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Anxiety Cells in a Hippocampal-Hypothalamic Circuit

Highlights

- Anxiogenic stimuli are differentially represented along the DV axis of the HPC
- Inhibition of the vHPC in anxiogenic environments reduces avoidance behavior
- vCA1 outputs to LHA but not BA control anxiety-related behavior
- The majority of vCA1-LHA projection neurons represent anxiogenic stimuli

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In Brief

Jimenez et al. show that vCA1 neurons exhibit stable representations of anxiogenic environments that are required for avoidance behavior. The direct projection from vCA1 to the lateral hypothalamus is enriched in anxiety cells and can rapidly control anxiety-related behavior.

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Anxiety Cells in a Hippocampal-Hypothalamic Circuit

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SUMMARY

The hippocampus is traditionally thought to transmit contextual information to limbic structures where it acquires valence. Using freely moving calcium imaging and optogenetics, we show that while the dorsal CA1 subregion of the hippocampus is enriched in place cells, ventral CA1 (vCA1) is enriched in anxiety cells that are activated by anxiogenic environments and required for avoidance behavior. Imaging cells defined by their projection target revealed that anxiety cells were enriched in the vCA1 population projecting to the lateral hypothalamic area (LHA) but not to the basal amygdala (BA). Consistent with this selectivity, optogenetic activation of vCA1 terminals in LHA but not BA increased anxiety and avoidance, while activation of terminals in BA but not LHA impaired contextual fear memory. Thus, the hippocampus encodes not only neutral but also valence-related contextual information, and the vCA1-LHA pathway is a direct route by which the hippocampus can rapidly influence innate anxiety behavior.

INTRODUCTION

Fear and anxiety are emotional responses to perceived threats, with proximal threats eliciting fear and distal threats eliciting anxiety. Under normal conditions, anxiety states promote adaptive avoidance behaviors that are critical to safely navigating an environment. Execution of appropriate avoidance behaviors requires the rapid recognition of threatening stimuli and routing that information to structures that can directly modulate these defensive behaviors.

While avoidance is adaptive under normal conditions, it can become maladaptive when responses are excessive and inappropriate. In humans, a shared feature of a number of anxiety disorders is the overestimation of threat, leading to enhanced avoidance (Jovanovic and Ressler, 2010; Kheirbek et al., 2012). Yet the mechanisms and neural circuits by which normal adaptive avoidance behaviors arise, and how these circuits become disordered in psychiatric illness, remain elusive.

While the hippocampus (HPC) is known to be critical for cognitive processes such as episodic memory and spatial navigation, it is also implicated in the pathogenesis of mood and anxiety disorders. One way the HPC may contribute to both cognitive and mood-related processes is via functional heterogeneity along its dorsoventral axis, with the dorsal HPC contributing to cognitive functions such as learning and memory and the ventral HPC (vHPC) modulating emotional regulation (Fanselow and Dong, 2010; Strange et al., 2014). Lesions of the ventral but not dorsal HPC are anxiolytic, with minimal effect on spatial learning (Bannerman et al., 2002; Kjelstrup et al., 2002; Moser et al., 1995), whereas dorsal HPC lesions affect spatial learning without affecting anxiety-related measures. Moreover, place cells, which are believed to contribute to a spatial representation of the environment, are more abundant, stable, and tuned in dorsal HPC relative to vHPC (Ciocchi et al., 2015; Jung et al., 1994; Keinath et al., 2014; Royer et al., 2010). In addition, recent optogenetic and pharmacological studies indicate that manipulation of the vHPC itself or its inputs and cortical outputs can directly impact anxiety-related behavior (Felix-Ortiz et al., 2013; Kheirbek et al., 2013; Kjaerby et al., 2016; Padilla-Coreano et al., 2016; Parfitt et al., 2017; Samuels et al., 2015; Wu and Hen, 2014).