Does the human ventromedial prefrontal cortex support fear learning, fear extinction or both? A commentary on subregional contributions

Does the human ventromedial prefrontal cortex support fear learning, fear extinction or both? A commentary on subregional contributions.

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Abstract

Current models of human fear learning processes emphasize a primary contribution of the ventromedial prefrontal cortex (vmPFC) to fear inhibition (i.e., fear extinction). Here, we discuss crucial findings from recent brain imaging studies that highlight the role of vmPFC and its subregions in how fear is acquired (i.e., fear conditioning).

Since the dawn of psychology, fear conditioning paradigms have been successfully used to reveal the psychological processes that govern the acquisition and expression of emotional memories and their neurobiological underpinnings. From an evolutionary perspective, learned fear serves to activate defensive behaviours in anticipation of harm, thus supporting an organisms' chances of survival and well-being. Fear conditioning has moved beyond the realm of associative learning theory to become a framework of substantial interest in the neuroscience of learning, memory, and emotion. Neural circuits have been mapped, synaptic plasticity in these circuits has been identified, and biochemical and genetic investigations are beginning to disentangle the molecular mechanisms responsible for the storage and expression of fear memories. It is anticipated that these advances will improve our understanding of common mental health conditions characterized by pathological fear and lead to future optimized treatments. However, despite a century of research, the neural circuitry underlying human fear-learning is still a matter of debate. One important issue in this regard relates to the contribution of the ventromedial prefrontal cortex (vmPFC) and its subregions. Specifically, while the predominant view of vmPFC function is that it underlies successful *fear extinction* [1, 2], recent work suggests that it may also play a major role in *fear conditioning* [3–5], as processed within its posterior subregion [6].

In 2020, Battaglia et al. provided direct evidence that naturally occurring bilateral lesions centred on the human vmPFC compromised fear conditioning as measured via skin conductance responses [3]. In this study, patients showed impaired fear conditioning (similar responses to

conditional (CS+) and non-conditional (CS-) stimuli), when compared to patients with a lesion outside of the vmPFC and healthy participants. Furthermore, impaired fear conditioning was found to be selectively correlated with vmPFC damage in a mid-posterior subregion corresponding with Brodmann area (BA) 11 (see Figure 1A). Although classical studies have shown abnormal SCR generation following a similar brain injury [7], vmPFC lesions in the Battaglia study were not found to compromise unconditional responses. This study demonstrated on a psychophysiological level that fear conditioning was impaired due to the patient's brain injury and thus, provided potential causal evidence of a crucial role of the mid-posterior vmPFC in the *acquisition* of fear. Importantly, this recent evidence finds support in the meta-analysis of Fullana et al. (2016), which summarized 27 independent functional MRI human fear conditioning experiments [4]. Specifically, in a sub-analysis that compared early and late phases of fear conditioning (threat vs safety, CS+ vs CS-) across several studies, greater activation of the posterior vmPFC (BA11) was prominently observed during *late conditioning* (see Figure 1B).

These recent observations, which support a facilitatory role of the posterior vmPFC in fear conditioning, have emerged in comparison to broader evidence linking the vmPFC to fear regulatory processes, including fear extinction and safety learning. In the Fullana et al., fear conditioning meta-analysis, it was shown that the anterior vmPFC, in particular, was consistently activated during safety vs threat (CS- vs CS+) presentations, adding to earlier imaging findings [1] (see Figure 1C). Separately, earlier evidence from brain imaging studies suggests that vmPFC activity is *negatively* correlated with sympathetic arousal [2]. However, recent evidence has identified *positive* associations between these variables [2, 8]. These conflicting findings suggest potentially distinct contributions of anterior vs posterior subregions of the vmPFC to affective processes. On the specific topic of fear and safety learning, Tashjian and colleagues have recently hypothesized that fear (i.e., threat) and safety computations can be reliably parsed along a gradient of function that spans posterior-to-anterior vmPFC [6]. In support of this claim, Tashijan and colleagues marshall evidence – synthesized broadly across imaging studies – to suggest that posterior vmPFC activity prepares organisms for anticipated threat, but that the anterior vmPFC, a region with distinct functional connectivity from its posterior counterpart, cues safety both in the presence and absence of threat. Noting that the anterior vmPFC is a central hub of metacognition and the default mode network (DMN), the authors suggest that its role in "safety-seeking" may represent an attempt to restore equilibrium [6]. This hypothesis has been previously advanced in Harrison et al. (2017), which demonstrated that greater anterior vmPFC activation in response to a safety signal (CS-) (see Figure 1D) correlated with increased ratings of positive affect towards it –

suggesting that anterior vmPFC, as a core region of the DMN, likely computes the self-oriented value or meaning of safety signals [5].

Together, these recent findings suggest a broader model of vmPFC function in fear learning and call for a greater focus on studying the contribution of vmPFC subregions [3–6]. The results of these studies might change not only how the neurobiology of human fear learning is characterized but also help refine existing clinical translational models of aberrant fear learning neural processes. In these efforts, it will be important to understand more precisely the computational neural dynamics through which vmPFC subregions underlie fear learning processes, as well as their principal interactions with extended subcortical and cortical components of the brain's so-called 'fear circuit'. Methodological innovation will be key in this endeavour [9], but keeping in mind the need for reproducibility and replication – a noted area of concern in this field of research [10]. Other approaches (e.g., conditioned fear inhibition) are likely to be important for understanding more discrete fear learning neural processes, including the characterization of excitatory versus inhibitory mechanisms. Clinical hypotheses could be tested. For example, lesions of vmPFC subregions could be associated with an increase or decrease in fear acquisition (i.e., fear symptoms after a traumatic experience) depending on the location of the lesion (i.e., posterior vs anterior).

In conclusion, a necessary effort still needs to be made to understand the unclear functional interplay within the vmPFC sub-regions as well as with the other brain structures implicated in human fear learning. Thus, the challenge of the upcoming decade for research in this theoretical framework must be to provide more causal-direct evidence of specific functional-contribution of vmPFC to processing safety-threat information or their relative value, and how specifically vmPFC orchestrates the acquisition of fear.

Declaration of interests

The authors declare no competing interests.

Contributions

SB and MAF conceived the idea. SB wrote the manuscript, MAF and BH provided revisions. All authors approved the final version of the manuscript.

References

1. Schiller D, Delgado MR. Overlapping neural systems mediating extinction, reversal and regulation of fear. Trends Cogn Sci. 2010;14:268–276.

2. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends Cogn Sci. 2011;15:85–93.

3. 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;40:8491–8500.

4. Fullana MA, Harrison BJ, Soriano-Mas C, Vervliet B, Cardoner N, Àvila-Parcet A, et al. Neural signatures of human fear conditioning: An updated and extended meta-analysis of fMRI studies. Mol Psychiatry. 2016;21:500–508.

5. Harrison BJ, Fullana MA, Via E, Soriano-Mas C, Vervliet B, Martínez-Zalacaín I, et al. Human ventromedial prefrontal cortex and the positive affective processing of safety signals. Neuroimage. 2017;152:12–18.

6. Tashjian SM, Zbozinek TD, Mobbs D. A Decision Architecture for Safety Computations. Trends Cogn Sci. 2021;25:342–354.

7. Bechara A, Damasio H, Damasio AR, Lee GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. J Neurosci. 1999;19:5473–5481.

8. Taschereau-Dumouchel V, Kawato M, Lau H. Multivoxel pattern analysis reveals dissociations between subjective fear and its physiological correlates. Mol Psychiatry. 2020;25:2342–2354.

9. Lonsdorf TB, Richter J. Challenges of Fear Conditioning Research in the Age of RDoC. J Psychol. 2017;225:189–199.

10. Lonsdorf TB, Klingelhöfer-Jens M, Andreatta M, Beckers T, Chalkia A, Gerlicher A, et al. Navigating the garden of forking paths for data exclusions in fear conditioning research. Elife. 2019;8:e52465.

Figure Legend

Figure 1. The ventromedial prefrontal cortex in fear conditioning. A) Patients with lesions in the mid-posterior part of the vmPFC show impaired fear conditioning (similar response to CS+ and CS-) as assessed with skin conductance (in orange, a voxel-based lesion-symptom mapping correlation between vmPFC lesion and skin conductance responses) **(**from Battaglia et al. (2020). **B)** Healthy participants show greater functional activation in the posterior vmPFC during late fear conditioning (CS+ versus CS-) compared to early fear conditioning (from Fullana et al., 2016). **C)** Healthy participants show greater functional activation in the anterior vmPFC during fear conditioning (CS- versus CS+) (from Fullana et al., 2016). **D)** In healthy participants, functional activation in the anterior vmPFC during CS- presentation during fear conditioning correlated with increased ratings of positive affect towards the CS- (from Harrison et al. (2017).