Review

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Neuronal Circuits for Fear Expression and Recovery: Recent Advances and Potential Therapeutic Strategies

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ABSTRACT

Recent technological developments, such as single unit recordings coupled to optogenetic approaches, have provided unprecedented knowledge about the precise neuronal circuits contributing to the expression and recovery of conditioned fear behavior. These data have provided an understanding of the contributions of distinct brain regions such as the amygdala, prefrontal cortex, hippocampus, and periaqueductal gray matter to the control of conditioned fear behavior. Notably, the precise manipulation and identification of specific cell types by optogenetic techniques have provided novel avenues to establish causal links between changes in neuronal activity that develop in dedicated neuronal structures and the short and long-lasting expression of conditioned fear memories. In this review, we provide an update on the key neuronal circuits and cell types mediating conditioned fear expression and recovery and how these new discoveries might refine therapeutic approaches for psychiatric conditions such as anxiety disorders and posttraumatic stress disorder.

Keywords: Amygdala, Anxiety disorders, Fear expression, Neuronal circuits, Prefrontal cortex, Single unit recordings

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Anxiety disorders are among the most common psychiatric conditions with a lifetime prevalence of around 6% in the population worldwide (1). In particular, posttraumatic stress disorder (PTSD) represents one of the most frequent anxiety disorders, which can develop following the experience of a traumatic event. Typically, PTSD patients present symptoms such as re-experiencing the traumatic experience, hyperarousal, and avoidance of situations, places, or objects that serve as reminders of the traumatic event. It is largely accepted that associative processes are involved in the etiology and maintenance of PTSD and anxiety disorders (2,3) and stimuli associated with the traumatic event can elicit conditioned fear responses (3). Despite a broad knowledge about brain structures involved in fear behavior, the mechanisms involved in the regulation of fear expression were, until recently, still largely unknown. Recent single unit recordings and optogenetic approaches have allowed a better identification of the circuits controlling fear expression in rodents. In the laboratory, fear behavior is classically studied using Pavlovian fear conditioning, which consists of repetitive associations of a neutral conditioned stimulus (CS), such as a sound or a context, with an unconditioned stimulus (US), usually a mild electric footshock. Following conditioning, re-exposure to the CS induces conditioned fear responses, including an immobility reaction termed freezing, which represents a reliable measure of the learned association (4). Inhibition of fear behavior can be observed following repetitive exposure to the CS without the US, a process termed fear extinction. Interestingly, fear extinction, which is known to represent a new learning process of the CS-no US association, is sensitive to contextual and temporal changes that can promote the recovery of the original fear memory (5,6). In this review, we will first provide a summary of data collected in humans and rodents that have allowed deciphering the gross anatomical structures involved in cued and contextual conditioned fear expression and recovery. Second, we will provide an update of the novel neuronal circuits that have recently been identified as central to fear expression and recovery. Lastly, we will discuss how these new discoveries may promote the development of new therapeutic strategies for anxiety disorders.

NEURONAL STRUCTURES MEDIATING FEAR EXPRESSION AND RECOVERY IN HUMANS

In humans, fear conditioning is usually studied by associating a CS, such as a tone or a visual cue, with an aversive US, such as a mild wrist or finger electrical shock. This aversive learning is evaluated by measuring skin conductance responses, which depend on the amygdala, a key structure for the processing of fear behavior (7–10). Functional neuroimaging approaches during and following fear conditioning in humans have been instrumental in deciphering the networks involved in physiologic or pathologic fear responses. However, because extinction learning is faster in humans compared with rodents and because some structures display within session habituation of functional magnetic resonance imaging (11,12), fear expression

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and extinction are usually explored simultaneously in human studies. We therefore review below studies related to both fear expression and extinction. These studies identified the amygdala, hippocampus, and prefrontal cortex as key structures for conditioned fear in normal and pathologic conditions. In functional neuroimaging studies, blood oxygen level-dependent (BOLD) signal (corresponding to changes in brain microvasculature oxygenation related to metabolic activity) revealed amygdala activation during fear conditioning in humans (11), particularly during fear expression (13–18). Amygdala activation was also observed several days after extinction of a conditioned threat memory but not if extinction was performed during fear memory reconsolidation (19). However, the above findings have not been consistently reproduced (20), probably due to the heterogeneity of fear conditioning paradigms used across neuroimaging studies. Finally, high-resolution functional imagery revealed different contributions of amygdala subnuclei during reversal of a conditioned fear procedure, with activation of the central and basolateral nuclei of the amygdala related to attentional and associative processes, respectively (21).

Besides the amygdala, a subset of functional imaging studies observed an activation of the hippocampus (HPC) during fear behavior (18,22–25). Given the role of this structure in the processing of contextual information (26–28), these data suggest a role of the HPC in the encoding of the contextual features associated with fear expression. Finally, several studies reported a role of the prefrontal cortex (PFC) during fear acquisition and expression, as well as during fear extinction. Specifically, decreases and increases of BOLD signals were observed in the ventromedial PFC (vmPFC) [an equivalent of the rodent infralimbic cortex (IL) (17,29)] during fear acquisition/expression and extinction, respectively (17,22,25,30). Interestingly, analyses of the dorsal anterior cingulate cortex (dACC) [an equivalent of the rodent prelimbic cortex (PL) (16,31)] revealed an increase in BOLD signal during fear acquisition and expression (15,17,25). Thus, these data indicated opposing roles of the human vmPFC and dACC in processing fear-related behavior. Functional connectivity analyses, which look for significant BOLD signal correlations between brain regions, have revealed a functional coupling between the vmPFC, dACC, amygdala, and HPC during fear expression (22,25) and between vmPFC, amygdala, and HPC during fear extinction (32). Although these studies did not evaluate the direction of changes, they indicated that fear expression and extinction depend on the joint activity of these structures.

In the context of human psychiatric conditions, increased dorsomedial PFC activation, as measured with resting metabolic activity, was shown to be a risk factor for the development of PTSD (33). Interestingly, functional imaging analyses during recollection of traumatic events in PTSD patients revealed decreased activity in the vmPFC and increased activity in the amygdala (34–42) [for a review, see (43)]. In line with these results, increased amygdala and dACC activation was observed in PTSD patients during extinction in a safety context, whereas healthy subjects presented increased amygdala and prefrontal activation in the danger context, suggesting inappropriate modulation of brain activity according to contextual information in PTSD patients (44). Higher amygdala activation (45) and lower vmPFC activation (46) were also observed in PTSD patients, as compared with control subjects, during presentations of fearful faces during functional magnetic resonance imaging. Together, these data suggest that dysfunctional vmPFC–amygdala interactions are at the core of anxiety disorders including PTSD (32,47–51). Moreover, persistent conditioned fear in PTSD patients was suggested to be related to a failure of vmPFC and HPC activation and to a hyperactivation of dACC and amygdala (52). Importantly, this hypothesis has received strong support from work performed in rodents (see below). Altogether, these data provide strong arguments for the hypothesis that a dedicated brain network comprised of the amygdala, HPC, and prefrontal regions is involved in fear-related behavior.

NEURONAL CIRCUITS OF FEAR EXPRESSION AND RECOVERY IN RODENTS

Data collected in rodents using lesion and inactivation approaches have confirmed the involvement of the amygdala, hippocampus, and prefrontal cortex in the regulation of fear expression (Figure 1), and it is now largely accepted that fear behavior relies on a functionally conserved network of structures in mammals. These data, which have been previously reviewed (7–10,53–57), are discussed in Supplement 1. More recently, optogenetic technical developments have provided unprecedented details of the circuits and mechanisms regulating fear expression. Optogenetic technology consists of the expression of light-sensitive proteins in neurons whose excitation at specific wavelengths can activate or inhibit neuronal activity at the millisecond timescale. Currently, these techniques represent one of the best strategies to identify neuronal populations and to manipulate dedicated circuits. Recently identified circuits are further described in the following sections.

Central Amygdala-Periaqueductal Gray Matter Neuronal Circuits in Fear Expression

One circuit, which includes the basolateral amygdala (BLA), central nucleus of the amygdala (CEA), and the periaqueductal gray matter (PAG), has been shown to drive the expression of fear behavior following auditory fear conditioning (Figure 2A). In this circuit, the PAG, which is involved in the genesis of various conditioned fear responses (58–60) and the generation of aversive instructive learning signals (61,62), receives direct anatomical and functional inputs from the CEA (63–65). Recent studies suggest that expression of fear behavior is driven by the activation of the medial division of the central nucleus of the amygdala (CEm) neurons projecting to the PAG (63,66). Indeed, CEm output neurons are tonically controlled by lateral subdivision of the central amygdala (CEl) inhibitory neurons and display CS-evoked firing activity during freezing (63,66,67). More specifically, the CEl contains two populations of inhibitory neurons forming a disinhibitory microcircuit controlling the activity of PAG-projecting CEm neurons. This microcircuit is composed of CEl inhibitory neurons activated during CS presentations (CEl_{ON} neurons), which inhibit protein kinase C-delta-expressing (PKC-δ^{+}) CEl neurons (CEl_{OFF} neurons) (Figure 2A). CS-evoked inhibition of CEl_{OFF}

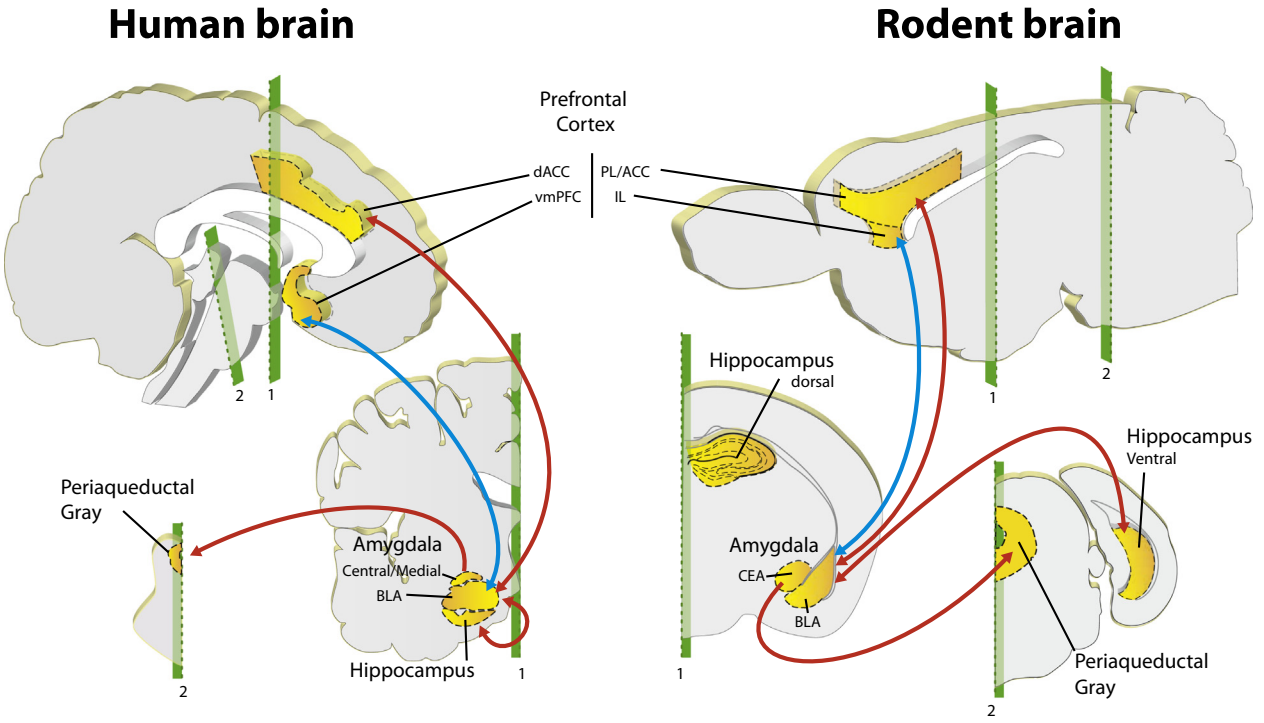

Figure 1. Human and rodent homologous neuronal structures involved in fear expression and recovery. The neuronal structures classically involved in fear expression and recovery in humans and rodents consist of the amygdala, composed of the basolateral amygdala (BLA), and central amygdala (central/medial amygdala in humans, central nucleus of the amygdala [CEA] in rodents) located in the medial temporal lobe; the prefrontal cortex, composed of the dorsal (dorsal anterior cingulate cortex [dACC] in humans), prelimbic (PL), and anterior cingulate cortex (ACC) in rodents, and ventral parts (ventral medial prefrontal cortex [vmPFC] in humans; infralimbic area [IL] in rodents); the hippocampus (ventrally located in humans, composed of a dorsal and ventral part in rodents); and the periaqueductal gray located in the brainstem. During fear expression (red lines), fear-related contextual information is relayed from the hippocampus to the amygdala. The bidirectional loop between the BLA and the dorsal part of the prefrontal cortex allows updating of fear-related information, which is further transmitted to the central amygdala and from there to the periaqueductal gray for fear expression. Fear inhibition during extinction depends on the bidirectional connectivity between the ventral part of the prefrontal cortex and the BLA (blue lines), which ultimately regulates central amygdala activity to reduce conditioned fear responses.

neurons facilitates the disinhibition of PAG-projecting CEm neurons during fear expression (63,68). In the same vein, a subpopulation of CEl inhibitory neurons expressing the oxytocin receptor (OR^+) was found to inhibit PAG-projecting CEm neurons. Consistently, the activation of OR^+-expressing CEl neurons through both local injection of the OR agonist [Thr^4, Gly^7]-oxytocin or local optogenetic manipulations reduced fear behavior (69,70). Interestingly, about 65% of PKC-δ^+ CEl neurons express the OR, suggesting that the oxytocin-mediated suppression of fear is mediated by inhibition of PKC-δ^+ CEl neurons, which, consequently, may disinhibit PAG-projecting CEm neurons (68–70).

In addition to the classical CEl-CEm-PAG pathway, it was recently demonstrated that a class of somatostatin-expressing (SOM^+) CEl neurons can modulate fear behavior independently of the CEm through direct projections to the PAG (64,71) (Figure 2A). In these two studies, the authors observed that optogenetic inhibition of SOM^+ CEl neurons suppresses fear expression, whereas their optogenetic activation drives unconditioned fear expression. Moreover, using retrograde tracers and immunohistochemistry, these authors demonstrated that among PAG-projecting CEl neurons, around 80% were SOM^+ neurons. All together, these data highlight two parallel circuits linking the CEl and PAG, which likely support conditioned fear behavior by increasing the activity of PAG-projecting CEm neurons and/or PAG-projecting SOM^+ CEl neurons (Figure 2A). Although, these studies identified key circuits within the central amygdala involved in fear expression, several questions remain. In particular, it is not clear whether the two distinct circuits are co-activated during fear expression or if they are independently recruited depending on the behavioral situation. Moreover, upstream circuits directly activating PKC-δ^+ CEl neurons and SOM^+ CEl neurons during fear expression need to be identified.

Amygdala-Prefrontal Circuits in Fear Expression and Recovery

Dorsal prefrontal regions are known to play a key role in the expression of defensive behavior. For instance, lesions of the frontal cortex in rats and monkeys following fear conditioning blocked fear expression (72–74). Conversely, activation of dorsal prefrontal regions produced conditioned fear expression (75). These studies raised important questions as to which prefrontal circuits are involved in fear expression and how these circuits are modulated by inputs from structures involved in the formation of fear memories, such as the BLA. Recently, some studies have begun to shed light on these

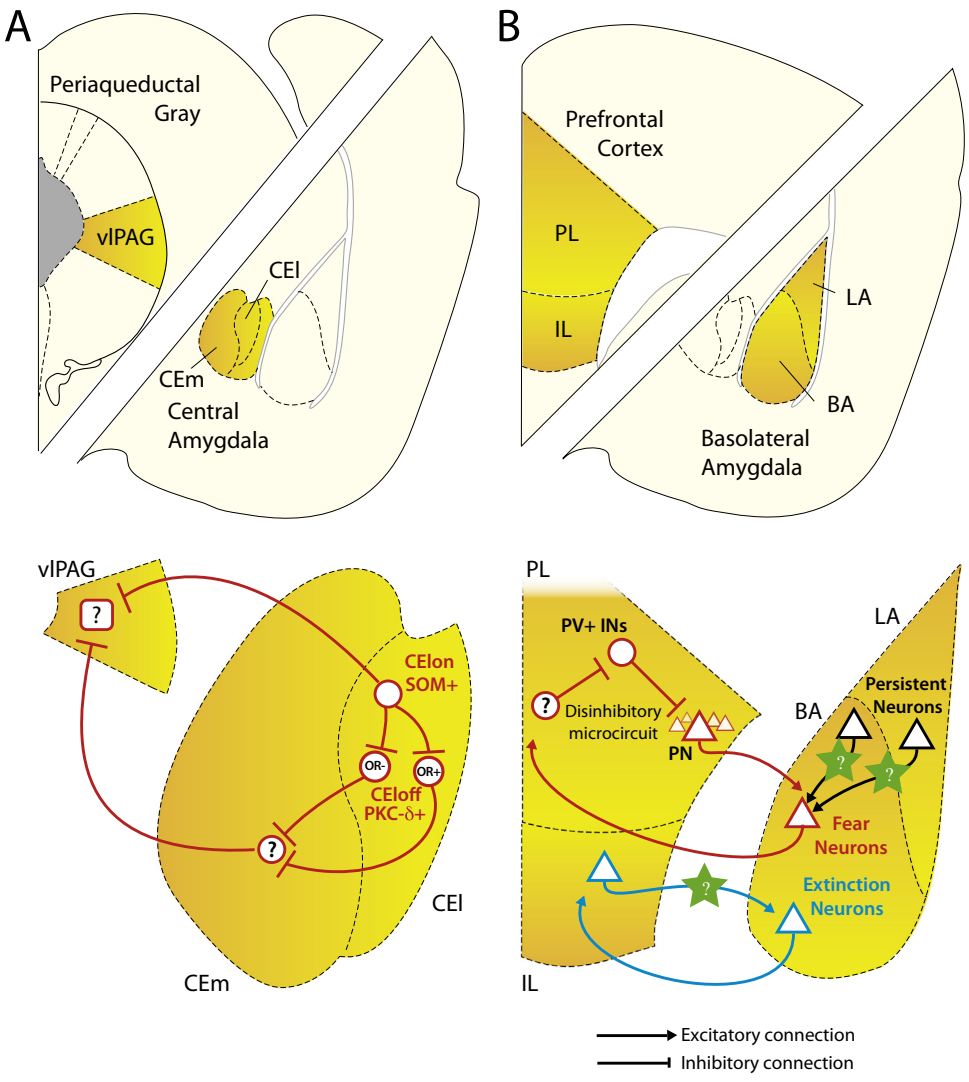

Figure 2. Novel neuronal circuits involved in fear expression and recovery. **(A)** A first circuit of fear expression located in the central amygdala is composed of lateral subdivision of the central amygdala (CEl) inhibitory neurons activated during presentations of conditioned stimuli (CEl_{ON} neurons), which preferentially inhibit a second class of CEl neurons (CEl_{OFF} neurons, also expressing protein kinase C-delta-expressing [PKC-δ^+] and oxytocin receptor [OR+]), thereby disinhibiting medial division of the central nucleus of the amygdala (CEm) inhibitory neurons. Increased activity of CEm neurons projecting to the ventrolateral periaqueductal gray (vlPAG) is associated with fear expression and recovery. A subset of CEl_{ON} neurons also expresses somatostatin (SOM) and directly projects to the vlPAG to regulate fear expression. **(B)** Three types of excitatory neurons in the basolateral amygdala activated during fear expression (fear neurons), during fear extinction (extinction neurons), or both (persistent neurons) have been recently described. Whereas the role of persistent neurons is still not clear, they might permanently store fear memories within the BLA. Extinction neurons project to the infralimbic area (IL), where they might activate neuronal circuits involved in the maintenance of fear extinction. Conversely, fear neurons are known to project to the prelimbic area (PL), where they could activate a disinhibitory circuit. This disinhibitory circuit is composed mainly of parvalbumin-expressing interneurons (PV^+ INs), whose inhibition during presentation of conditioned stimuli leads to the disinhibition of PL principal neurons (PN) contacting the BLA and the expression or recovery of conditioned fear responses. BA, basal nucleus of the amygdala; LA, lateral nucleus of the amygdala.

questions by identifying novel circuits within the PL and BLA that are causally related to fear expression.

Within the BLA, recording studies identified three neuronal populations displaying distinct changes in activity correlated with the expression of fear memory. The first population (persistent neurons), which displayed persistent CS-evoked activity after conditioning, has been suggested to encode the maintenance of CS-US associations after learning (76,77). In contrast, the second population (fear neurons) displayed a reduction in CS-evoked responses throughout extinction learning and has been suggested to encode fear expression (76–78). The last BLA population contains excitatory neurons activated by extinction learning (extinction neurons), which encode the formation of extinction memories (76) (Figure 2B). An important question related to fear and extinction BLA neurons is to know whether they represent functionally separated classes of neurons or if they correspond to a unique population of neurons displaying a gradual shift in their function through extinction learning. A partial answer to this question comes from the work by Herry *et al.* (76), who recorded simultaneously from BLA fear and extinction neurons using a dual fear conditioning paradigm. In this paradigm, two different CSs were associated with a mild footshock but only one of them was extinguished. They observed that the presentation of the nonextinguished CS was associated with high fear and the exclusive activation of fear neurons. Importantly, presentation of the extinguished CS produced low fear behavior and was associated with the inhibition and activation of fear and extinction neurons, respectively. These data strongly suggest that BLA fear and extinction neurons correspond to two different functional classes of neurons (76). Interestingly, BLA fear and extinction neurons have been shown to directly project to the medial PFC (mPFC), suggesting that they could directly modulate fear expression and extinction depending on their respective target in the mPFC (76,79) (Figure 2B). This hypothesis has recently been refined

and confirmed by Senn *et al.* (79), who demonstrated that fear neurons recorded in the BLA project to the PL region. Moreover, these authors demonstrated that the optogenetic activation or inhibition of PL-projecting BLA fear neurons during extinction learning facilitated or reduced subsequent fear recovery, respectively. Conversely, optogenetic activation or inhibition of BLA neurons projecting to the IL region reduced or promoted fear recovery (79). These data indicate that the modulation of fear recovery following extinction can be achieved at two distinct levels, by modulating a BLA-PL circuit involved in fear expression or by impacting a BLA-IL circuit involved in fear extinction (Figure 2B). The above data indicate that the modulation of BLA-PL or BLA-IL circuits is causally related to fear expression, which raises the question of the specific circuits within the PL or the IL that may regulate fear responses.

This question has been addressed over the past years and more recently, and several studies demonstrated roles of the PL and IL in the regulation of fear expression and extinction. For instance, IL stimulation that mimicked extinction-induced CS presentations reduced fear responses (80). Extinction retrieval correlates with an increase in CS-evoked single unit activity in the IL and changes in mPFC-evoked field potentials (81–83). In contrast, PL electrical microstimulation increased fear behavior, and fear expression correlates with increased CS-evoked single unit activity in the PL (80,84). More recently, Cho *et al.* (85) used slice physiology and optogenetic approaches to investigate synaptic plasticity mechanisms that developed between the IL and BLA during extinction. They demonstrated that extinction was associated with a reduction in the excitatory drive from IL inputs onto BLA principal neurons resulting from a decreased probability of neurotransmitter release (85). In another study, Do-Monte *et al.* (86) elegantly demonstrated using electrophysiological and optogenetic approaches that fear retrieval at early time points after conditioning depends on a PL-BLA circuit. In contrast, fear retrieval at later time points recruits a PL-paraventricular thalamic nucleus-CEA pathway (86). Moreover, it was recently shown that paraventricular thalamic nucleus neurons regulate fear behavior by a direct projection onto CEl SOM^+ neurons, a phenomenon dependent on brain-derived neurotrophic factor receptors (87).

Additional studies also investigated the cell types and mechanisms involved in the regulation of fear behavior at the level of prefrontal and amygdala circuits. For instance, Courtin *et al.* (88) identified a role played by a specific class of inhibitory interneurons in the dorsal PL and anterior cingulate cortex (ACC) during fear expression (Figure 2B). Using single unit recordings and optogenetic approaches, they observed that following fear conditioning, CS presentations inhibit PL and ACC fast-spiking interneurons (INs), which correspond to parvalbumin-expressing INs (PV). Furthermore, they showed that PV IN inhibition during CS presentations was causally related to fear expression via two mechanisms: a disinhibitory mechanism that increased the excitability of PL and ACC principal neurons (PNs) and the resetting of slow local oscillations in the theta range (8–12 Hz) that synchronizes prefrontal PNs to drive fear expression. These results identify two mechanisms, both mediated by prefrontal PV INs, that coordinate and enhance the efficiency of prefrontal PNs to drive fear expression (88). Over the past years, it has become clear that neuronal synchronization of activity during specific time windows represents an important form of information coding in the brain that depends on brain oscillations. The data reviewed above strongly suggest that this form of coding, which has been described in the HPC in relation to the formation and consolidation of spatial memory (89–92), also contributes to the expression of fear behavior.

The contribution of neuronal synchronization between mPFC and BLA circuits for encoding fear and safety signals was recently investigated in an elegant set of studies. In these studies, the authors recorded simultaneously in the mPFC, ventral HPC, dorsal HPC, and BLA while mice were submitted to differential fear conditioning and extinction paradigms (93,94). In animals that discriminate the safety CS (CS^-) from the aversive CS (CS^+), a strong theta (4–12 Hz) synchronization was observed between the mPFC and BLA, suggesting that the recruitment of the mPFC pathway is critical for inhibiting fear memory (93). Interestingly, enhanced fear behavior during retrieval was correlated with a strong coupling between BLA theta and gamma oscillations. However, during periods of safety, BLA gamma oscillations and firing activities were entrained by mPFC theta oscillations (94). It is worthy to note that recent data have also highlighted the role of hippocampal circuits in fear expression. These data are reviewed in Supplement 1.

Together, these data indicate that circuits from the BLA to the PL and from the mPFC to the BLA are critical for the regulation of fear behavior (Figure 2B). To date, however, it is unclear why this loop is necessary for fear expression or reduction and whether or not different mPFC inputs to the BLA are involved. In principle, synchronized mPFC inputs to the BLA during presentation of CS associated with safety or fear behavior may allow updating of fear and extinction memories via the strengthening of BLA excitatory synapses reactivated during tone presentations. Additional studies will be required to evaluate this possibility.

FOSTERING NEW THERAPEUTIC STRATEGIES FOR ANXIETY DISORDERS THROUGH THE IDENTIFICATION OF NEURONAL CIRCUITS INVOLVED IN FEAR EXPRESSION

Understanding the circuits involved in fear expression represents an important challenge for the refinement of current therapeutic approaches for anxiety disorders. These approaches, which include cognitive and behavioral therapies, are usually associated with short-term improvement of anxiety-related symptoms. Indeed, it has recently been demonstrated that pathologic fear responses can be reduced through extinction procedures (19,95). However, relapse of traumatic fear memories often occur spontaneously following extinction or can be precipitated by exposure to contextual cues (96). These observations indicate that the extinction procedure alone is probably insufficient to permanently reduce anxiety-related symptoms. Recent studies of the circuits involved in fear expression could be highly beneficial in fostering the development of new therapeutic strategies for anxiety disorders. Several methods based on brain stimulation, like electroconvulsive therapy (97), deep brain stimulation

(98), transcranial direct current stimulation (99), or transcranial magnetic stimulation (TMS) (100–102), are currently used to treat anxiety disorders and PTSD in a complement of behavioral and pharmacologic strategies. The use of these strategies in the context of pathologic anxiety and their potential refinement in light of the recent findings on circuits involved in fear expression are provided below.

Electroconvulsive shock treatment following memory reactivation has been shown to disrupt emotional memories (97), and these approaches seem relatively efficient for treating psychiatric diseases such as major depression or even PTSD (103,104). However, this treatment is limited by the fact that it requires general anesthesia and momentary muscle paralysis. Similarly, the efficacy of deep brain stimulation should be interpreted with respect to its invasiveness, although it has proven to be very efficient to treat Parkinson disease and major depression (105). Repetitive TMS (rTMS) is a noninvasive and well-tolerated technique used to treat several psychiatric disorders for over 20 years (106). Very few studies have investigated rTMS efficacy in PTSD treatment, and the results that were generated were mixed (107,101). Furthermore, there is neither clear rationale nor consensus regarding which stimulation parameters to use and which regions to target. Most of the rTMS studies used either low-frequency rTMS (known to be inhibitory) (101) or high-frequency rTMS (excitatory) (102) over the right dorsolateral PFC. It has been proposed that neutralizing the dACC, which is involved in the expression of behavioral and autonomic fear responses (108,109), might be an effective strategy for ameliorating anxiety (108). For example, anxiety disorders have been treated with anterior cingulotomy (110), in accordance with functional evidence (111,112) and the documented direct anatomical projections from the ACC to visceral circuits that regulate autonomic and visceral output (113). Until now, very few studies have attempted to target the dACC via TMS since the main limitation of this technique is the depth of penetration of the field, typically only reaching superficial cortices [but see (114)]. In humans, a recent study using a new TMS coil designed to stimulate deep prefrontal brain areas proved to be therapeutically beneficial in PTSD patients (100). Importantly, because dACC and vmPFC regions in humans play antagonistic roles in the regulation of fear behavior, it is critical to control so that TMS stimulation will not result in the activation of both regions, which could reduce the efficacy of the stimulation. Technical reports indicate that the electrical field beneath TMS penetrates only a few centimeters and ends very abruptly in the human brain (115,116). This constrained magnetic field of TMS decreases the likelihood of activating the vmPFC, which is deeply buried in the ventral surface of the human brain (Figure 1).

TMS stimulation of dACC could even be much more effective if precise patterns of stimulation are used to target specific cell classes according to their functional state at the time of the stimulation. For instance, recent advances in rTMS have shown that specific protocols allow for the precise modulation of PV INs, which appear to be sensitive to intermittent theta burst stimulation delivered through an intermittent stimulation paradigm (117,118). Although further experiments are required to define precise stimulation protocols for the activation of specific classes of neurons, it is very likely that these approaches will be beneficial for the development and refinement of therapeutic strategies for anxiety disorders.

CONCLUSIONS

Over the past years, our understanding of how conditioned fear memories are encoded and retrieved within the myriad of neurons in dedicated brain regions has grown considerably. In particular, innovative technologies allowing the tagging, recording, identification, and manipulation of large neuronal ensembles have greatly contributed to this knowledge. These approaches provide unprecedented spatial and temporal resolutions that reveal and elucidate the contribution of small distinct brain areas previously considered as unified structures and functional entities. The data collected have refined our understanding of the local circuitry and mechanisms involved at the level of the BLA, CEA, mPFC, HPC, and PAG in the regulation of conditioned fear expression and recovery. Novel circuits composed of specific cell populations, such as PL PV inhibitory interneurons, CEl SOM+ neurons projecting to the PAG, or CEl_{ON} and CEl_{OFF} cells, have been identified and proven to be critical for the control of fear expression. These studies have demonstrated that the manipulation of small subsets of excitatory or inhibitory neurons is often sufficient to reduce or enhance fear expression, which provides novel therapeutic avenues for anxiety disorders. It is conceivable that the refinement of rTMS might allow the selective activation of specific neuronal elements. In particular, specific rTMS activation of PV INs will be instrumental to precisely control the spiking activity of excitatory neurons controlling fear behavior. For instance, the efficiency of the manipulation of PV INs on the regulation of behavior has been the object of recent studies (88,119,120). Another important role of PV INs is their involvement in the regulation of neuronal oscillations throughout the brain (88,121). Neuronal oscillations play a key role in organizing the firing activity of neurons and provide a precise temporal frame to control behavior (89,92). Thus, the manipulation of PV INs at specific phases of cortical oscillations may represent an additional strategy to rescue traumatic fear memories. However, it remains to be demonstrated whether these laboratory findings, largely in rodents, are transferable to human patients.

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REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.
2. Pitman RK, Shin LM, Rauch SL (2001): Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. J Clin Psychiatry 62(suppl 17):47–54.
3. Rothbaum BO, Davis M (2003): Applying learning principles to the treatment of post-trauma reactions. Ann N Y Acad Sci 1008: 112–121.
4. Blanchard RJ, Blanchard DC (1969): Crouching as an index of fear. J Comp Physiol Psychol 67:370–375.
5. Bouton ME (2004): Context and behavioral processes in extinction. Learn Mem 11:485–494.
6. Herry C, Ferraguti F, Singewald N, Letzkus JJ, Ehrlich I, Luthi A (2010): Neuronal circuits of fear extinction. Eur J Neurosci 31:599–612.
7. Davis M (2000): The Role of the Amygdala in Conditioned and Unconditioned Fear and Anxiety. Oxford, UK: Oxford University Press.
8. LeDoux JE (2000): Emotion circuits in the brain. Annu Rev Neurosci 23:155–184.
9. Maren S (2001): Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci 24:897–931.
10. Pape HC, Pare D (2010): Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev 90:419–463.
11. Buchel C, Morris J, Dolan RJ, Friston KJ (1998): Brain systems mediating aversive conditioning: An event-related fMRI study. Neuron 20:947−957.
12. Plichta MM, Grimm O, Morgen K, Mier D, Sauer C, Haddad L, *et al*. (2014): Amygdala habituation: A reliable fMRI phenotype. Neuroimage 103:383–390.
13. Buchel C, Dolan RJ (2000): Classical fear conditioning in functional neuroimaging. Curr Opin Neurobiol 10:219–223.
14. LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA (1998): Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. Neuron 20:937–945.
15. Linnman C, Rougemont-Bucking A, Beucke JC, Zeffiro TA, Milad MR (2011): Unconditioned responses and functional fear networks in human classical conditioning. Behav Brain Res 221:237–245.
16. Milad MR, Quirk GJ, Pitman RK, Orr SP, Fischl B, Rauch SL (2007): A role for the human dorsal anterior cingulate cortex in fear expression. Biol Psychiatry 62:1191–1194.
17. Phelps EA, Delgado MR, Nearing KI, LeDoux JE (2004): Extinction learning in humans: Role of the amygdala and vmPFC. Neuron 43: 897–905.
18. Sehlmeyer C, Schoning S, Zwitserlood P, Pfleiderer B, Kircher T, Arolt V, Konrad C (2009): Human fear conditioning and extinction in neuroimaging: A systematic review. PloS One 4:e5865.
19. Agren T, Engman J, Frick A, Bjorkstrand J, Larsson EM, Furmark T, Fredrikson M (2012): Disruption of reconsolidation erases a fear memory trace in the human amygdala. Science 337:1550–1552.
20. Knight DC, Smith CN, Stein EA, Helmstetter FJ (1999): Functional MRI of human Pavlovian fear conditioning: Patterns of activation as a function of learning. Neuroreport 10:3665–3670.
21. Boll S, Gamer M, Gluth S, Finsterbusch J, Buchel C (2013): Separate amygdala subregions signal surprise and predictiveness during associative fear learning in humans. Eur J Neurosci 37:758–767.
22. Kalisch R, Wiech K, Critchley HD, Dolan RJ (2006): Levels of appraisal: A medial prefrontal role in high-level appraisal of emotional material. Neuroimage 30:1458–1466.
23. Klucken T, Tabbert K, Schweckendiek J, Merz CJ, Kagerer S, Vaitl D, Stark R (2009): Contingency learning in human fear conditioning involves the ventral striatum. Hum Brain Mapp 30:3636–3644.
24. Knight DC, Waters NS, Bandettini PA (2009): Neural substrates of explicit and implicit fear memory. Neuroimage 45:208–214.
25. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007): Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 62: 446–454.
26. Anagnostaras SG, Gale GD, Fanselow MS (2001): Hippocampus and contextual fear conditioning: Recent controversies and advances. Hippocampus 11:8–17.
27. Maren S (2014): Fear of the unexpected: Hippocampus mediates novelty-induced return of extinguished fear in rats. Neurobiol Learn Mem 108:88–95.
28. Rudy JW (2009): Context representations, context functions, and the parahippocampal-hippocampal system. Learn Mem 16: 573–585.
29. Kim H, Somerville LH, Johnstone T, Alexander AL, Whalen PJ (2003): Inverse amygdala and medial prefrontal cortex responses to surprised faces. Neuroreport 14:2317–2322.
30. Schiller D, Delgado MR (2010): Overlapping neural systems mediating extinction, reversal and regulation of fear. Trends Cogn Sci 14: 268–276.
31. Chiba T, Kayahara T, Nakano K (2001): Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, Macaca fuscata. Brain Res 888:83–101.
32. Milad MR, Quirk GJ (2012): Fear extinction as a model for translational neuroscience: Ten years of progress. Annu Rev Psychol 63: 129–151.
33. Shin LM, Lasko NB, Macklin ML, Karpf RD, Milad MR, Orr SP, *et al*. (2009): Resting metabolic activity in the cingulate cortex and vulnerability to posttraumatic stress disorder. Arch Gen Psychiatry 66:1099–1107.
34. Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, *et al*. (2004): Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry 61:168–176.
35. Bremner JD (1999): Alterations in brain structure and function associated with post-traumatic stress disorder. Semin Clinical Neuropsychiatry 4:249–255.
36. Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS (1999): Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. Biol Psychiatry 45:806–816.
37. Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, *et al*. (2001): Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. Am J Psychiatry 158:1920–1922.
38. Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, *et al*. (1999): Brain activation in PTSD in response to trauma-related stimuli. Biol Psychiatry 45:817−826.
39. Lindauer RJ, Booij J, Habraken JB, Uylings HB, Olff M, Carlier IV, *et al*. (2004): Cerebral blood flow changes during script-driven imagery in police officers with posttraumatic stress disorder. Biol Psychiatry 56:853–861.
40. Pissiota A, Frans O, Fernandez M, von Knorring L, Fischer H, Fredrikson M (2002): Neurofunctional correlates of posttraumatic stress disorder: A PET symptom provocation study. Eur Arch Psychiatry Clin Neurosci 252:68–75.
41. Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, *et al*. (1997): A positron emission tomographic study of symptom provocation in PTSD. Ann N Y Acad Sci 821:521–523.
42. Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, *et al*. (1999): Regional cerebral blood flow during script-driven

imagery in childhood sexual abuse-related PTSD: A PET investigation. Am J Psychiatry 156:575–584.
43. Rauch SL, Shin LM, Phelps EA (2006): Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research–past, present, and future. Biol Psychiatry 60:376–382.
44. Garfinkel SN, Abelson JL, King AP, Sripada RK, Wang X, Gaines LM, Liberzon I (2014): Impaired contextual modulation of memories in PTSD: An fMRI and psychophysiological study of extinction retention and fear renewal. J Neurosci 34:13435–13443.
45. Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, *et al*. (2000): Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. Biol Psychiatry 47:769–776.
46. Shin LM, Wright CI, Cannistraro PA, Wedig MM, McMullin K, Martis B, *et al*. (2005): A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry 62:273–281.
47. Graham BM, Milad MR (2011): The study of fear extinction: Implications for anxiety disorders. Am J Psychiatry 168:1255–1265.
48. Hughes KC, Shin LM (2011): Functional neuroimaging studies of post-traumatic stress disorder. Expert Rev Neurother 11: 275–285.
49. Jovanovic T, Norrholm SD (2011): Neural mechanisms of impaired fear inhibition in posttraumatic stress disorder. Front Behav Neurosci 5:44.
50. Kim MJ, Loucks RA, Palmer AL, Brown AC, Solomon KM, Marchante AN, Whalen PJ (2011): The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. Behav Brain Res 223:403–410.
51. Parsons RG, Ressler KJ (2013): Implications of memory modulation for post-traumatic stress and fear disorders. Nat Neurosci 16: 146–153.
52. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, *et al*. (2009): Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiatry 66:1075–1082.
53. Courtin J, Bienvenu TC, Einarsson EO, Herry C (2013): Medial prefrontal cortex neuronal circuits in fear behavior. Neuroscience 240:219–242.
54. Ehrlich I, Humeau Y, Grenier F, Ciocchi S, Herry C, Luthi A (2009): Amygdala inhibitory circuits and the control of fear memory. Neuron 62:757–771.
55. Quirk GJ, Russo GK, Barron JL, Lebron K (2000): The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J Neurosci 20:6225–6231.
56. Sierra-Mercado D, Padilla-Coreano N, Quirk GJ (2011): Dissociable roles of prelimbic and infralimbic cortices, ventral hippocampus, and basolateral amygdala in the expression and extinction of conditioned fear. Neuropsychopharmacology 36:529–538.
57. Sotres-Bayon F, Quirk GJ (2010): Prefrontal control of fear: More than just extinction. Curr Opin Neurobiol 20:231–235.
58. Vianna DM, Graeff FG, Brandao ML, Landeira-Fernandez J (2001): Defensive freezing evoked by electrical stimulation of the periaqueductal gray: Comparison between dorsolateral and ventrolateral regions. Neuroreport 12:4109–4112.
59. Vianna DM, Graeff FG, Landeira-Fernandez J, Brandao ML (2001): Lesion of the ventral periaqueductal gray reduces conditioned fear but does not change freezing induced by stimulation of the dorsal periaqueductal gray. Learn Mem 8:164–169.
60. Vianna DM, Landeira-Fernandez J, Brandao ML (2001): Dorsolateral and ventral regions of the periaqueductal gray matter are involved in distinct types of fear. Neurosci Biobehav Rev 25:711–719.
61. Di Scala G, Mana MJ, Jacobs WJ, Phillips AG (1987): Evidence of Pavlovian conditioned fear following electrical stimulation of the periaqueductal grey in the rat. Physiol Behav 40:55–63.
62. Johansen JP, Tarpley JW, LeDoux JE, Blair HT (2010): Neural substrates for expectation-modulated fear learning in the amygdala and periaqueductal gray. Nat Neurosci 13:979–986.
63. Ciocchi S, Herry C, Grenier F, Wolff SB, Letzkus JJ, Vlachos I, *et al*. (2010): Encoding of conditioned fear in central amygdala inhibitory circuits. Nature 468:277–282.
64. Penzo MA, Robert V, Li B (2014): Fear conditioning potentiates synaptic transmission onto long-range projection neurons in the lateral subdivision of central amygdala. J Neurosci 34:2432–2437.
65. Hopkins DA, Holstege G (1978): Amygdaloid projections to the mesencephalon, pons and medulla oblongata in the cat. Exp Brain Res 32:529–547.
66. Duvarci S, Popa D, Pare D (2011): Central amygdala activity during fear conditioning. J Neurosci 31:289−294.
67. Duvarci S, Pare D (2014): Amygdala microcircuits controlling learned fear. Neuron 82:966–980.
68. Haubensak W, Kunwar PS, Cai H, Ciocchi S, Wall NR, Ponnusamy R, *et al*. (2010): Genetic dissection of an amygdala microcircuit that gates conditioned fear. Nature 468:270–276.
69. Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, *et al*. (2012): Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73:553–566.
70. Viviani D, Charlet A, van den Burg E, Robinet C, Hurni N, Abatis M, *et al*. (2011): Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. Science 333:104–107.
71. Li H, Penzo MA, Taniguchi H, Kopec CD, Huang ZJ, Li B (2013): Experience-dependent modification of a central amygdala fear circuit. Nat Neurosci 16:332–339.
72. Maher BA, McIntire RW (1960): The extinction of the CER following frontal ablation. J Comp Physiol Psychol 53:549–552.
73. Streb JM, Smith K (1955): Frontal lobotomy and the elimination of conditioned anxiety in the rat. J Comp Physiol Psychol 48:126–129.
74. Waterhouse IK (1957): Effects of prefrontal lobotomy on conditioned fear and food responses in monkeys. J Comp Physiol Psychol 50: 81–88.
75. Milad MR, Vidal-Gonzalez I, Quirk GJ (2004): Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behav Neurosci 118:389–394.
76. Herry C, Ciocchi S, Senn V, Demmou L, Muller C, Luthi A (2008): Switching on and off fear by distinct neuronal circuits. Nature 454: 600–606.
77. Repa JC, Muller J, Apergis J, Desrochers TM, Zhou Y, LeDoux JE (2001): Two different lateral amygdala cell populations contribute to the initiation and storage of memory. Nat Neurosci 4:724–731.
78. Quirk GJ, Repa C, LeDoux JE (1995): Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: Parallel recordings in the freely behaving rat. Neuron 15:1029–1039.
79. Senn V, Wolff SB, Herry C, Grenier F, Ehrlich I, Grundemann J, *et al*. (2014): Long-range connectivity defines behavioral specificity of amygdala neurons. Neuron 81:428–437.
80. Vidal-Gonzalez I, Vidal-Gonzalez B, Rauch SL, Quirk GJ (2006): Microstimulation reveals opposing influences of prelimbic and infralimbic cortex on the expression of conditioned fear. Learn Mem 13:728–733.
81. Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ (2007): Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. Neuron 53:871–880.
82. Herry C, Garcia R (2002): Prefrontal cortex long-term potentiation, but not long-term depression, is associated with the maintenance of extinction of learned fear in mice. J Neurosci 22:577–583.
83. Milad MR, Quirk GJ (2002): Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420:70–74.
84. Burgos-Robles A, Vidal-Gonzalez I, Quirk GJ (2009): Sustained conditioned responses in prelimbic prefrontal neurons are correlated with fear expression and extinction failure. J Neurosci 29: 8474–8482.
85. Cho JH, Deisseroth K, Bolshakov VY (2013): Synaptic encoding of fear extinction in mPFC-amygdala circuits. Neuron 80:1491–1507.
86. Do-Monte FH, Quinones-Laracuente K, Quirk GJ (2015): A temporal shift in the circuits mediating retrieval of fear memory. Nature 519: 460–463.

87. Penzo MA, Robert V, Tucciarone J, De Bundel D, Wang M, Van Aelst L, *et al*. (2015): The paraventricular thalamus controls a central amygdala fear circuit. Nature 519:455–459.
88. Courtin J, Chaudun F, Rozeske RR, Karalis N, Gonzalez-Campo C, Wurtz H, *et al*. (2014): Prefrontal parvalbumin interneurons shape neuronal activity to drive fear expression. Nature 505:92–96.
89. Dupret D, O'Neill J, Pleydell-Bouverie B, Csicsvari J (2010): The reorganization and reactivation of hippocampal maps predict spatial memory performance. Nat Neurosci 13:995–1002.
90. Ego-Stengel V, Wilson MA (2010): Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. Hippocampus 20:1–10.
91. Huxter J, Burgess N, O'Keefe J (2003): Independent rate and temporal coding in hippocampal pyramidal cells. Nature 425: 828–832.
92. Huxter JR, Senior TJ, Allen K, Csicsvari J (2008): Theta phase-specific codes for two-dimensional position, trajectory and heading in the hippocampus. Nat Neurosci 11:587–594.
93. Likhtik E, Stujenske JM, Topiwala MA, Harris AZ, Gordon JA (2014): Prefrontal entrainment of amygdala activity signals safety in learned fear and innate anxiety. Nat Neurosci 17:106–113.
94. Stujenske JM, Likhtik E, Topiwala MA, Gordon JA (2014): Fear and safety engage competing patterns of theta-gamma coupling in the basolateral amygdala. Neuron 83:919–933.
95. Schiller D, Monfils MH, Raio CM, Johnson DC, Ledoux JE, Phelps EA (2010): Preventing the return of fear in humans using reconsolidation update mechanisms. Nature 463:49–53.
96. Bouton ME (2002): Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. Biol Psychiatry 52:976–986.
97. Kroes MCW, Tendolkar I, van Wingen GA, van Waarde JA, Strange BA, Fernández G (2014): An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. Nat Neurosci 17: 204–206.
98. Koek RJ, Langevin J-P, Krahl SE, Kosoyan HJ, Schwartz HN, Chen JW, *et al*. (2014): Deep brain stimulation of the basolateral amygdala for treatment-refractory combat post-traumatic stress disorder (PTSD): Study protocol for a pilot randomized controlled trial with blinded, staggered onset of stimulation. Trials 15:356.
99. Saunders N, Downham R, Turman B, Kropotov J, Clark R, Yumash R, Szatmary A (2014): Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. Neurocase 21:271–278.
100. Isserles M, Shalev AY, Roth Y, Peri T, Kutz I, Zlotnick E, Zangen A (2013): Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder–a pilot study. Brain Stimul 6:377–383.
101. Watts BV, Landon B, Groft A, Young-Xu Y (2012): A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Brain Stimul 5:38–43.
102. Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanhã C, *et al*. (2010): Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. J Clin Psychiatry 71: 992–999.
103. Lisanby SH (2007): Electroconvulsive therapy for depression. N Engl J Med 357:1939–1945.
104. Margoob MA, Ali Z, Andrade C (2010): Efficacy of ECT in chronic, severe, antidepressant- and CBT-refractory PTSD: An open, prospective study. Brain Stimul 3:28–35.
105. Bioulac B, Garcia L, Michelet T, Aouizerate B, Guehl D, Gross CE, *et al*. (2014): Cortico-subcortico-cortical loops, networks, high frequency stimulation: From experimental studies to clinical practice. Acad Natl Chir 13:12–23.
106. Kim DR, Pesiridou A, O'Reardon JP (2009): Transcranial magnetic stimulation in the treatment of psychiatric disorders. Curr Psychiatry Rep 11:447–452.
107. Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanha C, *et al*. (2010): Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. J Clin Psychiatry 71:992–999.
108. Milad MR, Vidal-Gonzalez I, Quirk GJ (2004): Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behav neurosci 118:389–394.
109. Peters J, Kalivas PW, Quirk GJ (2009): Extinction circuits for fear and addiction overlap in prefrontal cortex. Learn Mem 16:279–288.
110. Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA, *et al*. (2002): Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. Am J Psychiatry 159:269–275.
111. Critchley HD, Nagai Y, Gray MA, Mathias CJ (2011): Dissecting axes of autonomic control in humans: Insights from neuroimaging. Auton Neurosci 161:34–42.
112. Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, *et al*. (2003): Human cingulate cortex and autonomic control: Converging neuroimaging and clinical evidence. Brain 126:2139–2152.
113. Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215–222.
114. Harmer CJ, Thilo KV, Rothwell JC, Goodwin GM (2001): Transcranial magnetic stimulation of medial-frontal cortex impairs the processing of angry facial expressions. Nat Neurosci 4:17–18.
115. Walsh V, Pascual-Leone A (2003): Transcranial magnetic stimulation: A neurochronometrics of mind. Cambridge, MA: MIT Press.
116. Hallett M, Chokroverty S (2005): Magnetic Stimulation in Clinical Neurophysiology, 2nd ed. Philadelphia: Elsevier Butterworth-Heinemann.
117. Benali A, Trippe J, Weiler E, Mix A, Petrasch-Parwez E, Girzalsky W, *et al*. (2011): Theta-burst transcranial magnetic stimulation alters cortical inhibition. J Neurosci 31:1193–1203.
118. Funke K, Benali A (2011): Modulation of cortical inhibition by rTMS - findings obtained from animal models. J Physiol 589:4423–4435.
119. Siegle JH, Wilson MA (2014): Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. Elife 3:e03061.
120. Stark E, Eichler R, Roux L, Fujisawa S, Rotstein HG, Buzsaki G (2013): Inhibition-induced theta resonance in cortical circuits. Neuron 80:1263–1276.
121. Wulff P, Ponomarenko AA, Bartos M, Korotkova TM, Fuchs EC, Bahner F, *et al*. (2009): Hippocampal theta rhythm and its coupling with gamma oscillations require fast inhibition onto parvalbumin-positive interneurons. Proc Natl Acad Sci U S A 106:3561–3566.