Neuroscience and Psychiatry

Is Hippocampal Replay a Mechanism for Anxiety and Depression?

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Hippocampal Replay

Emotional learning (learning the value of stimuli or contexts) is central to the causative mechanisms of mood and anxiety disorders. During emotional learning, the hippocampus, long implicated in internalizing disorders, receives a snapshot of distributed cortical and subcortical activity. Synaptic plasticity promotes engram formation, the circuit-level instantiation of memory.[1] Hippocampal replay, the rapid, coordinated reactivation of encoding-activated cellular ensembles during sleep and resting wakefulness, also supports memory consolidation[2] and may contribute to prospection and decision-making. Even in rodent cognitive spatial tasks, learning fundamentally concerns the learning of value, a process critical to psychopathology. While unstudied (to our knowledge) in psychiatric disorders, hippocampal replay abnormalities may critically link animal models with human psychopathology and, in particular, with cognitive symptoms of worry and rumination. Hippocampal replay[2] is marked by ripple oscillations in the CA1 local field potential[1] of approximately 100 milliseconds at 140 to 250 Hz.[2] During replay, which is commonly observed after a rodent traverses a maze (reverse replay) or before it enters a familiar maze (forward replay), the hippocampal firing sequence recapitulates previously observed firing but is accelerated.[2] Reverse replay is not observed before an initial maze run, suggesting that replay represents previous experience. Forward replay is observed when, as the rodent approaches a decision point in a familiar maze, hippocampal place cells replay forward the sequences observed previously from that maze.[3] Forward replay is associated with the rodent's ultimate trajectory, potentially representing goal-directed future planning in anticipation of decision-making.[3] Hippocampal replay is the replay that has been most extensively studied, yet there is evidence that replay occurs elsewhere, including the prefrontal cortex (PFC), particularly the medial PFC (mPFC). While most evidence supports replay-associated CA1 sharp-wave ripples originating in the CA3, recent findings suggest a role for bidirectional mPFC-hippocampus communication in initiating and, in particular, sustaining replay.[4]

Cognitive Processes in Anxiety and Depression

Generalized anxiety disorder involves dysregulated worry about unpredictable or uncontrollable future events[5] and habitual, recurrent, future-oriented cognitions organized around threat detection and prevention. Because individuals with generalized anxiety disorder perceive the world as globally threatening, future-oriented cognitions frequently occur in inappropriate contexts. While maladaptive, worry becomes habitual by momentarily reducing negative affect by engaging planning, cognitive, and linguistic processes.[5] In contrast, depression is characterized by recurrent and uncontrollable ruminative thinking. Rumination is perseverative, habitual, and past focused.[5] People who ruminate believe they are solving potential future problems by focusing on past failures. Thus, rumination also temporarily reduces negative affect, becoming habitual via negative reinforcement. Worry and rumination are both recurrent thoughts about the self, which is thought to partially explain the frequent comorbidity of anxiety and depression.

Hippocampal Replay, Worry, and Rumination

Many neurobiological pathways may support worry and rumination. One pathway not previously considered (to our knowledge) is a potential connection between forward and reverse hippocampal replay and worry and rumination, respectively (**Figure**). With regard to worry, a recent finding demonstrated that as rodents approached an aversively conditioned area (*shock zone*), forward replay resembled the hippocampal sequence observed in initial fear conditioning.[6] The rodent then avoided the threat-linked location, suggesting forward hippocampal replay allows future threat expectations from experience to guide avoidance behavior.

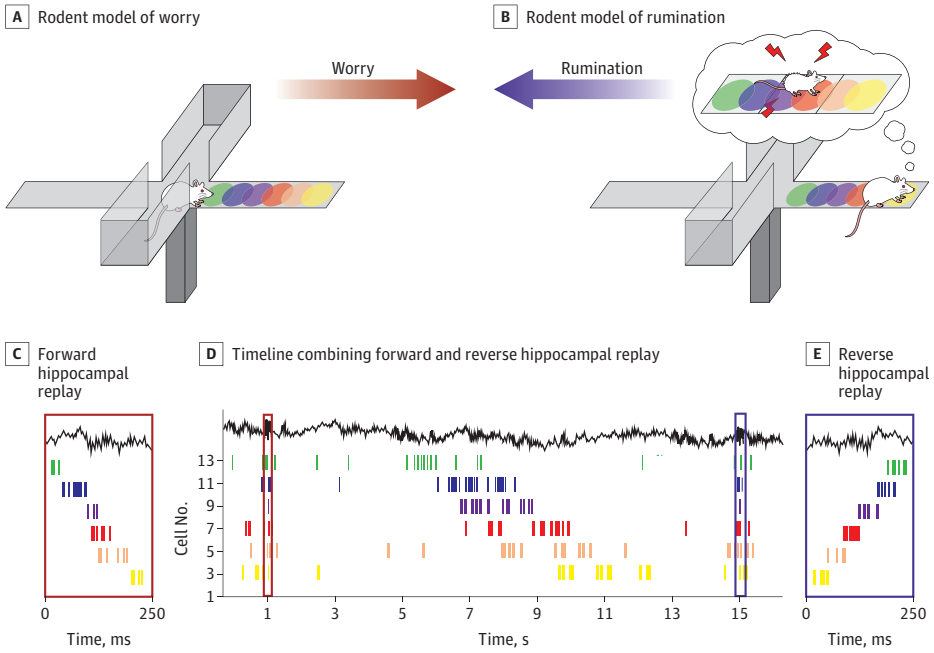
Vicarious trial and error (VTE), another rodent behavior in which forward hippocampal replay supports decision-making, may be similar to worry.[7] At decision points in relatively unfamiliar environments, rodents often pause and survey, suggesting deliberation before continued exploration. For example, on an elevated plus maze, so-called anxious rats spend more time in enclosed than open arms and pause in the center zone, exhibiting stretch-attend VTE before entering either arm. The VTE process, in which rodents display pausing-and-looking (interpreted as a hesitation to act while considering options), is accompanied by forward hippocampal replay.[7] This likely reflects simulation of the value of possible options. Intriguingly, there is evidence that VTE is modulated by noradrenaline, and reducing noradrenaline via the anxiolytic clonidine decreases VTE.[8] Extreme, repetitive VTE in which the value of potential actions are simulated with little action bears striking similarity to worry, suggesting forward replay as a neural mechanism of worry.

Similar to a potential role for forward replay in worry and anxiety, reverse hippocampal replay could underlie rumination. While there is minimal empirical work examining the effects of chronic stress, a key risk factor for anxiety and depression, on hippocampal replay, recent computational work[9] suggests habitual reverse replay of aversive experiences as a neural substrate of rumination.

Evidence that subcortical-cortical circuit activity supports replay is important, given known circuit-level dysfunction in depression and anxiety, including in the hippocampus-PFC. Hippocampal-mPFC synchrony is implicated in internalizing psychopathology.[10] Also, given the mPFC's role in maintaining task sets and representing generalized knowledge, hippocampal-mPFC interactions may support threat detection, even with limited context-specific experience. Lastly, while speculative, sustained neural oscillations via subcortical-cortical interactions may be a mechanism to sustain rapid hippocampal sharp-wave ripples over longer time scales, which could be experienced as rumination or worry.

Hippocampal replay has not been examined either in rodent psychopathology models or human clinical populations. We suggest that future work examine both, using animal chronic stress models to probe potential replay abnormalities and functional

Figure. Hippocampal Replay and Proposed Associations With Worry and Rumination



A, Worry, a prospective cognitive process that occurs when an organism anticipates future aversive outcomes even in absence of clear threat, is represented as the rat anticipates the anxiogenic experience of entering the open arm. B, Rumination is a retrospective cognitive process; a rat recalls the aversive experience it had while traversing the maze's open arm. Worry may be associated with forward hippocampal replay (C), a rapid reactivation of the same sequence of cell firing observed during actual exploration. C is derived from D, an extended timeline illustrating that accelerated forward replay precedes exploration of the maze. This is followed by accelerated reverse hippocampal replay (E), a rapid, reverse activation of the sequence of cell firing observed during exploration (this image is also derived from D). After repeated, generalized aversive experiences, reverse replay, which occurs after learning contingencies in a spatial decision-making paradigm and has been linked to memory consolidation, is hypothesized to support rumination. C, D, and E are adapted from a previously published figure.[3]

magnetic resonance imaging or intracranial electroencephalogram to determine if humans with internalizing psychopathology display abnormalities in hippocampal-cortical patterns when anticipating or reencountering threatening stimuli. Given inherent technical challenges to probing temporally precise human neural activity and uncertain human-rodent brain homology, parallel research in animals and humans will be critical to robustly assess the hypothesized role of hippocampal replay in anxiety and depression.

In humans, the habitual, maladaptive cognitive patterns that typify depression and anxiety emerge via lifelong associative learning. Accumulating adverse experiences can generalize learned associations to novel contexts, resulting in expectations of an unsafe world and causing habitual neural patterns subjectively experienced as worry and rumination. The processes of forward and reverse hippocampal replay may be mechanisms by which such cognitions are instantiated.

ARTICLE INFORMATION

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