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Neuronal coding mechanisms mediating fear behavior

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The behavioral repertoire of an organism can be highly diverse, spanning from social to defensive. How an animal efficiently switches between distinct behaviors is a fundamental question whose inquiry will provide insights into the mechanisms that are necessary for an organism's survival. Previous work aimed at identifying the neural systems responsible for defensive behaviors, such as freezing, has demonstrated critical interactions between the prefrontal cortex and amygdala. Indeed, this foundational research has provided an indispensable anatomical framework that investigators are now using to understand the physiological mechanisms of defined neural circuits within the prefrontal cortex that code for the rapid and flexible expression of defensive behaviors. Here we review recent findings demonstrating temporal and rate coding mechanisms of freezing behavior in the prefrontal cortex. We hypothesize that anatomical features, such as target structure and cortical layer, as well as the nature of the information to be coded, may be critical factors determining the coding scheme. Furthermore, detailed behavioral analyses may reveal subtypes of defensive behaviors that represent the principle factor governing coding selection.

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Introduction

The celebrated American architect Louis Sullivan stated that 'form ever follows function' [1]. Although architects such as Ludwig Mies van der Rohe, one of the directors of the German art school Bahaus, and Le Corbusier advanced this axiom during the modern period, it is observed in domains ranging from advanced aerodynamics engineering of F1 race cars to minimize drag, to the antiquated, such as the high shoulder of Bordeaux bottles intended to collect the sediment of these tannic wines or the thick glass and enlarged punt of Champagne bottles that enhances the strength necessary to contain these pressurized wines. However, due to selective pressure, perhaps biological systems illustrate this truism most consistently. Particularly, the central nervous system is rife with examples of how variations in form can lead to functional heterogeneity among neurons. Indeed, despite the principal similarity of electro-chemical signaling among neurons, the variety of chemical signals, morphology, and physical organization within neuronal populations gives rise to diverse functional properties.

One example of functional heterogeneity in the nervous system is observed when considering the multiple types of neural coding, ranging from rate to temporal coding. These forms of coding have long been described for sensory and cognitive processing, especially for spatial navigation [2–6] and more recently investigated for emotional memories [7••,8]. Decades of research have led to a global understanding of the interactions occurring between anatomically defined circuits during associative fear learning. This work has provided a comprehensive description of the functional relationship between the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), and periaqueductal grey matter (PAG) to support associative fear learning. Although the specificity of the intrinsic and extrinsic anatomical connectivity of mPFC and BLA is continually under refinement [9], over the past years it has become reasonably well understood how sensory inputs shape neuronal responses in the mPFC and BLA during associative learning. In particular, whereas the formation of conditioned fear memories is known to depend on the integrity of the BLA, there is now strong evidence that the mPFC plays a key role in the regulation of fear behavior, including active (avoidance) and passive (freezing) fear responses [10–15]. Moreover, increasing evidence demonstrates that both the BLA and mPFC can regulate fear behavior through direct projections to the PAG [16•,17•]. Yet brain functions are not only derived from anatomically defined circuits, but also by specific functional dynamics. This is particularly true for neuronal circuits mediating fear behavior, which have been shown to exhibit distinct coding strategies depending on the network studied [7••,11,16•,18]. However, to date, the factors that determine how information is encoded and driven in specific fear circuits is unclear. In this short review, we discuss recent work investigating specific coding mechanisms linked to distinct fear circuits and explore the hypothesis

that defined mPFC fear circuits are tuned to specific forms of neural coding.

Rate coding within BLA-mPFC networks

Among neural coding schemes, rate or frequency coding is the most intuitive one in which neuronal firing increases as a function of stimulus intensity [19]. During rate coding, the precise timing of firing is less important than the average firing rate. Although this form of neuronal coding has largely been described in the past, it is strongly limited by the fact that over long distances, rate codes are suboptimal for the fast information transmission that is required for rapid behavioral adaptation when facing threatening stimuli [20,21]. Moreover, rate codes provide much less information content compared to other coding strategies [22]. Nevertheless, over the past decades, rate code analyses have been the choice methodology to address whether, and how, specific cell types within fear networks change their activity in response to threatening events [12]. During fear conditioning, a conditioned stimulus (the CS, typically auditory) is repeatedly associated with a mild unconditioned stimulus (the US, usually a mild footshock), which leads to a constellation of conditioned fear responses including freezing behavior. Following conditioning, BLA PNs display short-term latency CS-evoked activity [23–28], which is specific to the CS associated with the US [27,29]. Similarly, short-latency CS-evoked activity has been recorded in the mPFC during fear expression in both PN and IN populations [11,18,30,31]. Importantly, among the PNs recorded in the mPFC, ~25% have been shown to display sustained elevated activity during fear episodes, strongly suggesting that a pure rate coding mechanism could encode the expression of fear behavior [18].

Temporal coding within BLA-mPFC networks

Recent studies have challenged this rate coding view by demonstrating the contribution of a temporal coding scheme for behavioral expression of fear. During temporal coding, neurons with different and specific firing sequences may cooperate and collectively provide information. In temporal coding, precise timing of firing is important, whereas average firing rates can remain stable [32,33]. Therefore, distributed firing within a neuronal assembly is requisite for temporal coding, which endows great flexibility. The obvious advantage of temporal coding is that neurons could rapidly switch between multiple functional networks according to sensory and internal inputs to generate specific behavioral outputs. Brain oscillations are thought to be instrumental in temporal coding by binding cell assemblies, organizing individual firing into meaningful collective activity, and coordinating remote areas [2,34].

Previous studies are shedding light on these questions. For instance, using an appetitive trace-conditioning task, Paz and colleagues demonstrated that theta oscillations (3–12 Hz) synchronize mPFC cells in a learning-dependent manner and that mPFC activity modulates the transfer of information during learning [8,35]. Moreover, theta range oscillations in the mPFC were strongly correlated with fear memory and fear expression. Besides theta oscillations, increased gamma oscillations (30–80 Hz) have been observed in the mPFC during fear behavior and are hypothesized to promote the synchronization of neuronal assemblies during emotional states [36•]. Importantly, fast gamma oscillations have also been linked to oscillatory coupling between two remote areas at a time scale consistent with spike-timing dependent plasticity [37] and could provide a causal mechanism for orchestrating temporal coding during fear-related behavior. More recently we investigated the contribution of mPFC parvalbumin-expressing INs (PVINs) during fear expression encoding [11]. We observed that during post-conditioning CS presentations, PVINs were strongly inhibited which promoted fear expression via two mechanisms: a disinhibitory mechanism which increased the excitability of mPFC PNs and the resetting of slow local theta oscillations (8–12 Hz) that synchronizes prefrontal PNs projecting to BLA to drive fear expression. Recent genetic strategies provided a detailed account of mechanisms regulating the mPFC-BLA circuit, placing particular emphasis a subpopulation of PVINs, chandelier cells. The authors observed that chandelier cells preferentially contact mPFC PNs projecting to the BLA and control their firing activity [38•]. Interestingly, recent studies have investigated synchronization in this mPFC-BLA circuit during the encoding of fear and safety signals [36•,39]. In these studies, mice were submitted to differential fear conditioning and extinction. In mice discriminating a safe CS (CS^-) from an aversive one (CS^+), the authors observed a strong theta (4–12 Hz) synchronization between the mPFC and BLA [39]. Moreover, enhanced fear behavior during retrieval was associated with a strong coupling between BLA theta and gamma oscillations, whereas during safety periods, BLA gamma oscillations and firing activities were entrained by mPFC theta oscillations [36•]. In accordance, BLA to mPFC synchronization in the theta range similarly encoded aversive stimuli during learning [40•]. Furthermore, the phase in which slow prefrontal oscillations bind assembly spiking was demonstrated to be a critical component in fear expression. Indeed, mPFC oscillations ~4 Hz causally determine the dynamics of freezing behavior through phase-specific recruitment of neuronal assemblies and the synchronization mPFC-BLA networks [7••,41•]. Importantly, these neuronal assemblies were composed of mPFC cells with heterogeneous CS-evoked responses, suggesting a functional segregation between cells displaying sharp changes in firing activity [18] and those participating to neuronal assemblies [7••]. All together these data indicate that rate and temporal coding coexist within the mPFC-BLA network to control the valence, magnitude, timing, and duration of fear responses.