day 1, 10-20 min after fear acquisition,
13 participants underwent brain stimulation (12 min, 1 mA). The tDCS electrodes were placed on the
14 left dlPFC (electrode position F3, according to the electroencephalogram (EEG) electrode
15 placement system, and the left mastoid as the reference electrode). On day 2, participants underwent
16 an extinction procedure in which both the CS+ and CS- were presented in the absence of the US.
17 The effects of fear acquisition and consolidation (24 hours later) were measured by means of SCRs.
18 The authors found that cathodal stimulation of the left dlPFC, **delivered few minutes after the**
19 **acquisition of a fear memory, disrupted its consolidation through an inhibitory action**, as indicated
20 by a decreased SCR to the CS+ when compared to CS- during extinction learning on day 2. **No**
21 **changes in SCR were observed after anodal or sham stimulation.** These data demonstrated the
22 crucial role of the left dlPFC in the consolidation of fear memories.

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53 In a subsequent study (Guhn et al., 2014), healthy volunteers underwent a FC paradigm and
54 subsequently received an rTMS session over the mPFC to affect the consolidation process by
55 increasing the inhibitory top-down regulation by the mPFC over amygdala activity. During day 1,
56 participants underwent a FC protocol in which two neutral faces (CSs) were paired with a **loud**
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1 auditory tone (US). On the same day, before extinction, the experimental group received rTMS (10
2 Hz, pulse intensity at 110% of the individual resting motor threshold—rMT) over the mPFC (Fpz
3 electrode), while the control group received sham stimulation. Immediately after stimulation,
4 participants underwent extinction learning. On day 2, participants underwent the extinction recall.
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10 Fear potentiated startle (FPS) responses and SCRs were used as dependent variables to assess fear
11 responses. The authors found that participants who received rTMS showed decreased fear CRs to
12 CS+ during extinction learning (i.e., lower FPS) and to a lesser extent, they showed decreased SCRs
13 to the CS+, as well as altered subjective arousal ratings (i.e., the rTMS group discriminated
14 significantly less between CS+ and CS-). The rTMS effect persisted in the recall of extinction, as
15 demonstrated by FPS results. Conversely, the sham group showed CRs characterized by greater
16 arousal during extinction learning (i.e., the sham group persisted in evaluating the CS+ as more
17 arousing than the CS-). These findings demonstrated that active stimulation of the mPFC improves
18 the retention of extinction memories. These data showed that it is possible to modulate FC by
19 inhibiting the dlPFC immediately after the acquisition phase (Asthana et al., 2013) or by increasing
20 mPFC activity (Guhn et al., 2014), suggesting that these two areas act in potentially opposite ways
21 during the consolidation of fear memories.
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41 **3.2 Changing fear memories by interfering with the extinction process**

42 It has been demonstrated that NIBS applied soon after the end of the acquisition phase is effective
43 in manipulating the consolidation of fear memories (Asthana et al., 2013; Guhn et al., 2014).
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48 However, PTSD patients may be treated many years after the traumatic event or events have
49 occurred; therefore, it appears to be necessary to act on a subsequent process, that is, attempting to
50 impact the extinction process with the application of NIBS.
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55 Van't Wout and colleagues (2016) assessed whether anodal tDCS applied over the vmPFC during
56 extinction learning could increase extinction and subsequent recall in healthy volunteers. The
57 experimental paradigm consisted of a 2-day crossover design. On day 1, participants underwent fear
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1 acquisition and extinction learning, while on day 2, extinction memories were recalled. Two CS+
2 (i.e., colored squares) paired with a US (i.e., mild electrical stimulation) were presented during the
3 acquisition phase, and SCR was used as a dependent variable to evaluate fear learning and
4 extinction. The extinction phase was divided into two blocks, and in each block, only one CS+ was
5 extinguished. Furthermore, one group of participants received anodal tDCS (10 min, 2 mA) over the
6 vmPFC (AF3 electrode with the contralateral mastoid as a reference electrode) before and during
7 the first extinction block, while sham stimulation was applied during the second block. The other
8 group received the opposite stimulation protocol (sham stimulation before and during the first
9 extinction block and anodal stimulation during the second block). The results showed that the group
10 that selectively underwent tDCS stimulation before and during the first extinction block exhibited
11 rapid extinction of the unextinguished CS+ compared to the other group. No effects were found in
12 the group that underwent anodal tDCS stimulation during the second block. These results
13 demonstrated that NIBS is selectively effective if applied immediately at the onset of the extinction
14 process, suggesting a time-locked window of action.

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33 In a similar attempt to increase extinction learning, anodal tDCS (20 min, 1.5 mA) was applied over
34 the vmPFC (F7 as anode electrode with F8 as a reference electrode) (Dittert et al., 2018). This
35 double-blind randomized study was conducted in one day: participants underwent the acquisition of
36 FC (i.e., two neutral-looking female faces were used as CSs paired with a loud auditory tone which
37 acts as US), which was evaluated by means of SCRs. A few minutes after fear acquisition, anodal
38 tDCS was applied, and the stimulation lasted until the end of the extinction phase. The results
39 showed that tDCS enhanced the extinction learning process (i.e., weaker fear response to the CS+
40 with a simultaneous increase in response to the CS-). Thus, it seems that stimulation could interfere
41 with CS safety information processing, usually acquired during conditioning, which is typically
42 mediated by the vmPFC (Battaglia et al., 2020; Fullana et al., 2018, 2016; Suarez-Jimenez et al.,
43 2018). However, mPFC has been shown to be involved in different stages of FC (Battaglia et al.,
44 2020; Fullana et al., 2016) but it also seems to be important for the suppression of fear reactions.

1 The background mechanism of these reduced fear reactions can be explained by an improvement of
2 extinction learning, or by the simple reduction of fear expressions. Thus, authors could not
3 definitively decide whether the tDCS in their study improved extinction learning or just suppressed
4 fear expressions.
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9 A further demonstration that anodal tDCS (10 min, 2 mA) during extinction learning had a
10 facilitatory effect on extinction learning comes from a recent study in which the group that received
11 anodal tDCS over the vmPFC (AF3 electrode with the contralateral mastoid as a reference
12 electrode), compared to the control group, did not show significant differences between the CS+
13 and CS-, evaluated with SCRs (Vicario et al., 2019).
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21 In another study, Raij and colleagues (2018) investigated the possibility of modulating fear memory
22 extinction by means of rTMS over the vmPFC. This experimental design was divided into three
23 days: on day 1, participants were fear-conditioned towards two different CSs (i.e., colored lights)
24 paired with a mild electrical stimulation (US). On day 2, rTMS was paired with one of the two CSs
25 during extinction learning (CS+^{TMS} and CS+^{noTMS}). The rTMS protocol consisted of short trains of
26 impulses (300 ms at 20 Hz; pulse intensity at 100% of the rMT), which started 100 ms after the
27 onset of the CS+. rTMS was applied over two target areas in the left frontal cortex: one functionally
28 connected with the vmPFC and the other unconnected (control stimulation site). Authors conducted
29 a psychophysiological interaction (PPI) analysis of functional magnetic resonance imaging (fMRI)
30 data recorded during FC to reveal surface candidate areas connected to vmPFC that can be directly
31 stimulated by TMS. The SCR was used as an index of FC. On day 3, the authors assessed the
32 effects of rTMS stimulation through extinction recall. The results showed that during extinction
33 recall, fear expression was strongly reduced only for the CS+^{TMS} when rTMS was selectively
34 applied to the area connected with the vmPFC, thus ruling out the possibility that rTMS may act as
35 an occasion setter. This result suggested that similar to tDCS, rTMS is capable of enhancing
36 extinction learning.
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Taken together, these studies provide evidence that NIBS applied in a state-dependent manner during fear extinction (i.e., rTMS or anodal tDCS over the vmPFC and cathodal tDCS over the dlPFC) facilitates fear extinction, resulting in a diminished capacity to respond to CS+ and CS- presentations as discriminative stimuli, thus weakening the strength of FC. Moreover, it has been reported a crucial role of timing of the application of the NIBS protocol, which needs to be applied at the onset of the extinction learning (Van 't Wout et al., 2016). Importantly, studies suggest that extinction learning which takes place directly after conditioning may have distinct neuronal mechanisms compared to extinction learning that is started after the completion of the consolidation of fear acquisition. Indeed, different processes seem to be at play, such as learning deleting processes for immediate extinction, whereas a new associative learning process for delayed extinction learning (Myers et al., 2006).

Although promising, none of these studies can ensure that fear memories were definitively erased, since none of them have investigated possible return of fear. Indeed, the new frontier of NIBS is the connectivity-based rTMS, which allows the indirect modulation of deep brain structures (i.e., the amygdala) by applying rTMS over a cortical node highly connected to these regions (Baeken et al., 2010; Beynel et al., 2020).

3.3 Changing fear memories by interfering with the reconsolidation process

In the previous sections, we described that NIBS techniques are able to interfere with the consolidation process, namely, affecting acquisition or, in most cases, extinction learning. This was dictated by the clinical urge to improve anxiety treatments to support existing therapies, such as exposure-based therapy, which, however, seem to not be powerful remedies (McNally, 2007). Indeed, one of the main issues associated with the treatment of PTSD is the return of fear, even after extinction learning procedures (Milad et al., 2008). This is a critical point since extinction learning does not overwrite traumatic memories but creates a new inhibitory memory trace that decays over time, allowing the return of aversive memories (Bouton, 2004). To overcome this issue, many

1 studies have investigated the possibility of modulating fear memories by means of modifying the
2 original traumatic trace by interfering with the reconsolidation process (Kindt et al., 2009; Schiller
3 et al., 2010; Schiller and Phelps, 2011).
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6 Reconsolidation refers to the process through which consolidated memories may return to an
7 unstable state when reactivated by a reminder (i.e., external information associated with the stored
8 memory). These memories can be consolidated again or reconsolidated (Nader et al., 2000). Thus,
9 reconsolidation refers to a time-locked process that can restabilize memory after reactivation
10 (Alberini and LeDoux, 2013; Monfils et al., 2009; Nader and Hardt, 2009; Schwabe et al., 2014).
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13 During the reconsolidation time window, memories are subjected to modifications. However,
14 reconsolidation does not occur every time a memory is reactivated. Several factors mediate the
15 activation of this process: the strength of the memory trace (Suzuki et al., 2004), the length of the
16 reactivation, and the generation of a prediction error during the reactivation (Milekic and Alberini,
17 2002; Pedreira et al., 2004). It is necessary to violate previously learned expectations to induce the
18 extinction as well as the reconsolidation process (Merlo et al., 2014), through which memories can
19 be updated and possibly modified (Forcato et al., 2009; Pedreira et al., 2004). The studies presented
20 in this section shed new light on the possibility of manipulating fear memories by applying NIBS
21 during the reconsolidation process. Compared to previous studies, these experimental designs
22 consist of three days (Agren, 2014), and the reactivation of the acquired fear memory through the
23 use of a reminder on day 2 is a prerequisite for the reconsolidation process (Sevenster et al., 2013).
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26 The effects of tES on the reconsolidation of fear memories have been investigated in the study by
27 Abend and colleagues (2016). On day 1, participants underwent acquisition of FC (photographs of a
28 light-haired woman and a dark-haired woman displaying neutral, closed-mouthed neutral
29 expressions were used as CSs and paired with a loud auditory tone used as US). On day 2, a single
30 CS+ was presented together with the US as a reminder of the fear memory trace, and subsequently,
31 the participants underwent the extinction phase. During the extinction phase on day 2, participants
32 were randomly divided into two stimulation groups: direct current (20 min, 1.5 mA) to yield
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1 memory-enhancing effects associated with long-term potentiation and alternating current (20 min, 1
2 Hz) to affect cortical oscillations in the mPFC. In the control group, sham stimulation was applied
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4 over the mPFC (anode electrode was placed centrally over the forehead). On day 3, the results
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6 showed that alternating current stimulation enhanced fear responses, while direct current
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8 stimulation led to a generalization of the fear response to nonconditioned stimuli (i.e., the response
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10 to the CS- was comparable to the response to the CS+). These data demonstrate the complex role of
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12 vmPFC function during fear extinction; for example, inducing enhanced activation during
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14 extinction learning did not directly translate into enhanced extinction retrieval. Similarly, low-
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16 frequency alternating current stimulation, which is expected to interfere with reconsolidation of fear
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18 memory, was found to enhance fear responses.

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24 Another study that investigated the effect of NIBS on the reconsolidation process applied tDCS
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26 over the right dlPFC (Mungee et al., 2014). The authors hypothesized that anodic tDCS (20 min, 1
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28 mA) over the right dlPFC (F4 electrode with the left supraorbital area as a reference electrode)
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30 could induce facilitatory plasticity in the cortex, which would result in stronger fear memory. On
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32 day 1, fear acquisition took place (colored squares as CSs paired with a mild electrical stimulation
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34 which acts as US), and 24 hours later (day 2), all participants were reminded of the CS+ through a
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36 single presentation without the US. According to the authors, this procedure should have induced
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38 the reconsolidation process. Subsequently, anodal tDCS was applied over the right dlPFC. On day
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41 3, the authors tested whether the fear CR had been influenced by the stimulation through
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43 presentations of the CS+ and CS-, both without a US. The anodic tDCS-stimulated participants
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45 showed a stronger CR (i.e., mean differential SCR on day 3), indicating that anodal tDCS of the
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47 right dlPFC may have resulted in a strengthening of the memory trace encoding for conditioned fear
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56 In a subsequent study with the same paradigm, Mungee et al. (2016) demonstrated that the
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58 application of cathodal tDCS (20 min, 1 mA), aimed at decreasing neuron excitability, over the
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60 right dlPFC (F4 electrode with the left supraorbital area as a reference electrode) did not affect fear
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1 memories, as suggested by the lack of significant differences in fear CRs between the stimulated
2 and control (sham) groups. Furthermore, a recent study (Ganho-Ávila et al., 2019) found that
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4 cathodal tDCS (20 min, 1 mA) over the right dlPFC (F4 electrode with the contralateral deltoid as a
5
6 reference electrode) affected extinction (1 to 3) months after the tDCS session. The experiment
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8 consisted of the acquisition of FC (i.e., colored squares paired with a loud auditory tone used as US)
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10 on day 1, cathodal tDCS after verbally recalling the CS+ to induce reconsolidation and extinction
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12 on day 2, and a follow-up session of reinstatement and re-extinction one to three months later. The
13
14 reinstatement phase consisted of four consecutive un signaled US presentations, and the subsequent
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16 re-extinction phase was similar to day 2. Fear responses were measured with self-report ratings on
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18 valence, arousal, contingency and expectancy, SCR, and implicit avoidance tendencies (approach-
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20 avoidance task). The results showed no effects in extinction, according to self-reports and SCR on
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22 day 2. However, one to three months after tDCS stimulation and re-extinction, there were
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24 differences between groups measured by the approach-avoidance task; in particular, the tDCS-
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26 stimulated group (but not the sham-stimulated group) showed safety behavior (a positive bias
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28 towards the CS-, which was not present in the sham group). Accordingly to Kindt et al. (2009),
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30 cathodal tDCS did not improve explicit memory-associated measures. However, the reported
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32 findings suggested that cathodal tDCS may have enhanced long-term distinctiveness between
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34 threatening and safety cues.

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43 Finally, in a 3-day study, our group of researchers (Borgomaneri et al., 2020a) employed rTMS (1
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45 Hz, pulse intensity at 110% of the rMT) over the dlPFC 10 min after a reminder cue that reactivated
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47 a fear memory acquired 1 day before. The day after rTMS, participants exhibited decreased
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49 physiological expressions of fear, as shown by their SCR. Similar fear reductions were observed
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51 when targeting the left and right dlPFC. In contrast, no decrease was observed in participants tested
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53 immediately after dlPFC-rTMS or in participants receiving either control rTMS (i.e., active control
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55 site and sham stimulations) or dlPFC-rTMS without the preceding fear-memory reactivation; these
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57 data showed both the site and time specificity as well as the state dependency of the rTMS
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1 intervention. In fact, the expression of fear was reduced only when dlPFC-rTMS was administered
2 within the reconsolidation time window. Moreover, dlPFC-rTMS prevented the subsequent return
3 of fear after extinction training. These findings highlighted the causal role of the dlPFC in fear-
4 memory reconsolidation and suggested that rTMS can be used in humans to prevent the return of
5 fear.
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11 Taken together, these data demonstrated that enhancing dlPFC activity within the reconsolidation
12 window results in increased fear memory (Mungee et al., 2014), while its inhibition leads to a
13 decrease in fear memory (Borgomaneri et al., 2020a; Ganho-Ávila et al., 2019).
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41 **4. Optogenetic stimulation as a tool to reveal the causal relationship between neural** 42 **firing and behavior** 43 44

45 Many studies have assessed the role of brain circuits in fear memory acquisition, storage, extinction
46 and reinstatement by using brain lesions, pharmacological manipulations and electrophysiological
47 techniques (Davis, 1992; Fanselow and Poulos, 2005; LeDoux, 2000; Maren and Quirk, 2004; Pape
48 and Pare, 2010). For example, the development of rationally designed pharmaceuticals that directly
49 act on fear-inhibiting circuitry depends on discovering the molecular identities of neuronal
50 populations that specifically mediate fear extinction. Thus, to dissect the function of different cell
51 subtypes, a variety of techniques have been introduced. One of the most revolutionary techniques,
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optogenetics, has offered advanced temporal precision using a combination of light presentation with genetic manipulations (Boyden et al., 2005). By injecting **animals** with viral vectors encoding specific rhodopsin variants **(e.g., channelrhodopsin or halorhodopsin)** under specific promoters, the genes are altered to change the membrane ion channels of selected subpopulations of neurons in the brain. The changes to the membrane ion channels make these specific neurons sensitive to different types of light (e.g., red, green, blue). By inserting fiber optics into the specific brain region and shining a particular type of light, action potentials are triggered in the neurons of interest **(e.g., channelrhodopsin depolarizes the neuronal membrane under light stimulation)** (Williams and Deisseroth, 2013). Using similar techniques, it is also possible to modify neurons so that firing is inhibited when light is presented **(e.g., halorhodopsin hyperpolarizes the neuronal membrane under light stimulation)** (Berndt et al., 2014). Thus, this technique provides precise control over when a neuron fires, enabling us to better understand the causal relationship between neural firing and behavior. In fact, *in vivo* optogenetic techniques allow for examination of the effects of acute and reversible neural activation or silencing on behavior in the same experimental subjects, with a high degree of temporal precision. For example, turning on **BLA glutamatergic projection neurons in the CeA exerted an acute, reversible anxiolytic effect, while direct photostimulation of the BLA somata** led animals to react more anxiously (Tye et al., 2011). Turning off **ventral tegmental area afferent to nucleus accumbens core as well as nucleus accumbens core projections to dorsolateral ventral pallidum** reduced cocaine use in animals addicted to that drug (Stefanik et al., 2013). The development of optogenetics is an excellent example of how cutting-edge methods allow researchers to ask increasingly direct questions about biology and behavior in FC (Gafford and Ressler, 2016).

5. Optogenetic manipulation effects on fear acquisition and consolidation

Adopting a gain-of-function strategy to test the role of the activation and/or reactivation of fear memory ensembles in acquisition and consolidation, many optogenetic manipulations have been

1 performed by stimulating or inhibiting specific neurons characterized by specific types of
2 neurotransmission in specific brain areas involved in fear learning (Beyeler et al., 2014; Hardt and
3 Nadel, 2018). Although a complete literature review evaluating the studies that have used
4 optogenetic manipulations to modulate fear acquisition is out of the scope of the present work (for
5 discussions of this topic see: Belzung et al., 2014; Beyeler et al., 2014; K. M. McCullough et al.,
6 2016), some studies are reported, for the sake of clarity.

7 First, it has been demonstrated that optogenetic activation of pyramidal neurons in the lateral
8 amygdala (LA) along with the presentation of a tone in the absence of any US was sufficient to
9 produce fear learning, but only when many training trials were used (Johansen et al., 2010) or when
10 a beta noradrenergic receptor agonist was microinjected directly into the LA before auditory CS-
11 photostimulation pairings (Johansen et al., 2014). The norepinephrine-enhanced effect was in line
12 with the evidence points to the release of norepinephrine and stimulation of beta noradrenergic
13 receptors as a key mechanism by which to increase the amygdaloid neural plasticity mediating
14 threat conditioning (Bush et al., 2010).

15 Erythropoietin-producing hepatocellular (Eph) receptors, further divided into two subfamilies EphA
16 and EphB, comprise the largest receptor tyrosine kinase family in mammals (Boyd et al., 2014),
17 regulating important developmental processes by responding to cell-cell contacts and transmitting
18 downstream signals into the respective cells that results in the so-called ‘forward’ signaling
19 downstream (Lisabeth et al., 2013). Namely, EphB2 is brain-expressed and crucial for dendritic
20 spine development, and synapse maintenance (Locke et al., 2017).

21 Activation of EphB receptors enhances glutamatergic transmission and gene expression molecular
22 events involved in memory formation (Lamprecht and LeDoux, 2004) and long-term memory
23 (LTM) (Takasu et al., 2002). Locke and colleagues (2017) used optogenetic techniques to induce
24 EphB2 forward signaling by light at the highest required spatiotemporal resolution *in vivo*. The
25 activation of EphB2 forward signaling in LA pyramidal neurons during learning, but not afterward,
26 enhances long-term, but not short-term, auditory FC by controlling its consolidation (Alapin et al.,
27 2017).

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2018). Moreover, EphB2 forward signaling during FC activates Ca²⁺/cAMP-responsive element binding protein (CREB) in LA neurons.

In a recent paper (Jiang et al., 2016), BLA cholinergic fibers were concurrently photoactivated with each CS-US pairing during the training period and 24 hours posttraining; the extent of fear learning was assessed to the CS+ alone, and photostimulation was without any significant effect. Conversely, photoinhibition of cholinergic terminal fields within the BLA during training resulted in a strong and immediate inhibition of the freezing response to CS-US pairings. Measures of recall of fear learning 24 hours after training again revealed significantly increased freezing behavior in response to the CS+ in both control and photoinhibited mice. However, comparisons of the extent of recall revealed that the learned associations were decreased by photoinhibition during training. In the same phase, pairing optogenetic activation of BLA glutamatergic pyramidal neurons with CS-US presentations inhibited fear consolidation, as indicated by the attenuated freezing that the animals showed when tested the following day in the absence of optogenetic stimulation (Jasnow et al., 2013). However, inhibition of glutamatergic neurons during acquisition caused no changes in within-session freezing behavior (Kenneth M. McCullough et al., 2016). Furthermore, the BLA contains a variety of inhibitory interneurons having a role in FC (Ehrlich et al., 2009). One of the major interneuron subclasses in the BLA expresses the calcium binding protein parvalbumin and preferentially forms synapses at the perisomatic region of their target cells, thus controlling neuronal activity and spike output (McDonald and Betette, 2001; Muller et al., 2006). Conversely, other interneurons expressing somatostatin preferentially contact the distal dendrites, thus controlling the impact of inputs to their target cells (Muller et al., 2007). During the associative learning, the parvalbumin- and somatostatin-expressing inhibitory interneurons exert bidirectional control on BLA output/input by influencing perisomatic domain or dendrites of principal neurons. Specifically, pairing optogenetic activation of parvalbuminergic neurons within the BLA with entire CS-US presentations or just during US presentations resulted in decreased freezing responses during the CS+ presentations the following day when the mice were tested in the absence of

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optogenetic stimulation. Interestingly, when parvalbuminergic neurons were optogenetically stimulated only during CS+ presentations, freezing levels were increased, which demonstrated the opposite roles of these neurons during CS+ and US processing (Wolff et al., 2014). Additionally, the inhibition of parvalbuminergic neurons during US presentations caused an increase in freezing the following day in the absence of optogenetic stimulation. Importantly, manipulation of somatostatin-containing neurons during CS+ presentations resulted in the opposite behavioral effects. Additionally, the effects of FC on parvalbumin-positive and somatostatin-positive pyramidal neurons in the IL-mPFC in male preadolescent, adolescent, and adult mice were evaluated using an *in vitro* optogenetic approach (Koppensteiner et al., 2019). While synaptic inhibition mediated by parvalbumin-positive pyramidal neurons did not result in age-specific or fear behavior-specific plasticity, synaptic inhibition mediated by somatostatin resulted in adolescence-specific enhanced plasticity and was suppressed by fear learning, which overlapped with reductions in calcium-permeable glutamate receptors.

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In addition, the tachykinin 2 (Tac2) pathway has been shown to be necessary for the modulation of fear memories in mice (Andero et al., 2014). In fact, upregulation of Tac2 expression in the amygdala 30 min after auditory FC has been reported. In transgenic mice, *in vivo* optogenetic stimulation of CeA Tac2-expressing neurons during fear acquisition enhanced fear memory consolidation, and these effects were blocked by osanetant, a potent non-peptide antagonist of the tachykinin NK3 receptor, and that is considered to be a drug generally safe and well tolerated in humans (Malherbe et al., 2011). These findings could potentially be rapidly translated into clinical practice, unlike the findings of studies using animal models focused on modulating the original fear memory with traditionally-used chemicals that impair synapses or neurons (Nader et al., 2000; Shema et al., 2007). In fact, such compounds are not allowed for use in humans, making these approaches inappropriate for clinical purposes.

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By using a c-fos-based genetic tagging system that also selectively expresses a channelrhodopsin (the light-activated cation channel) variant in neurons naturally activated during contextual FC

(Cowansage et al., 2014), the activated neuronal ensembles in the retrosplenial cortex (RSC) were stimulated at a high frequency (De Sousa et al., 2019), shown to be connected to both hippocampus and neocortical areas, and required for recent and remote contextual FC retrieval (Todd and Bucci, 2015). Posttraining stimulation of the RSC, activated during contextual FC, produced a recent memory that displayed numerous features of consolidated remote contextual FC memories, including decreased hippocampal dependence, context generalization, and greater engagement of neocortical areas during retrieval (De Sousa et al., 2019). Overall, these findings suggested that this kind of activity is able to provoke physiological changes similar to those observed during natural consolidation. Moreover, these changes were observed only when ensemble reactivation was performed during light anesthesia or natural sleep but not during active awake states. In this regard, it has been noted that without explicit external stimuli, cortical neurons exhibit spontaneous activity, which may not only be increased but even suppressed by sensory stimuli (Hromádka et al., 2008; Zhou et al., 2010). This inhibition-based modulation may contribute to stimulus-driven behaviors and associative memories of sensory stimuli (Harris and Mrsic-Flogel, 2013). To silence excitatory neurons in the auditory cortex (ACx), an adeno-associated virus vector expressing activity-regulated cytoskeleton-associated protein (Arc) under the control of the calcium/calmodulin-dependent protein kinase II (CaMKII) promoter was injected (Nomura et al., 2015). Notably, Arc protein has been particularly linked to plasticity processes and cognitive demands, and it is frequently used as a marker of cell activation, allowing each cell activated during particular behavioral outcomes to be identified (Nakamura et al., 2006; Sauvage et al., 2013). Green light illumination of Arc-expressing neurons induced an outward current and inhibited action potentials induced by depolarizing currents. Three weeks after injection of adeno-associated virus and implantation of optical fibers in the ACx, mice underwent 16 pairings of foot shocks and green light delivery to the ACx. On the next day, mice showed robust freezing during light-on periods, indicating that temporal silencing of ACx neurons can represent a CS+ in a FC paradigm.

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Finally, in accordance with Baratta and colleagues (2016), who demonstrated that pharmacological and optogenetic inhibition of serotonergic dorsal raphe neurons during conditioning reduced fear in stressed animals with exaggerated fear levels, Sengupta and Holmes (2019) recently showed that the dorsal raphe/amygdala serotonergic pathway is engaged during fear memory formation and retrieval and that the activity of these projections facilitates fear and impairs extinction. These data provided a way to overcome a critical barrier in the successful treatment of stress-induced trauma disorders. Thus, the benchmark for any successful treatment of these disorders should not be the elimination of fear but simply its reduction to normal, adaptive levels. In fact, administration of a serotonergic receptor antagonist, such as agomelatine, which is already approved by the Food and Drug Administration for human use, might prevent or treat PTSD by reducing the consolidation or reconsolidation of traumatic memories (Baratta et al., 2016).

6.1 Optogenetic manipulation effects on fear extinction and reconsolidation

Inhibition of glutamatergic neurons during 15 or 30 CS+ presentations during fear extinction sessions increased freezing time throughout the session, suggesting that inhibition of BLA glutamatergic neurons **enhanced fear expression and blunted fear extinction consolidation** (Kenneth M. McCullough et al., 2016). Once a fearful association was extinguished, the inhibition of BLA glutamatergic neurons during the final extinction session was not sufficient for reinstatement and did not drive spontaneous fear expression.

In this framework, does attenuation of BLA-mPFC synaptic transmission lead to changes in the representation of cued fear in mPFC neurons? To answer this question, Klavir and colleagues (2017) injected mice with **viral vectors encoding the fast channelrhodopsin variant ChETA_{TC} under a CaMKII α promoter** into the BLA and implanted them with fixed multielectrode arrays targeting the ipsilateral mPFC. On the day following the conditioning to fear, mice were tested in a different context by exposing them to CS+ presentations, followed by sham or high-frequency optogenetic stimulations that evoked action potentials with high temporal precision and spike fidelity. In

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optogenetically stimulated mice, the magnitude of cue-evoked responses was significantly reduced after the stimulation schedule was initiated, consistent with the recruitment of the BLA-mPFC network in transmitting learned CS-US associations to the mPFC (Senn et al., 2014; Sotres-Bayon et al., 2012). To elucidate whether the information carried by the projections from the BLA to the PrL was necessary for fear learning, other mice were bilaterally injected with adeno-associated virus vectors into the BLA and implanted with optical fibers above the PrL subregion (Klavir et al., 2017). The mice underwent high-frequency optogenetic stimulation, followed by FC in context A. On the following day, mice underwent extinction training in context B, and those that received optogenetic stimulation exhibited reduced freezing during fear recall. In particular, the reduction appeared during early extinction training but not during the later stages, suggesting that modified synaptic transmission in the BLA-PrL network during fear acquisition interfered with long-term consolidation of fear but not with extinction. This finding was also confirmed by applying optogenetic stimulation immediately before extinction training and the day after fear acquisition.

Klavir and colleagues (2017) repeated the experiments by implanting fibers in the IL subregion of the mPFC to examine how this region contributes to fear extinction and maintenance (Sotres-Bayon and Quirk, 2010). When optogenetic stimulation was applied to BLA-IL projections before fear acquisition, mice showed reduced freezing responses during extinction training. When optogenetic stimulation was applied immediately before extinction training, mice showed reduced cue-associated freezing, both during extinction learning and extinction retrieval testing.

Similarly, Kim and coworkers (2016) used mice in which adeno-associated virus expressing channelrhodopsin-2 under the CaMKII promoter was injected into the right IL cortex. These mice were submitted to auditory FC and subsequent extinction. In the extinction retrieval test, optogenetic stimulation delivered to the IL during the first four trial blocks of CS+ presentations induced a strong reduction in freezing behavior. Furthermore, the same authors determined the effect of IL optogenetic inhibition on the expression of extinction memories, by using mice in which adeno-associated virus expressing halorhodopsin (eNpHR3.0), a light-activated chloride

1 pump driven by the neuron-specific human synapsin (hSyn) promoter, was injected into the IL
2 cortex. These virus-injected mice were subjected to FC with extinction training and testing (Kim et
3 al., 2016). The expression of fear extinction memories was impaired by IL photoinhibition at the
4 time of retrieval. This impairment was reversible and specific: freezing returned to control levels in
5 virus-injected mice in the absence of photoinhibition. Furthermore, the impairment of extinction
6 retrieval was specific to silencing the activities of both glutamatergic and GABAergic neurons. Kim
7 and coworkers (2016) also reported no effect of IL inactivation on the expression of conditioned
8 fear that did not undergo extinction and simply enhanced the freezing evoked by CS+ presentations.
9 Thus, IL activity is specifically involved in the expression of fear extinction but not the expression
10 of fear memory *per se*, consistent with previous findings (Sierra-Mercado et al., 2011). However, it
11 must be noted that the preceding studies reported that electrical stimulation of IL reduced
12 conditioned freezing in animals that did not undergo extinction (Milad et al., 2004; Milad and
13 Quirk, 2002; Vidal-Gonzalez et al., 2006). Thus, artificially activated IL neurons alone were
14 sufficient to induce extinction-like inhibition of conditioned fear expression, even without
15 extinction training.

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36 By using *ex vivo* electrophysiology combined with optogenetic techniques, it was shown that
37 fear extinction had decreased the efficacy of glutamatergic synaptic transmission in projections
38 from the mPFC to the BLA, whereas inhibitory responses were not altered (Cho et al., 2013). In
39 parallel, BLA projection neurons targeting the PrL subdivision of the mPFC were active during
40 states of high fear, whereas those targeting the IL subdivision were recruited and exhibited cell-
41 type-specific plasticity during fear extinction (Senn et al., 2014). Thus, pathway-specific
42 optogenetic manipulations have demonstrated that the balanced activity between the BLA and
43 mPFC is causally involved in fear extinction. By using transgenic mice expressing
44 channelrhodopsin in pyramidal neurons, very recently Laricchiuta et al., 2021 showed that the
45 optogenetic activation of PrL pyramidal neurons in fear-conditioned transgenic mice induces fear
46 extinction deficits, reflected in an increase of cellular excitability, excitatory neurotransmission, and
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spinogenesis of PrL pyramidal neurons, and associated to strong modifications of the transcriptome of amygdala pyramidal neurons.

In another study, BLA pyramidal neurons received optogenetic stimulations coincident with presentations of the CS+ alone during fear extinction training. On the following day, during unstimulated extinction retention test conditions, memory for extinction was enhanced (Jasnow et al., 2013). Additionally, the selective photoactivation of GABAergic neurons in the anterior insular cortex, a region anatomically and functionally connected to the amygdala, promoted cued fear extinction (Shi et al., 2020).

Regarding the retrieval of extinction, mice exposed to optogenetic stimulation of the cholinergic terminal fields in the BLA during the initial training were more resistant to extinction learning than controls (Jiang et al., 2016). Interestingly, a form of muscarinic acetylcholine receptor (mAChR)-dependent long-term depression in the PFC is involved in appropriate fear responses (Walker et al., 2015) and could serve to reduce cortical hyperactivity following stress. By using optogenetic manipulations with extracellular and whole-cell electrophysiology, the effect of mAChR activation on the synaptic strength of PFC inputs was assessed, and by using selective pharmacological tools, the involvement of M1 mAChRs in conditioned fear extinction was evaluated in control and stressed mice, which represent an enhanced fear-learning model (Maksymetz et al., 2019). In stressed mice, while systemic treatment with an M1 mAChR antagonist impaired contextual fear extinction, treatment with an M1-positive allosteric modulator enhanced contextual fear extinction consolidation. In parallel, M1 mAChR activation induced long-term depression in the pathway from the ventral hippocampus (VH) and BLA to the PFC (Maksymetz et al., 2019). Through its direct excitatory projections, the VH may regulate the neural activity of the mPFC and amygdala, which is necessary for the recall of contextual fear memory (Corcoran and Quirk, 2007; Goshen et al., 2011; Zhu et al., 2014). Based on evidence that the inhibition of hippocampal activity interferes with extinction learning and the context dependency of extinction retrieval (Corcoran and Maren, 2004, 2001; Hobin et al., 2006), how the activity of

1 hippocampal circuits may regulate the expression of extinction memory has been investigated. In
2 particular, by using an *in vivo* optogenetic approach, the role of the VH in the recall of fear
3 memories after contextual FC was investigated (Kim and Cho, 2017a). To silence neural activity,
4 adeno-associated virus encoding the eArch3 gene was bilaterally injected into the VH (Chow et al.,
5 2010; Mattis et al., 2012), and eArch3 was expressed in CA1 pyramidal neurons of the VH. After
6 contextual FC, mice were tested for freezing behavior once per day for 3 successive days. Freezing
7 behavior in optogenetically stimulated eArch3 mice was strongly reduced, suggesting that VH
8 activity is necessary for the recall of contextual fear memory.

19 To elucidate the specific contribution of the hippocampal CA1 to the reinstatement of fear
20 memories and to evaluate the long-term effects of destabilizing memory traces on neuronal activity,
21 Lux and colleagues (2017) interfered with the reinstatement of a contextual FC memory trace by
22 infecting CA1 pyramidal cells with a light-driven outward proton pump that allowed optogenetic
23 inhibition of cell firing in the CA1 region shortly after the retrieval of the contextual fear memory.
24 Subsequently, the same authors investigated memory performance and activation patterns in
25 hippocampal CA1 and CA3 regions and the BLA during memory retrieval by using high-resolution
26 molecular imaging, a technique based on the detection of the immediate early gene Arc. Light-
27 controlled inhibition of cell firing in the CA1 region led to reduced strength of the US-CS
28 association, that is, the memory trace was **depotentiated**. One day after optogenetic inhibition of
29 hippocampal CA1, Arc RNA levels in the CA1, CA3 and BLA of light-stimulated animals were
30 lower than those in control animals. Furthermore, inhibition of cell firing in the CA1 region also
31 reduced the percentage of Arc-positive cells in the BLA and CA3. These findings suggested that the
32 decreased Arc levels observed in the optogenetically stimulated mice, in which the memory trace
33 was **depotentiated**, were likely associated with a failure to recall this memory.

56 Continuing the examination of hippocampal involvement in the fear process, the dentate
57 gyrus (DG) appears to also play a significant role in the acquisition of contextual fear memory,
58 which in fact activates a sparse ensemble of DG granule fear engram cells, whose reactivation is

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necessary (Denny et al., 2014) and sufficient (Liu et al., 2012; Ramirez et al., 2013; Redondo et al., 2014; Ryan et al., 2015) for the expression of contextual conditioned fear. Furthermore, in accordance with the hippocampal re-engagement upon remote memory recall (Gräff et al., 2014), the reactivation of recall-induced neurons in the DG not only accompanied behavioral attenuation of a 4-week-old fear memory, but the continued activity of recall-induced neurons is necessary for memory attenuation (Khalaf et al., 2018). When optogenetically stimulated, DG engram cells retain their ability to evoke fear at remote time points (Kitamura et al., 2017) and after amnesic treatments (Roy et al., 2016; Ryan et al., 2015). Bernier and colleagues (2017) evaluated the effects of transient optogenetic inhibition of the dorsal DG during contextual FC, recall, generalization, and extinction. DG inhibition during training impaired contextual fear acquisition, while the same inhibition during recall did not impair fear expression in the training context unless mice had to distinguish between feared and neutral contexts. Furthermore, DG inhibition increased generalization of fear to an unfamiliar context that was similar to a feared one, impaired fear expression in the conditioned context when it was similar to a neutral one, and impaired fear extinction.

Lacagnina and colleagues in 2019 used an activity-dependent neuronal tagging transgenic mouse model (Denny et al., 2014) to permanently label and manipulate dorsal DG granule cells that were active during either contextual fear acquisition or extinction. Namely, in these ArcCreER^{T2}-channelrhodopsin transgenic mice, the activity of the immediate early gene Arc drives expression of tamoxifen-dependent CreER^{T2} recombinase. An injection of 4-hydroxytamoxifen (4-OHT) transiently activates recombinase activity, thereby permanently tagging Arc-expressing neurons with a reporter. The optogenetic stimulation of the neurons tagged during fear acquisition increased fear, while the optogenetic silencing of the neurons tagged during fear acquisition decreased fear, and the silencing of the neurons tagged during extinction training increased fear after extinction.

Additionally, Mendez and coworkers (2018) used an activity-dependent neuronal tagging transgenic mouse model to permanently label and manipulate dorsal DG granule cells active during

1 contextual fear acquisition (Guenther et al., 2013) and showed that mice that received optogenetic
2 stimulation in the DG during extinction training displayed reduced freezing levels compared to
3 control littermates. These results suggested that homeostatic synaptic adaptations induced by spike
4 trains provoked by optogenetics during recall facilitated long-term fear memory extinction.
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6 Interestingly, freezing levels during the retention test in control and optogenetically stimulated mice
7 were undistinguishable when spikes were delivered in anesthetized animals, indicating that
8 simultaneous fear memory recall is required for optogenetic facilitation of extinction.
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11 Applying a very similar methodology, Kim and Cho (2017b) demonstrated that
12 postsynaptically expressed long-term potentiation is selectively induced in the ACx and in the
13 medial geniculate nucleus (MGN), a pathway conveying CS information to the amygdala in
14 discriminative fear learning. In this study, low-frequency photostimulations *in vivo* were applied to
15 induce depotentiation in the CS-specific ACx/MGN-amygdala pathways, which were potentiated
16 after FC. The adeno-associated virus encoding channelrhodopsin and fluorescent protein gene in a
17 double inverse open reading frame was injected into the ACx and MGN in activity-dependent
18 neuronal tagging transgenic mice, and in the same mice, the contralateral amygdala was
19 excitotoxically lesioned. Then, mice received behavioral training, thereby labeling ACx/MGN
20 neurons responding to the auditory CS and fear conditioned with US-CS pairings. Mice then
21 received photostimulations and displayed reduced freezing behavior in response to the CS+.
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25 As previously reported, Nomura and coworkers (2015) injected adeno-associated virus
26 expressing Arc under the control of CaMKII promoter and implanted optical fibers into the ACx.
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28 Mice underwent pairings of foot shock with light delivery to the ACx. They showed robust freezing
29 during light-on periods, even 30 days after FC.
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33 Regarding the examination of the involvement of the thalamus in the fear process, recent
34 studies have revealed the critical role of the limbic part of this structure in the persistent attenuation
35 of fear by using pharmacological and optogenetic manipulations (Do-Monte et al., 2015) and in fear
36 extinction by using genetic (Lee et al., 2012) and chemogenetic (Ramanathan et al., 2018)
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1 manipulations. The thalamic reticular nucleus (TRN), a shell of GABAergic neurons surrounding
2 the anterior and lateral parts of the thalamus, provides monosynaptic inhibitory inputs to the dorsal
3 thalamus (Pinault and Deschênes, 1998), And an anatomical study in primates showed that the
4 thalamus (Pinault and Deschênes, 1998), And an anatomical study in primates showed that the
5 limbic sector of the TRN receives input from the amygdala (Zikopoulos and Barbas, 2012). Lee and
6 colleagues in 2019 found that TRN neurons were activated during extinction learning, suppressing
7 the spiking activity of dorsal midline thalamus (dMT) neurons to the CeA, in turn promoting fear
8 extinction. These results suggest a novel neural hub underlying fear extinction.
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17 Finally, Salinas-Hernández and colleagues (2018) attempted to elucidate the neuronal
18 mechanisms that initiate extinction learning. By using single-unit electrophysiology and cell-type
19 specific fiber photometry (dopamine neuron-specific calcium recordings), they showed that
20 dopamine neurons in the ventral tegmental area were activated by the omission of the aversive US
21 during fear extinction. The dopamine signal occurred specifically during the beginning of
22 extinction, when US omission was unexpected, and correlated strongly with extinction learning.
23 Furthermore, temporally specific optogenetic inhibition or excitation of dopamine neurons at the
24 time of US omission revealed that this dopaminergic signal is both necessary for and sufficient to
25 accelerate normal fear extinction learning. These results identified a prediction error-like neuronal
26 signal necessary to initiate fear extinction and revealed a crucial role of dopamine neurons in this
27 form of safety learning.
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46 **5.2 Optogenetic manipulation effects on long-lasting fear attenuation and fear renewal**

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48 To explore the role of the PrL in extinction recall, Kim and colleagues (2016) injected adeno-
49 associated virus **carrying halorhodopsin (eNpHR3.0), which hyperpolarizes the neuronal membrane**
50 **under light stimulation**, specifically into the PrL area of the mPFC, and mice were then trained in an
51 auditory FC paradigm, followed by extinction training. During extinction retrieval tests, mice in the
52 virus-injected and control groups displayed similar and normal expression of fear extinction.
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61 Furthermore, while the expression of extinction has been associated with reactivation of neurons
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1 that were active during extinction training, the expression of fear during spontaneous recovery has
2 been associated with the reactivation of hippocampal DG neurons that were active during fear
3 acquisition (Lacagnina et al., 2019). To achieve better temporal resolution in the fear renewal
4 experiment, an optogenetic inhibition technique was implemented. Namely, mice injected with
5 adeno-associated virus carrying halorhodopsin and control littermates were bilaterally implanted
6 with optical fibers targeting the dorsal DG. After 2-4 weeks, mice were subjected to contextual FC
7 training followed immediately by an injection of 4-OHT, which permits the expression of
8 halorhodopsin only in neurons active during fear acquisition, and then a course of extinction
9 training. Contextual fear decreased across the 10 days of extinction. Five days after the final
10 extinction session, mice were returned to the context for an extinction retrieval test, and silencing
11 the fear acquisition-tagged neurons had no effect on freezing. When mice were returned to the
12 conditioning context for a spontaneous recovery test 28 days later, silencing the fear acquisition-
13 tagged neurons reduced contextual fear, demonstrating that the neurons active during fear
14 acquisition are not required for extinction retrieval but are necessary for spontaneous fear recovery.
15 Similarly, adeno-associated virus carrying halorhodopsin was injected 3 weeks before behavioral
16 training into the posterior parietal cortex (PPC) (Joo et al., 2020), which receives diverse sensory
17 and cognitive inputs (Andersen and Buneo, 2002; Morcos and Harvey, 2016; Raposo et al., 2014)
18 and integrates multisensory signals (Andersen and Buneo, 2002; Najafi and Churchland, 2018;
19 Song et al., 2017). Sensory information is processed by the PPC and transformed into behavioral
20 outcomes. After extinction training, the mice were exposed to a novel context (context C), in which
21 neither FC (context A) nor extinction (context B) had occurred (Joo et al., 2020). The relapse of fear
22 was tested in the novel context (context C). Mice with optogenetic inactivation of the PPC did not
23 display significant fear renewal relative to the last CS+ of extinction. However, optogenetic
24 inactivation of the PPC did not impair fear renewal in a familiar context (ABA renewal).

25 Among the current clinical treatments that produce a long-lasting attenuation of fear, several
26 effective psychotherapeutic methods use visual stimulation, eye movements or attentional control of

1 cognitive processes (Badura-Brack et al., 2015; Shapiro, 2001). In eye movement desensitization
2 and reprocessing (EMDR), for example, patients are instructed to recall a traumatic memory and
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4 simultaneously to orient to alternating bilateral sensory stimulation (ABS) (Shapiro, 2001; Wurtz et
5
6 al., 2016). Given that modulation of visual-attentional processes is a common component in
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8 treatment regimens for PTSD, a neuronal pathway driven by the superior colliculus (SC) has been
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10 reported to mediate the persistent attenuation of fear and its long-lasting effects (Baek et al., 2019).
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12 Optogenetic manipulations have revealed that the SC-midiodorsal thalamus (MD) circuit was
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14 necessary and sufficient to prevent the return of fear. Given that the MD is important for fear
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16 extinction and subsequent fear recovery (Herry and Garcia, 2002; Lee et al., 2012), optogenetic
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18 silencing of the MD-BLA pathway completely blocked the fear-attenuating effect of ABS (Baek et
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20 al., 2019).
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29 **6. A general overview of fear processing across species**

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31 The robust correspondences between the networks associated with fear processing in humans and in
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33 other species underscore the potential utility of analyzing the modulation of brain circuitry in
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35 animal models as a crucial step to inform the comprehension of physiological processes underlying
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37 fear and the development of treatments for fear-related disorders in humans (Schiller and Delgado,
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39 2010; Suarez-Jimenez et al., 2020). Since the resulting physiological and cellular mechanisms are
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41 quite elaborate, a comprehensive description of the fear mechanisms has not been provided to date.
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43 The development of new clinical and experimental tools, such as NIBS and optogenetics, partially
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45 overcomes this gap, allowing a more accurate characterization of specific circuits and their
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47 particular interactions within the overall fear processing network.
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53 Both in humans and animals, learned fear has been extensively studied using the FC paradigm, in
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55 which a CS is associated with a US. The acquisition of CS-US associative memories requires brain
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57 processes of coordinated and distributed neural activity within the amygdala, PFC, hippocampus,
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59 thalamus and brainstem (Corcoran and Quirk, 2007; Goshen et al., 2011; Zhu et al., 2014). After
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1 conditioning, suppression of fear memory in the absence of danger is crucial to permit other
2 survival functions, and impairments in such coping mechanisms to attenuate fear memories may
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4 lead to maladaptive behaviors. Acquisition and maintenance of extinction memories critically
5 depend on amygdala-mPFC projections (Lacagnina et al., 2019; Tovote et al., 2015; Trouche et al.,
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7 2013). Thus, it should be noted that fear expression, fear extinction and extinction retention are
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9 overlapping processes, depending on the balance of signaling processes, rather than unitary
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11 elements acting independently (Figure 2).
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16 In the “fear matrix” of the brain, control centers, integrative sites and effector sites can be
17 distinguished. Specifically, during fear conditioning, reconsolidation, and extinction phases, the PrL
18 and IL subregions of the control center represented by the mPFC receive from and project back to
19 integrative sites in the BLA. This region in turn directly projects to the CeA or indirectly projects
20 via inhibitory intercalated cells (ITCs), a scattered group of GABAergic neurons mainly located
21 around the BLA area. Finally, from the output neurons of the CeA, information is relayed to the
22 effector sites in the periaqueductal gray and premotor structures that mediate fear CRs. In other
23 words, the BLA is the station receiving thalamic and cortical information about the CS and US that
24 is sent in turn to the CeA, which targets such information to the midbrain and hypothalamus nuclei
25 to mediate motor and autonomic responses to fear. The BLA-CeA pathway is currently considered
26 the main route in the fear-processing network (Herry et al., 2008).
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43 During fear memory consolidation, thalamic and cortical inputs conveying CS and US sensory
44 information cause a marked increase in evoked activity in the BLA due to local long-term
45 potentiation of excitatory synapses. The integrated information increases the firing activity of the
46 “*fear neurons*” that stimulate the CeA, causing a strong increase in output from the entire amygdala
47 and triggering fear behavior. Moreover, mutual connections between the BLA and cortical PrL area
48 are able to stimulate the activity of *fear neurons*, causing further increases in CeA activity.
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58 During fear extinction, inhibitory signaling in the amygdala reduces whole BLA excitability and
59 elicits a general downregulation of CeA output, thus becoming a crucial element in extinguishing
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1 memories (Lee et al., 2013). Notably, the glutamatergic input from the cortical IL suppresses the
2 activity of BLA *fear neurons* by acting on BLA intrinsic inhibitory interneurons and inhibits CeA
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4 activity through activation of the ITC. The BLA intrinsic inhibitory circuit further reduces
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6 amygdala activity, thereby suppressing the fear response.
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9 Overall, consistent with a serial model of amygdala information processing, FC strengthens BLA
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11 excitatory synapses, increases excitatory transmission onto CeA, and changes the responsiveness of
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13 intra-CeA cell populations, ultimately promoting the fear expression (Li et al., 2013). However, it
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15 has to be underlined that the described serial processing in the amygdala fear nuclei does not
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17 represent the unique view, and an alternative parallel processing is possible (Figure 2). Interesting
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19 evidence supports that the CeA has many of the same characteristics that originally implicated the
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21 BLA as a critical site for fear learning and it may participate in both the acquisition and storage of
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23 conditioned fear memories (Fadok et al., 2018; Wilensky et al., 2006). CS-evoked neural responses
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25 of subpopulation of cells within the CeA undergo learning dependent modifications, similarly to
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27 what occurs in the BLA (Haubensak et al., 2010; Penzo et al., 2014). Very importantly, activity of
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29 protein kinase C δ expressing cells in the lateral division of the CeA is necessary for FC induced
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31 synaptic strengthening in the LA, just playing an important role in conveying information about the
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33 US to the LA (Yu et al., 2017). These findings suggest that BLA and CeA may not be organized
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35 only in series but in parallel and that both subnuclei encode the same type of CS-US association
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37 (Balleine and Killcross, 2006; Ressler and Maren, 2019). The serial and parallel models emphasize
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39 the importance of coordinated or distributed amygdaloid plasticity, respectively, but future
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41 experiments will be necessary to determine the precise roles and interactions of the various intra-
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43 amygdala regions in the fear learning, reconsolidation, and extinction processes.
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53 As a final note, it has to be reported that in detecting and responding to fearful stimuli, the
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55 amygdala (and not only this brain area) might work in terms of a non-conscious defensive survival
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57 circuit than a conscious fear one (LeDoux, 2012). Facing dangers, sensory systems detect
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59 threatening stimuli and defensive responses and feelings of fear may co-occur. Sensory system
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connections to the amygdala trigger fear behavioral responses, while sensory system connections to the PFC permit the integration of information arising the feeling of fear (LeDoux, 2020).

Findings in humans have demonstrated that interfering with the consolidation process, that is, inhibitory stimulation of the dlPFC, disrupted fear memory consolidation (Asthana et al., 2013). During reconsolidation, it is possible to modulate fear responses in humans by administering drugs (Kindt et al., 2009) and behavioral procedures (Schiller et al., 2010) or delivering inhibitory rTMS over the dlPFC (Borgomaneri et al., 2020a). Such state-dependent effects appear to be critical for consideration in psychiatric populations, such as PTSD patients, in which the optimal conditions to induce reconsolidation may be to recall traumatic events while rTMS is applied rather than by applying rTMS *per se*, which was found to be ineffective in healthy participants (Borgomaneri et al., 2020a). Again, human findings have demonstrated that interfering with the extinction process, e.g., excitatory stimulation applied over the vmPFC and inhibitory stimulation over the dlPFC, increased extinction (Dittert et al., 2018; Raij et al., 2018; Van 't Wout et al., 2016; Vicario et al., 2019).

Within this framework, to initiate extinction learning, the absence of the expected aversive outcome must be detected and signaled to the brain regions mediating fear extinction and reconsolidation. New extinction learning is initiated, and reconsolidation is possible when outcomes violate expectations (Rescorla and Wagner, 1972). Such violations are thought to cause 'prediction error' signals that initiate neural processes that ultimately lead to changes in behavior (Den Ouden et al., 2012; Friston, 2012; Garofalo et al., 2017). During fear extinction, the absence of the US is an unexpected event and likely generates a prediction error signal that initiates extinction learning. More specifically, the omission of the aversive US can be conceptualized as a better-than-expected outcome. It is well established that the activity of midbrain dopamine neurons represents the degree to which outcomes are better or worse than expected (Bayer and Glimcher, 2005; Eshel et al., 2016, 2015; Schultz et al., 1997; Schultz and Dickinson, 2000).

1 Although a better understanding of fear processing has been achieved, innovative technical tools
2 such as NIBS and optogenetics will allow a more specific identification and manipulation of the
3 neurobiology of fear, leading to the identification of a possible therapeutic target for pathological
4 fear states caused by trauma, stress and anxiety (Borgomaneri et al., 2021).
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34 **Declaration of Competing Interest**

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36 The authors report no declarations of interest.
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Figure Legend

Figure 1: Talairach coordinates of the targeted cortical sites in the rTMS and electrodes placement for stimulation in the tDCS/tES studies were converted in Talairach coordinates (Koessler et al., 2009). The targeted cortical sites were reconstructed using Surf Ice (<https://www.nitrc.org/projects/surface>).

Figure 2: A) During fear conditioning, thalamic and cortical afferents convey conditioned stimulus (CS) and unconditioned stimulus (US) sensory information into the baso-lateral amygdala (BLA), causing a marked potentiation of excitatory synapses by long-term synaptic plasticity (LTP). This phenomenon causes indeed an increase of firing activity of a specific class of neurons, called “*fear neurons*”. *Fear neurons* stimulate central amygdala (CeA) (*serial processing*) causing a strong increase of the whole amygdala output triggering both motor and autonomic fear behaviour by involving periaqueductal gray matter (PAG) and hypothalamus. Connection between cortical prelimbic (PrL) and BLA neurons is able to stimulate the activity of BLA *fear neurons* causing a further increase in CeA activity. BLA neurons activity is also potentiated by a backward excitatory pathway originating from CeA. CS-US association induces in CeA neurons similar learning-dependent modifications occurring in BLA (*parallel processing*). From BLA, CS-US information is also redirected to Basal Ganglia which support the instrumental response.

B) During the extinction phase, the input from cortical infralimbic (IL) area suppresses the BLA *fear neurons* activity by the interplay with intrinsic inhibitory interneurons. Moreover, IL area directly inhibits the CeA through activation of intercalated cells (ITCs), a scattered group of GABAergic neurons mainly located around the BLA area. The local inhibitory circuit further reduces the neural activity of *fear neurons* of BLA neurons and the subsequent BLA-CeA pathway, thereby suppressing the fear response.

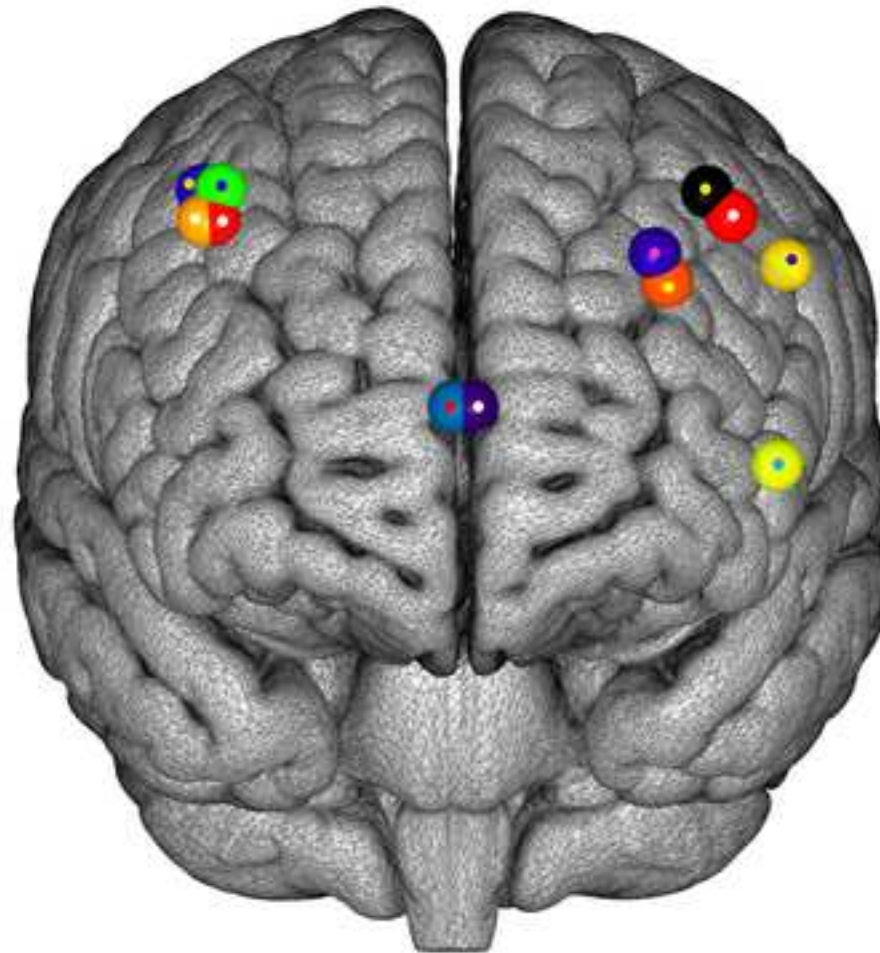
Box 1: Schematic overview representing the overall effect in fear processing triggered by optogenetic stimulation together with the receptorial modulation.

Abbreviations, FC: Fear Conditioning, ChR2: Channelrhodopsin2, eNpHR: Halorhodopsin, eArch3: Activity-regulated cytoskeleton-associated protein, EphB: Erythropoietin-producing hepatocellular-B, Tac2: Tachykinin 2, PV⁺: Parvalbuminergic positive neurons, M1-ACh: Muscarinic 1 acetylcholine receptors, DA: Dopaminergic neurons, LA: Lateral Amygdala, BLA: Basolateral Amygdala, CeA: Central Amygdala, VH: Ventral Hippocampus, VTA: Ventral Tegmental Area, PFC: Prefrontal Cortex

Tables

Table 1. Summary of NIBS methods used in fear conditioning studies.

Table 2: Summary of NIBS findings in fear conditioning. Studies that reported coordinates based on the Montreal Neurological Institute were converted into Talairach coordinates through the application of the Yale BioImage Suite Package (Lacadie et al., 2008).



Memory Consolidation

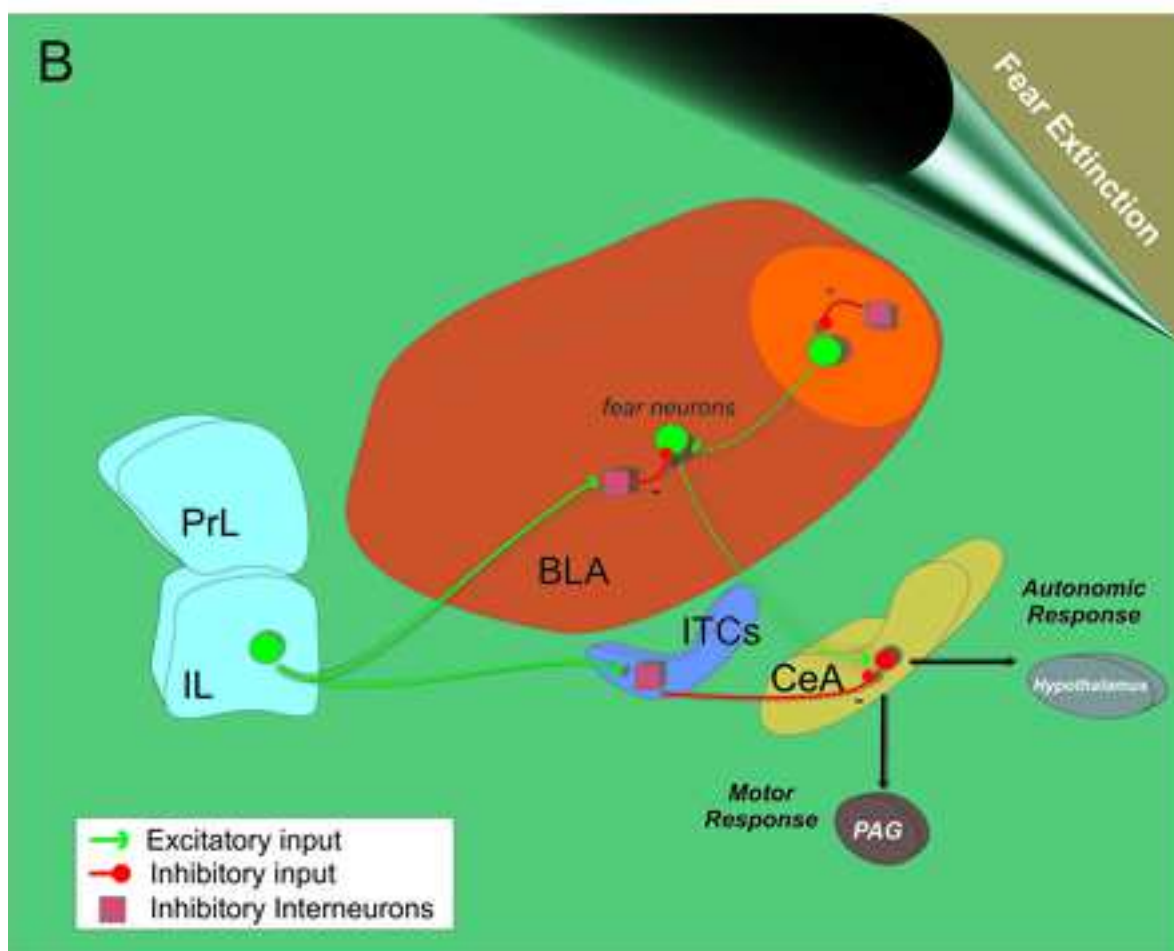
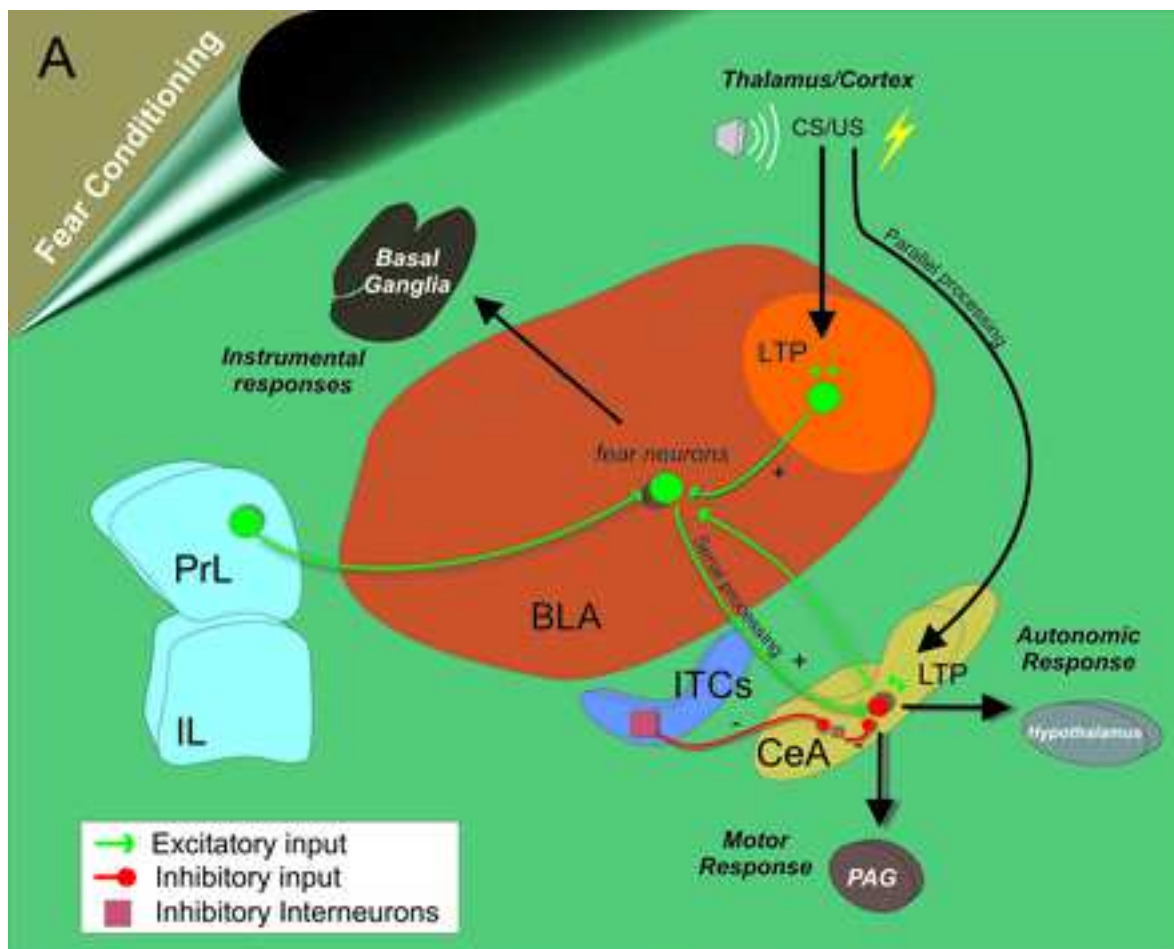
- Asthana et al., 2013 [*dIPFC*]
- Guhn et al., 2014 [*mPFC*]

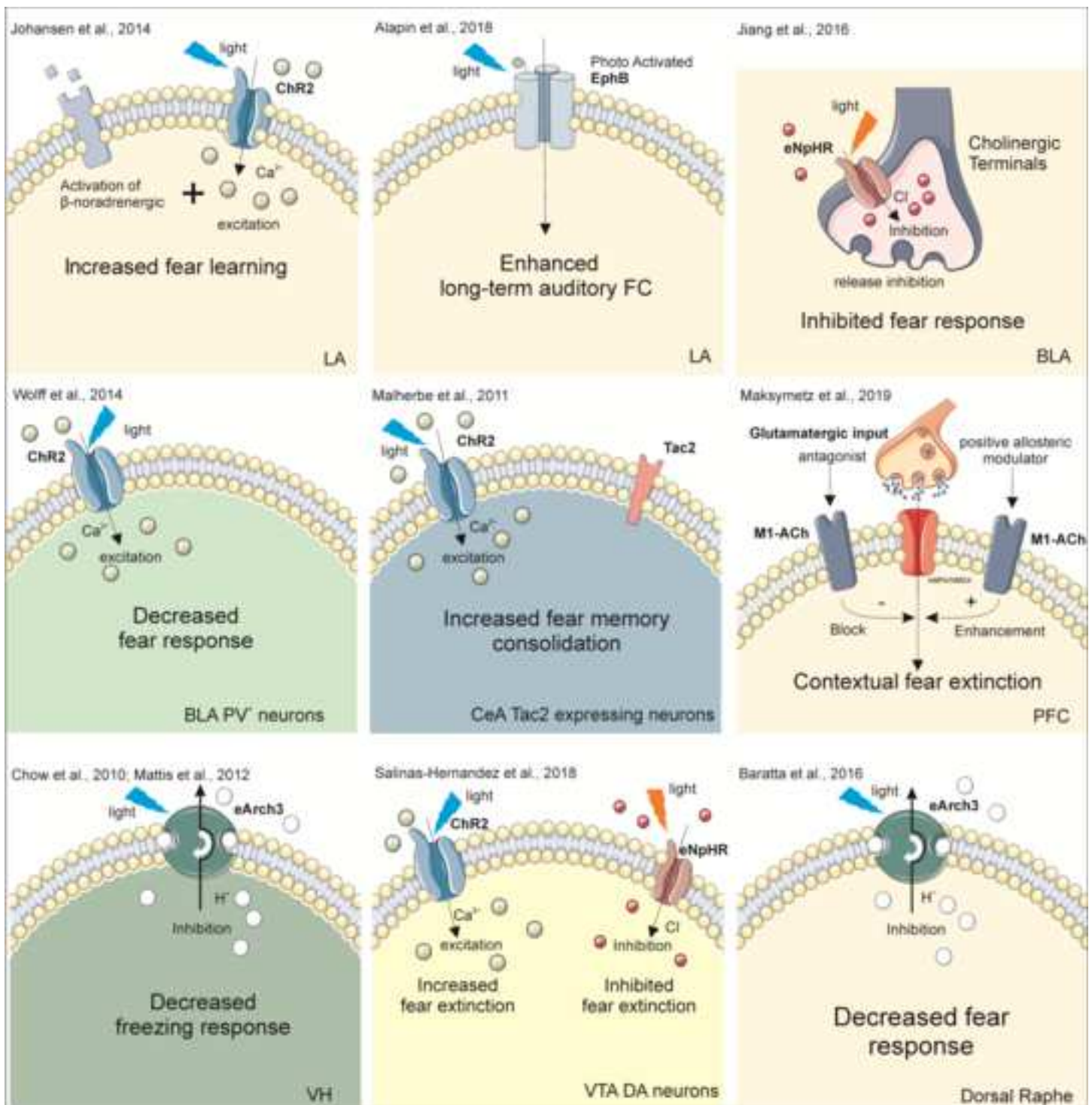
Memory Extinction

- Van 't Wout et al., 2016 [*PFC*]
- Dittert et al., 2018 [*PFC*]
- Vicario et al., 2019 [*PFC*]
- Raij et al., 2018 [*PFC*]










Memory Reconsolidation



- Abend et al., 2016 [*mPFC*]
- Mungee et al., 2014 [*dIPFC*]
- Mungee et al., 2016 [*dIPFC*]
- Ganho-Ávila et al., 2019 [*dIPFC*]
- Borgomaneri et al., 2020 [*dIPFC*]





Method	Excitatory Mode	Inhibitory Mode
<i>rTMS</i>	High frequency [> 5 Hz]	Low frequency [0.2 – 1 Hz]
<i>tES</i>	Anodal [1 – 2 mA]	Cathodal [1 – 2 mA]
<i>tDCS</i> <i>tACS</i>		

Study	Experimental Paradigm	Physiological index	N	Stimulation					Main Findings	
				Method	Talairach Coordinates (x, y, z) or Electrode	Duration	Intensity / Frequency	Online/Offline		
Memory Consolidation										
Asthana et al., 2013	 2-days	SCR	69	Anodal/Cathodal tDCS	F3	12 min	1.0 mA	Offline	Cathodal tDCS disrupts fear memory	
Guhn et al., 2014	 2-days	FPS and SCR	45	rTMS	FPz	20 min (1560 pulses)	10 Hz 110% rMT	Offline	Enhances extinction	
Memory Extinction										
Van 't Wout et al., 2016	 2-days	SCR	44	Anodal tDCS	AF3	10 min	2.0 mA	Online/Offline	Enhances extinction	
Dittert et al., 2018	 1-days	SCR	84	Anodal tDCS	F7	20 min	1.5 mA	Online	Enhances extinction	
Vicario et al., 2019	 2-days	SCR	32	Anodal tDCS	AF3	10 min	2.0 mA	Online	Enhances extinction	
Raij et al., 2018	 3-days	SCR	28	rTMS	[-54, 2, 38]	300ms after CS (28 pulses)	20 Hz 100% rMT	Online	Enhances extinction	
Memory Reconsolidation										
Abend et al., 2016	 3-days	SCR	45	tACS/tDCS	FPz	20 min	tACS: 1 Hz tDCS: 1.5 mA	Online	Anodal tDCS disrupts fear memory	
Mungee et al., 2014	 3-days	SCR	74	Anodal tDCS	F4	20 min	1.0 mA	Offline	Anodal tDCS enhances fear memory	
Mungee et al., 2016	 3-days	SCR	17	Cathodal tDCS	F4	20 min	1.0 mA	Offline	No effects	

Ganho-Ávila et al., 2019		2-days	SCR	41	Cathodal tDCS	F4	20 min	1.0 mA	Offline	No effects
Borgomaneri et al., 2020		3-days	SCR	84	rTMS	F3	15 min (900 pulses)	1 Hz 120% rMT	Offline	Disrupt fear memory before and after reinstatement
