

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
<http://dx.doi.org/10.1016/j.biopsych.2015.03.017>

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

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 CEI contains two populations of inhibitory neurons forming a disinhibitory microcircuit controlling the activity of PAG-projecting CEm neurons. This microcircuit is composed of CEI inhibitory neurons activated during CS presentations (CEI_{ON} neurons), which inhibit protein kinase C-delta-expressing (PKC- δ^{+}) CEI neurons (CEI_{OFF} neurons) (Figure 2A). CS-evoked inhibition of CEI_{OFF}

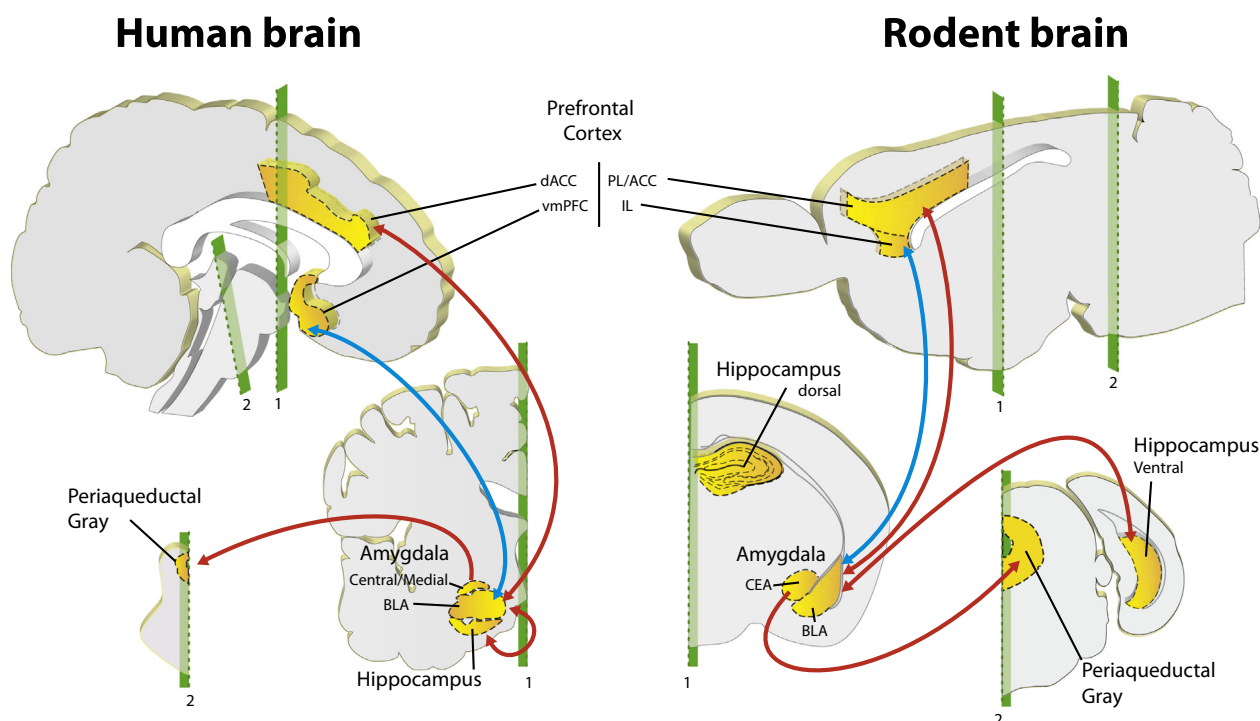


Figure 1. Human and rodent homologous neuronal structures involved in fear expression and recovery. The neuronal structures classically involved in fear expression and recovery in humans and rodents consist of the amygdala, composed of the basolateral amygdala (BLA), and central amygdala (central/medial 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 CEI inhibitory neurons expressing the oxytocin receptor (OR^+) was found to inhibit PAG-projecting CEm neurons. Consistently, the activation of OR^+ -expressing CEI 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 $PKC-\delta^+$ CEI neurons express the OR , suggesting that the oxytocin-mediated suppression of fear is mediated by inhibition of $PKC-\delta^+$ CEI neurons, which, consequently, may disinhibit PAG-projecting CEm neurons (68–70).

In addition to the classical CEI-CEm-PAG pathway, it was recently demonstrated that a class of somatostatin-expressing (SOM^+) CEI 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^+ CEI 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 CEI neurons, around 80% were SOM^+ neurons. All together, these data highlight two parallel circuits linking the CEI and PAG, which likely

support conditioned fear behavior by increasing the activity of PAG-projecting CEm neurons and/or PAG-projecting SOM^+ CEI 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 $PKC-\delta^+$ CEI neurons and SOM^+ CEI 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

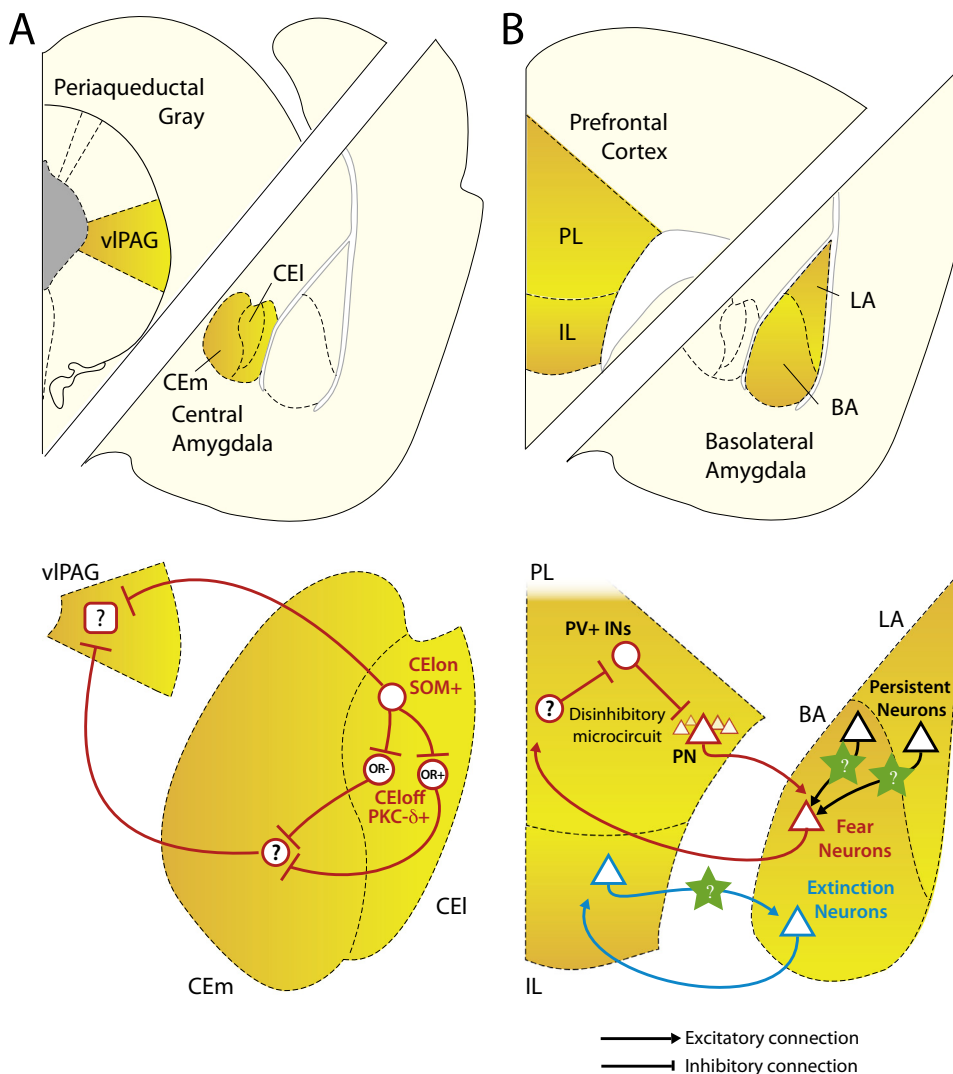


Figure 2. Novel neuronal circuits involved in fear expression and recovery. **(A)** A first circuit of fear expression located in the central amygdala is composed of lateral subdivision of the central amygdala (CEI) inhibitory neurons activated during presentations of conditioned stimuli (CEI_{ON} neurons), which preferentially inhibit a second class of CEI neurons (CEI_{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 (vPAG) is associated with fear expression and recovery. A subset of CEI_{ON} neurons also expresses somatostatin (SOM) and directly projects to the vPAG 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 CEI 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 non-invasive 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, CEI SOM⁺ neurons projecting to the PAG, or CEI_{ON} and CEI_{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.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by grants from the French National Research Agency (ANR-2010-BLAN-1442-01; ANR-10-EQPX-08 OPTOPATH; LABEX BRAIN ANR 10-LABX-43, LABEX TRAIL ANR 10-LABX-57), the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC Grant agreement n°281168, and the Conseil Régional d'Aquitaine.

We thank the members of the Herry laboratory for helpful discussions and comments on this manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Institut National de la Santé et de la Recherche Médicale U862 (CD, JC, RRR, MCB, VD, CH), Neurocenter Magendie, Physiopathologie de la Plasticité Neuronale; Université de Bordeaux (MCB, VD), Institut de Bio-imagerie de Bordeaux; Unite Mixte de Recherche Centre National de la

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Received Nov 4, 2014; revised Feb 18, 2015; accepted Mar 11, 2015.

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.biopsych.2015.03.017>.

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