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Ventral Hippocampus Projections to Prelimbic Cortex Support Contextual Fear Memory

Alexandra O. Cohen[1] **and Heidi C. Meyer**[2]

[1]Department of Psychology, New York University, New York, New York 10003, and [2]Department of Psychiatry, Weill Cornell Medicine, New York, New York 10065

Review of Twining et al.

Learning from and remembering salient features of the environment is essential for survival. Fear conditioning is a well studied experimental model that can be used to delineate the neural mechanisms through which cued and contextual components of associative learning contribute to fear memory. During cued fear conditioning, a conditioned stimulus (CS), such as a sound, comes to elicit a fear response after it is repeatedly paired with an aversive unconditioned stimulus (US), such as an electric shock. During contextual fear conditioning, the surrounding environment where a US is encountered (with or without a CS) comes to elicit a fear response. Whereas associating a specific CS with a US during cued fear conditioning relies on the amygdala, processing spatial and temporal context information during various forms of fear learning is thought to rely on the hippocampus (Maren et al., 2013). The ventral hippocampus (VH) also encodes salient information related to emotion and stress, including aversive stimuli used in fear conditioning (Fanselow and Dong, 2010). VH sends glutamatergic projections to the prelimbic (PL) region of medial prefrontal cortex (mPFC; Parent et al., 2010), another area critical for the acquisition and expression of fear responses in environments where timing and context contribute to the prediction of threatening events (Gilmartin et al., 2014). Temporal complexity is added to associative learning in trace fear conditioning, where the CS and US are separated by a time, or "trace," interval. Disrupting local hippocampal and PL activity, individually, impairs the acquisition of trace fear conditioning (Raybuck and Lattal, 2014), suggesting that these brain areas support trace fear learning.

The hypothesis that VH–PL circuitry contributes to trace-cued and contextual fear conditioning more broadly was tested in a recent study by Twining et al. (2020). The authors optogenetically silenced VH inputs to PL during trace fear conditioning trials, starting 20 s before the auditory CS and continuing through the trace interval until 20 s after the shock US. Importantly, each day of conditioning and testing began with a baseline period (6 m) that provided additional time for animals to encode the context and allowed the authors to examine contextual fear memory. Retention of cued fear was examined in a separate, novel context before conditioning on each training day.

Contrary to the authors' hypothesis, silencing VH–PL projections during trace fear conditioning trials did not impair learning: animals in which projections were silenced froze as much as controls in response to the auditory CS during both training and testing. In contrast, during context retention tests, animals in which VH–PL projections had been silenced showed significantly less fear expression than controls in the context where they were shocked. Notably, however, all animals froze more after training than before, yet fear expression emerged later in the session—and to a lesser extent—in animals in which VH–PL projections had been silenced during conditioning. Thus, silencing VH–PL communication during conditioning diminished, but did not eliminate, contextual fear. Together, the findings indicate that VH inputs play a role in updating PL with contextual information, but do not play a role in trace-cued fear learning. Contextual learning can occur, albeit more slowly, via other pathways. This slower learning might depend on contextual information encoded outside the silencing interval, which is consistent with previous work showing that exposure to a context preceding any aversive association can strongly influence contextual fear learning (Fanselow, 1990).

Twining et al. (2020) next investigated whether blocking VH–PL communication during the shock alone, rather than the whole trial, would induce similar contextual learning deficits. The authors silenced VH–PL communication starting 1 s before the shock and continuing until 20 s after shock delivery, leaving communication during the tone presentation and most of the trace period intact. Silencing solely

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Correspondence should be addressed to Alexandra O. Cohen at ali.cohen@nyu.edu.

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during the shock epoch was insufficient to decrease fear expression, indicating that VH input to PL during the 20 s lead up to the shock was key for subsequent rapid expression of contextual fear. This result suggests that the relay of contextual information from VH to PL during a relatively brief period before shock delivery is critical for forming contextual fear memory.

To further probe the mechanism underlying the contextual fear memory deficit produced by silencing VH–PL circuitry, the authors silenced VH–PL projections during retrieval both in animals that had experienced silencing during conditioning and in control animals. When VH–PL projections were silenced during both conditioning and contextual test trials, contextual fear expression was restored. Furthermore, silencing VH–PL projections solely during retrieval did not influence fear expression: control animals still froze in context tests. These results suggest that the brain state formed by silencing VH–PL projections during conditioning becomes an important factor in predicting the shock. Thus, when this encoding state is recapitulated by silencing VH–PL projections during testing, fear expression occurs.

Slow contextual learning in the absence of VH–PL communication suggests that compensatory brain mechanisms encode an intact yet weaker contextual fear memory. The authors propose that VH–amygdala connections contribute to context encoding and that the thalamic nucleus reuniens and its projections to PL might facilitate contextual memory formation in the absence of hippocampal input. Another possible compensatory mechanism may originate in the dorsal hippocampus (DH). Previous research suggests distinct functional roles for VH and DH in rodents, with VH facilitating emotional and motivational behaviors and DH supporting general cognitive functions (Fanselow and Dong, 2010). Despite these putative functional differences, chemogenetic silencing of DH–PL communication blocks enhancements in fear memory that occur after re-exposure to a fear context, suggesting that DH can relay contextual information to PL (Ye et al., 2017). Retrosplenial cortex (RSC) may provide another pathway for contextual fear processing via connections with both the hippocampus and mPFC. Indeed, Kwapis et al. (2015) found that blocking protein synthesis in RSC before trace fear conditioning disrupted contextual fear memory formation. Thus, in the absence of VH–PL communication, it is possible that DH or RSC contributes to weaker, delayed expression of contextual fear.

If VH–PL projections serve as the default pathway for providing contextual information relevant to threats, the return of VH–PL communication during retrieval in rats with silenced VH–PL communication during acquisition might override contextual fear memories formed by the alternative circuitry described above. A similar mechanism allows VH–PL communication to override inhibitory learning about a fear cue during extinction when the animal is re-exposed to the original fear context (Wang et al., 2016). The existence of multiple neural mechanisms that can subserve motivationally salient learning and memory likely provides flexibility that allows an animal to respond appropriately to threats across variable and complex environments.

The findings of Twining et al. (2020) add to the growing body of work that highlights the importance of VH for complex learning processes. VH has been implicated in many associative learning processes including fear acquisition (Maren and Holt, 2004; Sierra-Mercado et al., 2011), conditioned inhibition (Meyer et al., 2019), and context-dependent learning and retrieval (Komorowski et al., 2013; Wang et al., 2016). Twining et al. (2020) provide evidence that VH continuously updates PL with information about contextual state, and that suppressing this communication during learning causes deficits in contextual fear memory expression. Together, these findings suggest that a general function of VH may be to resolve the current state of the world and relay this information to various target brain regions.

Further research may clarify specific functions of VH within learning and memory circuits and in defining a "context." Contemporary findings suggest that dynamic changes in the timing and salience of events in the environment of an animal can break up the context in meaningful ways and lead to differential activity of VH and DH. However, mixed results have precluded clear definitions of hippocampal subregion functions in temporally and contextually complex learning (Raybuck and Lattal, 2014). Furthermore, questions remain regarding what features of the environment signal a shift in context (Clewett and Davachi, 2017). Does VH communication to target regions vary with changes in the external environment, or does VH simply communicate information about the current context and the passage of time? Future studies examining the temporal dynamics of VH and DH function may provide insights into how the hippocampus defines a context and whether VH primes neural circuits to rapidly retrieve salient events.

Twining et al. (2020) demonstrate the power of optogenetic approaches in illuminating neural mechanisms underlying different facets of associative fear learning. Similarly, studying the relational structure of brain regions across development may reveal both individual and coordinated neural contributions to complex learning and memory processes. Research examining simple cued fear acquisition and extinction across development have shown that the amygdala can support both of these learning processes without the involvement of mPFC (Kim et al., 2009). But can mPFC support temporally or contextually complex learning without input from the hippocampus, or vice versa? Given the dynamic restructuring and refinement of connectivity among the amygdala, hippocampus, and mPFC across age (Pattwell et al., 2016), developmental studies might yield insights into the necessity and sufficiency of VH and mPFC in complex learning processes. Integrating evidence from converging lines of research can help us understand features of the environment that influence how we learn and remember.

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