Neurobiological advances of learned fear in humans

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Abstract

In the whole animal kingdom, fear learning is an essential process that allows living beings to survive. Therefore, revealing the neurophysiological processes that govern the expression of emotional fear memory and exploring its neurobiological underpinnings are the imperatives of affective neuroscience. Learned fear memories activate defensive behaviors in anticipation of harm, thus minimizing the impact of the threat. However, despite a century of research, the neural circuitry underlying fear learning in humans is still a matter of debate. This editorial will discuss recent evidence of the neural and behavioral correlates of fear learning in humans, with an emphasis on the role of the human prefrontal cortex (PFC).

Key words: prefrontal cortex, amygdala, hippocampus, fear conditioning, fear neural network

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The state of art

Learning to recognize and respond to certain stimuli or external contingencies that signal imminent threats is a widely useful and adaptable function for both animals and humans.[1] Fear conditioning is the most frequently adopted experimental design to investigate this circumstance that produces both behaviorally and physiologically conditioned responses.[2] From an evolutionary perspective, it is highly advantageous to preserve clear memories of the main significant experiences in life. Nonetheless, the so-called indissoluble nature of emotional memory can be extremely damaging and have negative consequences for those individuals who have experienced traumatic events and may endure dreadful memories and severe anxiety. For these reasons, fear conditioning is broadly acknowledged to be a model for translational framework of psychiatric disorders.[3–6] Thus, to further understand mechanisms of fear learning, many new techniques that allow studying physiological responses of fear conditioning are being developed. These techniques might be applied as measures for dysfunctional and altered fear learning and may help in identifying the individuals who are at risk for developing psychiatric disorders.[5] In fact, human fear conditioning is generally investigated on different levels: as subjective verbal reports about the experienced fear, as well as behavioral, physiological and neurobiological changes.[7,8] Among these, physiological changes are the most frequently used measures in the study of human acquired fear memories, as a consequence of their benefit of being unaffected by the participant itself, as well as because of the possibility of a direct comparison with animal research.

Pavlovian fear conditioning is one of the most widely investigated fear-induced behavioral models in the history of cognitive psychology and behavioral neuroscience. It was developed upon the appetitive conditioning paradigm utilized by Pavlov in animals (1903/1928). Its effect occurs as a consequence of repetitive association of an initially innocuous stimulus (i.e., a tone) with an innately aversive stimulus (i.e., a shock pulse). By associating cue to consequence, stimulus presentation usually induces different types of psychophysiological reactions indicating fear. This simple procedure is a fundamental paradigm not only for behavioral and cognitive sciences, but also for medicine, since its application is useful in both psychiatry and neurology. It has taken almost a century of scientific investigation to utilize the classic fear conditioning paradigm in both animals and humans[9] in order to gain a broad and thorough knowledge of learned fear and its associated processes, such as learning mechanisms, memorization and retrieval. This experimental and clinical paradigm has been extremely effective and valuable in defining the psychological processes governing the genesis and expression of fear and the functioning of emotional and general memory, together with uncovering the neurobiological basis of emotion and learning in healthy subjects and psychiatric populations.[6,10,11]

The neurobiological model

Currently, the fear conditioning framework has moved beyond the realm of associative learning theory and has become a framework of substantial interest in the neuroscience of learning, memory and emotion.[12,13] Neural circuits have been mapped, synaptic plasticity in these circuits has been identified, and biochemical and genetic investigations have begun disentangling the mechanisms of fear memories.[3,14–17] However, despite a century of research, the neural circuitry underlying fear learning in humans is still a matter of debate. Modern neuroimaging technologies have made a significant contribution to the understanding of neuroanatomical brain circuits of human fear conditioning.[18] Specifically, amygdala plays a key role in the acquisition of fear learning, while the prefrontal cortex (PFC) and hippocampus are 2 other crucial neural structures that contribute to this process, representing together the neural network of fear conditioning.[19–21] It is broadly assumed that connections between these regions govern the acquisition, storage, retrieval, expression, and contextual modulation of fear conditioning (for a review, see the paper by Milad and Quirk[22]). In accordance to animal model research, functional neuroimaging, ad hoc lesion studies, and morphology, extinction of previously learned fear is dependent on the integrated functioning of this network, indicating that the brain mechanisms underlying fear acquisition and extinction are phylogenetically maintained throughout species.[23]

Over the last century, ad hoc surgical lesions, pharmacological drug administration and physiological data from animal and human studies have established a comprehensive framework of the neural network that supports fear conditioning. Among all, when the amygdala involvement in fear conditioning was recognized, it was acknowledged as the key structure of this network.[2] Precisely, this brain region is commonly recognized as 'the locus of fear conditioning'.[15] Furthermore, anatomical studies highlighted the interactions between the central nucleus of the amygdala and downstream structures involved in the expression of fear conditioned responses, namely the hypothalamus, periaqueductal gray, pons, and other brainstem regions.[24] Other studies reported the inhibitory mechanisms within the amygdala that have been involved in fear extinction as well, including the lateral division of the central nucleus,[25] and inhibitory cells within the lateral and basolateral nuclei.[26]

Another structure, the hippocampus, is considered essential in contextual fear learning, along with the acquisition and the extinction of context conditioning: lesion studies have provided pivotal insights on the direct projections that the ventral hippocampus (vHPC) has with both infralimbic cortex (IL, in PFC) and the basolateral amygdala,[27] suggesting a crucial role of this region in the modulation of contextual fear responses.[28] In addition, the hippocampus is supposed to be necessary

in monitoring the context-specific recall of extinction, both directly through connections with the amygdala and indirectly via projections to the ventromedial PFC (vmPFC) (for a review, see the paper by Maren et al.[29]). Moreover, it has been acknowledged that different hippocampal subregions are involved in different human behavior features – specifically, the dorsal part in spatial-related behaviors and the ventral region in anxiety-related behaviors (for a review, see the paper by Bannerman et al.[30]). Increasing evidence suggests that the hippocampus and its subregions are involved in several aspects of fear conditioning.[15]

Crucially, latest available evidence has identified the PFC as a critical core component in the neural circuit underlying fear conditioning, particularly for the ability of PFC to bidirectionally modulate the expression of previously learned fear. On one hand, the activation in the dorsomedial PFC (dmPFC) occurs for the long-term storage and retrieval of old memories[31]; on the other, the vmPFC forms strong reciprocal connections with the amygdala and other subcortical structures as well as with the lateral cortex. Thus, this subregion seems to be necessary for controlling fear relative to a stimulus that no longer predicts danger,[32] representing a relay-station for "bottom-up" information from limbic and subcortical structures signaling emotion detection, as well as for information from lateral PFC (LPFC), conveying response selection and control.[33] Furthermore, Harrison et al.[34] have suggested different contributions of anterior and posterior subregions of the vmPFC to the fear learning processes, showing greater anterior vmPFC activity in response to a safety stimulus, as it is likely to compute the value or meaning of safety signals. Nonetheless, recent work suggests that vmPFC may also have a crucial role in fear acquisition, which is processed in its posterior subregion[35]: crucially, naturally occurring bilateral lesions in the human vmPFC were found to compromise fear conditioning (measured by skin conductance responses), proving that fear conditioning was impaired due to brain injury.[36] These findings were supported in a recent meta-analysis[21] that identified greater activation of the posterior vmPFC (BA11) during late fear conditioning, providing potential causal evidence of a crucial role of the mid-posterior vmPFC in the acquisition of fear.

Converging lines of research have also brought insight on the involvement of PFC in the extinction of fear learning: in concert with the animal studies, neuroimaging studies reported that, besides amygdala activation, vmPFC is particularly important for consolidation of the extinction memory and is especially involved in the recall of extinction in subsequent testing.[37] In particular, this subregion may not simply inhibit the expression of amygdala-dependent conditioned threat responses, but signal a change in previously acquired contingencies in order to select the most appropriate response to the current situation.[32] The extinction of conditioned fear appears to involve also dorsolateral PFC (dlPFC). This could be due to its capacity of shifting the attention from the stimulus to the context, but may also be a consequence of its role as a site of explicit short-term memory processes in humans, aimed at maintaining the trace interval.[38]

Importantly, consistently with signs of PFC functional impairment, it has been observed that patients with posttraumatic stress disorder (PTSD) show normal conditioned fear acquisition and extinction, but appear to be impaired in the recall of extinction memory the following day.[39] Specifically, extinction recall was compromised due to the hypoactivation in the vmPFC and hyperactivation in the dorsal anterior cingulate cortex (dACC).[40] Similar findings were also observed in schizophrenic patients with functionally damaged vmPFC.[41] Taking everything into consideration, this evidence reveals that fear conditioning circuits may be altered in many different psychiatric disorders in humans.[42]

Conclusions and future perspectives

In conclusion, functional alterations of the neural network underlying fear conditioning or in the emotional regulatory mechanisms might contribute to the etiology of anxiety-related disorders, including panic disorder, specific phobias and PTSD.[43] These altered mechanisms are regarded as pivotal factors in the pathogenesis and development of psychiatric disorders characterized by anxiety.[44–46] Hence, a deep understanding of the psychological and molecular mechanisms underlying such disorders is necessary, and fear conditioning paradigm appears to be the most effective for this purpose. Furthermore, a deeper understanding of fear learning neural networks may also contribute to the advancement of alternative, more precise and individualized treatments for psychiatric disorders.

On this note, some issues and questions come to mind. According to corroborated literature, the human PFC modulates the activity of the amygdala and hippocampus after fear conditioning (i.e., extinction learning) like in animals; however, such assumption is based on limited empirical data. Differently from the classical view,[47] recent work suggests that the vmPFC may also play a major role in the acquisition of fear,[21,34–36,48] as processed within its posterior subregion.[49]

Consequently, it is plausible to assume that there are differences between humans and animals in the functional neuroarchitecture of PFC. Thus, it is reasonable and timely relevant now to address this question: what exactly is the role of the prefrontal cortex in human fear conditioning?

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References

1. Bouton ME. Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biol Psychiatry*. 2002;52(10):976–986. doi:10.1016/s0006-3223(02)01546-9
2. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000; 23(1):155–184. doi:10.1146/annurev.neuro.23.1.155
3. Milad MR, Quirk GJ. Fear extinction as a model for translational neuroscience: Ten years of progress. *Annu Rev Psychol*. 2012;63:129–151. doi:10.1146/annurev.psych.121208.131631
4. Vervliet B, Craske MG, Hermans D. Fear extinction and elapse: State of the art. *Annu Rev Clin Psychol*. 2013;9(1):215–248. doi:10.1146/annurev-clinpsy-050212-185542
5. Sevenster D, Hamm A, Beckers T, Kindt M. Heart rate pattern and resting heart rate variability mediate individual differences in contextual anxiety and conditioned responses. *Int J Psychophysiol*. 2015; 98(3):567–576. doi:10.1016/j.ijpsycho.2015.09.004
6. Borgomaneri S, Battaglia S, Avenanti A, di Pellegrino G. Don't hurt me no more: State-dependent transcranial magnetic stimulation for the treatment of specific phobia. *J Affect Disord*. 2021;286:78–79. doi:10.1016/j.jad.2021.02.076
7. Bradley MM, Lang PJ. Measuring emotion: Behavior, feeling and physiology. In: Lane RD, Nadel L, eds. *Cognitive Neuroscience of Emotion*. New York, USA: Oxford University Press; 2000:242–276.
8. Borgomaneri S, Battaglia S, Sciamanna G, Tortora F, Laricchiuta D. Memories are not written in stone: Re-writing fear memories by means of non-invasive brain stimulation and optogenetic manipulations. *Neurosci Biobehav Rev*. 2021;127:334–352. doi:10.1016/j.neubiorev.2021.04.036
9. Beckers T, Krypotos AM, Boddez Y, Effting M, Kindt M. What's wrong with fear conditioning? *Biol Psychol*. 2013;92(1):90–96. doi:10.1016/j.biopsycho.2011.12.015
10. Craske MG, Hermans D, Vansteenwegen D, eds. *Fear and Learning: From Basic Processes to Clinical Implications*. Washington, USA: American Psychological Association; 2006. doi:10.1037/11474-000
11. Hartley CA, Fischl B, Phelps EA. Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cereb Cortex*. 2011;21(9):1954–1962. doi:10.1093/cercor/bhq253
12. Dunsmoor JE, Niv Y, Daw N, Phelps EA. Rethinking extinction. *Neuron*. 2015;88(1):47–63. doi:10.1016/j.neuron.2015.09.028
13. Dunsmoor JE, Kroes MCW, Moscatelli CM, Evans MD, Davachi L, Phelps EA. Event segmentation protects emotional memories from competing experiences encoded close in time. *Nat Hum Behav*. 2018;2(4):291–299. doi:10.1038/s41562-018-0317-4
14. Maren S. Neurobiology of Pavlovian fear conditioning. *Annu Rev Neurosci*. 2001;24(1):897–931. doi:10.1146/annurev.neuro.24.1.897
15. Kim JJ, Jung MW. Neural circuits and mechanisms involved in Pavlovian fear conditioning: A critical review. *Neurosci Biobehav Rev*. 2006; 30(2):188–202. doi:10.1016/j.neubiorev.2005.06.005
16. Borgomaneri S, Battaglia S, Garofalo S, Tortora F, Avenanti A, di Pellegrino G. State-dependent TMS over prefrontal cortex disrupts fear-memory reconsolidation and prevents the return of fear. *Curr Biol*. 2020;30(18):3672–3679.e4. doi:10.1016/j.cub.2020.06.091
17. Battaglia S, Garofalo S, di Pellegrino G. Context-dependent extinction of threat memories: Influences of healthy aging. *Sci Rep*. 2018; 8(12592):1–13. doi:10.1038/s41598-018-31000-9
18. Sehlmeyer C, Schöning S, Zwitserlood P, et al. Human fear conditioning and extinction in neuroimaging: A systematic review. *PLoS One*. 2009;4(6):e5865. doi:10.1371/journal.pone.0005865
19. Maren S, Quirk GJ. Neuronal signalling of fear memory. *Nat Rev Neurosci*. 2004;5(11):844–852. doi:10.1038/nrn1535
20. Lonsdorf TB, Haaker J, Kalisch R. Long-term expression of human contextual fear and extinction memories involves amygdala, hippocampus and ventromedial prefrontal cortex: A reinstatement study in two independent samples. *Soc Cogn Affect Neurosci*. 2014;9(12): 1973–1983. doi:10.1093/scan/nsu018
21. Fullana MA, Harrison BJ, Soriano-Mas C, et al. Neural signatures of human fear conditioning: An updated and extended meta-analysis of fMRI studies. *Mol Psychiatry*. 2016;21(4):500–508. doi:10.1038/mp.2015.88
22. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*. 2002;420(6911):70–74. doi:10.1038/nature01138
23. Dunsmoor JE, Kroes MCW, Li J, Daw ND, Simpson HB, Phelps EA. Role of human ventromedial prefrontal cortex in learning and recall of enhanced extinction. *J Neurosci*. 2019;39(17):3264–3276. doi:10.1523/JNEUROSCI.2713-18.2019
24. LeDoux JE, Iwata J, Cicchetti P, Reis DJ. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *J Neurosci*. 1988;8(7):2517–2529. doi:10.1523/jneurosci.08-07-02517.1988
25. Sun N, Cassell MD. Intrinsic GABAergic neurons in the rat central extended amygdala. *J Comp Neurol*. 1993;330(3):381–404. doi:10.1002/cne.903300308
26. Mahanty N, Sah P. Calcium-permeable AMPA receptors mediate long-term potentiation in interneurons in the amygdala. *Nature*. 1998;394(6694):683–687. doi:10.1038/246170a0
27. Hugues S, Garcia R. Reorganization of learning-associated prefrontal synaptic plasticity between the recall of recent and remote fear extinction memory. *Learn Mem*. 2007;14(8):520–524. doi:10.1101/lm.625407
28. Gewirtz JC, McNish KA, Davis M. Is the hippocampus necessary for contextual fear conditioning? *Behav Brain Res*. 2000;110(1–2):83–95. doi:10.1016/S0166-4328(99)00187-4
29. Maren S, Phan KL, Liberzon I. The contextual brain: Implications for fear conditioning, extinction and psychopathology. *Nat Rev Neurosci*. 2013;14(6):417–428. doi:10.1038/nrn3492
30. Bannerman DM, Rawlins JNP, McHugh SB, et al. Regional dissociations within the hippocampus: Memory and anxiety. *Neurosci Biobehav Rev*. 2004;28(3):273–283. doi:10.1016/j.neubiorev.2004.03.004
31. Dixsaut L, Gräff J. The medial prefrontal cortex and fear memory: Dynamics, connectivity and engrams. *Int J Mol Sci*. 2021;22(22):12133. doi:10.3390/ijms222212113
32. Phelps EA, Delgado MR, Nearing KI, Ledoux JE. Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*. 2004;43(6): 897–905. doi:10.1016/j.neuron.2004.08.042
33. Myers-Schulz B, Koenigs M. Functional anatomy of ventromedial prefrontal cortex: Implications for mood and anxiety disorders. *Mol Psychiatry*. 2012;17(2):132–141. doi:10.1038/mp.2011.88
34. Harrison BJ, Fullana MA, Via E, et al. Human ventromedial prefrontal cortex and the positive affective processing of safety signals. *Neuroimage*. 2017;152:12–18. doi:10.1016/j.neuroimage.2017.02.080
35. Battaglia S, Harrison BJ, Fullana MA. Does the human ventromedial prefrontal cortex support fear learning, fear extinction or both? A commentary on subregional contributions [published online ahead of print on October 20, 2021]. *Mol Psychiatry*. 2021. doi:10.1038/s41380-021-01326-4
36. Battaglia S, Garofalo S, di Pellegrino G, Starita F. Revaluing the role of vmPFC in the acquisition of Pavlovian threat conditioning in humans. *J Neurosci*. 2020;40(44):8491–8500. doi:10.1523/JNEUROSCI.0304-20.2020
37. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biol Psychiatry*. 2007;62(5): 446–454. doi:10.1016/j.biopsych.2006.10.011
38. Ewald H, Glotzbach-Schoon E, Gerdes ABM, et al. Delay and trace fear conditioning in a complex virtual learning environment-neural substrates of extinction. *Front Hum Neurosci*. 2014;8:1–11. doi:10.3389/fnhum.2014.00323
39. Garfinkel SN, Abelson JL, King AP, et al. Impaired contextual modulation of memories in PTSD: An fMRI and psychophysiological study of extinction retention and fear renewal. *J Neurosci*. 2014;34(40): 13435–13443. doi:10.1523/JNEUROSCI.4287-13.2014
40. Milad MR, Pitman RK, Ellis CB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biol Psychiatry*. 2009;66(12):1075–1082. doi:10.1016/j.biopsych.2009.06.026.
41. Holt DJ, Lebron-Milad K, Milad MR, et al. Extinction memory is impaired in schizophrenia. *Biol Psychiatry*. 2009;65(6):455–463. doi:10.1016/j.biopsych.2008.09.017
42. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry Online*. 2010;167(7):748–751. doi:10.1176/appi.ajp.2010.09091379
43. Rosen JB, Schulkin J. From normal fear to pathological anxiety. *Psychol Rev*. 1998;105(2):325–350. doi:10.1037/0033-295X.105.2.325

44. Duits P, Cath DC, Lissek S, et al. Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depress Anxiety*. 2015;32(4): 239–253. doi:10.1002/da.22353
45. Lissek S, Baas JMP, Pine DS, et al. Airpuff startle probes: An efficacious and less aversive alternative to white-noise. *Biol Psychol*. 2005; 68(3):283–297. doi:10.1016/j.biopsycho.2004.07.007
46. Lissek S, Powers AS, McClure EB, et al. Classical fear conditioning in the anxiety disorders: A meta-analysis. *Behav Res Ther*. 2005;43(11): 1391–1424. doi:10.1016/j.brat.2004.10.007
47. Schiller D, Delgado MR. Overlapping neural systems mediating extinction, reversal and regulation of fear. *Trends Cogn Sci*. 2010;14(6): 268–276. doi:10.1016/j.tics.2010.04.002
48. Tashjian SM, Zbozinek TD, Mobbs D. A decision architecture for safety computations. *Trends Cogn Sci*. 2021;25(5):342–354. doi:10.1016/j.tics.2021.01.013
49. Taschereau-Dumouchel V, Kawato M, Lau H. Multivoxel pattern analysis reveals dissociations between subjective fear and its physiological correlates. *Mol Psychiatry*. 2020;25(10):2342–2354. doi:10.1038/s41380-019-0520-3