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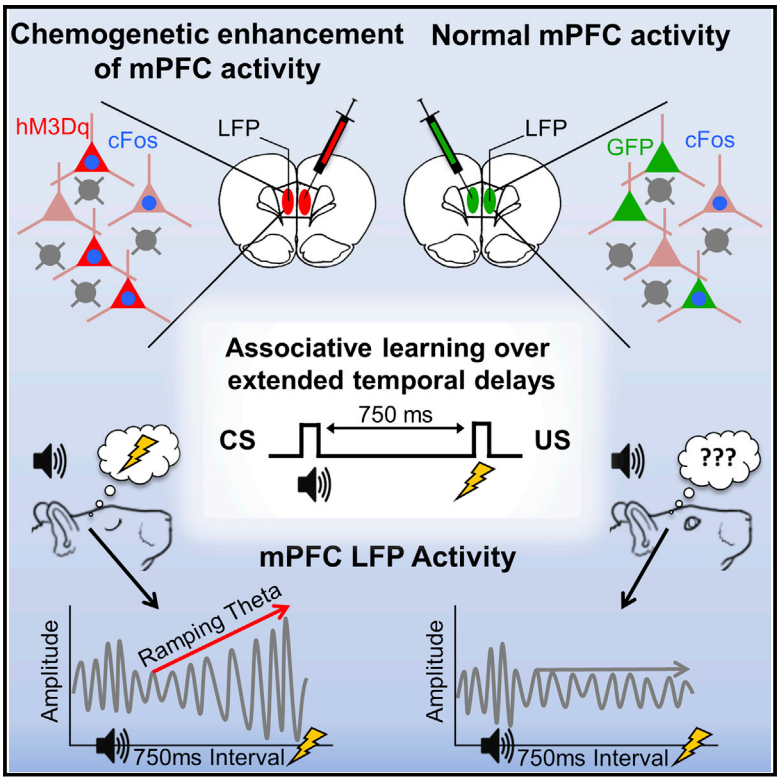
Enhancing Prefrontal Neuron Activity Enables Associative Learning of Temporally Disparate Events

Graphical Abstract



Highlights

- Increasing excitation in the rat mPFC enables learning over extended time intervals
- LFP theta and beta are ramped up during successful learning
- LFP ramping is correlated with conditioned responses on a trial-by-trial basis
- The ramping is not correlated with the same movements in other conditions

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In Brief

Volle et al. show that a relatively coarse manipulation of the mPFC in rats facilitates the formation of adaptive associations between temporally disparate experiences and demonstrates physiological correlates of the cognitive enhancement.

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Enhancing Prefrontal Neuron Activity Enables Associative Learning of Temporally Disparate Events

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SUMMARY

The ability to link events that are separated in time is important for extracting meaning from experiences and guiding behavior in the future. This ability likely requires the brain to continue representing events even after they have passed, a process that may involve the prefrontal cortex and takes the form of sustained, event-specific neuron activity. Here, we show that experimentally increasing the activity of excitatory neurons in the medial prefrontal cortex (mPFC) enables rats to associate two stimuli separated by a 750-ms long temporal gap. Learning is accompanied by ramping increases in prefrontal theta and beta rhythms during the interval between stimuli. This ramping activity predicts memory-related behavioral responses on a trial-by-trial basis but is not correlated with the same muscular activity during non-memory conditions. Thus, the enhancement of prefrontal neuron excitability extends the time course of evoked prefrontal network activation and facilitates the formation of associations of temporally disparate, but correlated, events.

INTRODUCTION

On a moment-to-moment basis, the brain is exposed to a medley of stimuli, which are chunked together according to correlations experienced in the past. Often, stimuli that are correlated with one another also co-occur in time, but in some cases, stimuli predict future positive or negative events that occur after temporal gaps. Previous work in the medial prefrontal cortex (mPFC) of rodents suggests that this region is important for learning associations between temporally discontiguous events (Gilmartin and Helmstetter, 2010; Gilmartin et al., 2013; Runyan et al., 2004; Takehara-Nishiuchi et al., 2005). The mPFC has also been implicated in other behaviors that rely on the temporal organization of information, including learning stimulus sequences (Barker et al., 2007; Devito and Eichenbaum, 2011; Hannesson et al., 2004a; Mitchell and Laiacona, 1998) and remembering which locations in an environment have been previously visited (Chiba et al., 1997; Hannesson et al., 2004b). At the physiological level, mPFC neurons have been found to sustain firing rates over short temporal intervals (Hattori et al., 2014; Rainer et al., 1999; Siegel, 2014; Takehara-Nishiuchi and McNaughton, 2008). These patterns parallel well-established observations of neuron activity in the primate dorsolateral prefrontal cortex (dlPFC) during working memory tasks (Fuster and Alexander, 1971; Kojima and Goldman-Rakic, 1982; Quintana and Fuster, 1992). Accordingly, increased neuron firing in the mPFC during intervening gaps may signal a relevant correlation between two stimuli. To test this possibility, we activated excitatory neurons in the mPFC of rats by using a chemogenetic approach (Alexander et al., 2009) and examined the effect on associative learning across otherwise prohibitively long delays. We also analyzed the impact of increased excitation on local network dynamics by recording local field potentials (LFPs) from the mPFC during learning. We found that enhanced prefrontal neuron activity enabled rats to form associations across extended delays and that this accompanied increases in LFP theta and beta amplitudes during the delays.

RESULTS

Excitatory Pyramidal Neurons in the mPFC Were Selectively Activated by Virally Transduced DREADDs

We used recombinant adeno-associated viral vectors (rAAVs) to transduce the evolved human M3-muscarinic receptor (hM3Dq) gene into a subset of pyramidal neurons in the prelimbic region of the mPFC in adult male Long-Evans rats. The hM3Dq receptor has a high affinity for the pharmacologically inert ligand, clozapine-*N*-oxide (CNO) but not endogenous neurotransmitters (Alexander et al., 2009). To target the expression in excitatory pyramidal neurons, the hM3Dq gene was expressed under the control of the α-CaMKII promoter. As a control, we used a rAAV vector that carried the GFP gene under the control of the α-CaMKII promoter. The expression of hM3Dq receptors (detected by co-expression of mCherry) was restricted to the prelimbic region