Anxiety and Beyond: Diversity in Ventral Hippocampus Circuits and Function

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Abstract

The ventral hippocampus (vHPC), initially implicated in anxiety regulation, is now recognized for its broader role in integrating emotional, motivational, and contextual information. This review synthesizes recent insights presented at our 2025 Society for Neuroscience minisymposium, detailing how local inhibitory microcircuits, long-range projection-defined pathways, and neuromodulatory inputs interact to shape fear, anxiety and reward behaviors. We emphasize how distinct circuits segregate fear and anxiety, resolve approach avoidance conflicts and integrate reward history. Serotonergic modulation, particularly from the median raphe, emerges as a critical regulator of vHPC dynamics, with pronounced sex-specific functional implications. Finally, we examine how vCA1 ensemble activity encodes emotionally salient stimuli and supports latent state inference, thereby enabling flexible decision making under uncertainty. Collectively, these findings recast the vHPC as a modular, computationally rich structure essential for adaptive behavior, which may provide new insights into circuit level dysfunction in affective disorders.

Introduction

While early research emphasized the role of the dorsal hippocampus (dHPC) in spatial memory and navigation (Scoville and Milner, 1957; O'Keefe and Nadel, 1978), growing evidence highlights a distinct set of functions for the ventral hippocampus. Beyond mapping space, the vHPC is critically involved in threat detection, approach-avoidance regulation, and reward processing (Bannerman et al., 2004; Ciocchi et al., 2015; Turner et al., 2022). Recent work has begun to

illuminate how specific microcircuits, projection-defined pathways, neuromodulatory inputs, and ensemble dynamics within the vHPC contribute to highly complex emotional and motivational processes (Turner et al., 2022; Biane et al., 2023; Li et al., 2024; Mishchanchuk et al., 2024; Iyer et al., 2025; Patterson et al., 2025). These investigations collectively position the vHPC as a computational hub that encodes internal states and context, thereby shaping behavioral outputs across changing environmental demands.

This minisymposium review synthesizes new insights into the structure and function of vHPC circuits. Drawing on approaches including *in vivo* imaging, optogenetics, chemogenetics, and computational modeling, the work described here dissects how the vHPC mediates core components of affective behavior. We begin at the microcircuit level, where distinct interneuron populations shape pyramidal neuron output and contribute to the differentiation of fear and anxiety. We then transition to how the vHPC orchestrates behavioral responses in approach-avoidance conflict through parallel long-range pathways. Next, we examine how oscillatory dynamics and neuromodulation, particularly serotonergic tone, coordinate these computations and exhibit sex-specific tuning. From here, we explore how the vHPC integrates reward history trough its projections to the nucleus accumbens. We conclude with emerging evidence that, at the assembly level, vHPC encodes emotionally salient stimuli, and supports abstract representations of latent task states. This progression—from microcircuits to population level representations, and from anxiety to broader domains of motivation and behavioral flexibility, illustrates our expanding insight in the vHPC's role in shaping adaptive behavior.

vHPC microcircuits for emotional discrimination of fear and anxiety

Specifically, scientific insight in the vHPC has evolved substantially since early lesion and manipulation studies identified this region as a key regulator of unconditioned fear and anxiety-like behaviors (Kjelstrup et al., 2002; Fanselow and Dong, 2010). Although fear and anxiety were traditionally considered as overlapping in both behavioral manifestation and neural circuitry - particularly involving the amygdala, medial prefrontal cortex and hippocampus (Maren et al., 2013; Calhoon and Tye, 2015; Tovote et al., 2015), emerging evidence suggests that the vHPC supports partially dissociable computations underlying these affective states. This refinement has been driven in part by work revealing distinct patterns of local circuit recruitment depending on behavioral context (Li et al., 2024).

The activity of the main output neurons of the hippocampus, pyramidal cells (PCs), is tightly regulated by a diverse array of local interneurons (Klausberger and Somogyi, 2008; Pelkey et al., 2017; Soltesz and Losonczy, 2018). The different classes of interneurons provide direct inhibition onto PCs or onto other interneurons, enabling forms of disinhibition that shape HPC activity, oscillatory dynamics and behavioral output in precise and complementary ways (Lee et al., 2014; Amilhon et al., 2015; Dudok et al., 2021).

In fear-related behaviors, a specific disinhibitory circuit composed of vasoactive intestinal peptide (VIP) and somatostatin (Sst) interneurons is engaged (Fig. 1A). VIP interneurons inhibit Sst interneurons, which normally suppress pyramidal neuron activity. This disinhibition permits a selective population of pyramidal neurons to become active during conditioned stimulus

presentation, facilitating the encoding of associations between conditioned and unconditioned stimuli and thereby supporting the formation of stable fear memories. This disinhibitory mechanism appears to serve as a gating system, allowing excitatory inputs from upstream brain regions, such as the entorhinal cortex and CA3 hippocampus, to activate the precise populations of pyramidal neurons necessary for fear learning.

In contrast, anxiety-related behaviors are regulated by a separate inhibitory circuit centered around parvalbumin (PV) interneurons (Fig. 1A). PV interneurons exert strong perisomatic inhibition onto pyramidal neurons, regulating their activation during states of uncertainty or potential threat. Optogenetic inhibition of PV interneurons increases activity of pyramidal neurons, resulting in heightened anxiety behaviors, such as reduced exploration of anxiogenic environments. Thus, PV interneurons appear critical for maintaining an activity balance, ensuring that anxiety responses are appropriately scaled.

Although both the fear and anxiety circuits reside within the vHPC, their influence is mediated through distinct downstream projections: Whereas the vHPC fear microcircuit primarily interfaces with structures such as the basolateral amygdala, central amygdala, and prelimbic cortex to orchestrate fear learning and expression (Sotres-Bayon et al., 2012; Xu et al., 2016; Jimenez et al., 2020; Kim and Cho, 2020), the vHPC anxiety circuit modulates projections to the medial prefrontal cortex, lateral hypothalamus and lateral septum (Adhikari et al., 2010, 2011; Ciocchi et al., 2015; Padilla-Coreano et al., 2016; Parfitt et al., 2017; Jimenez et al., 2018; Sánchez-Bellot et al., 2022). These projection-specific activity patterns highlight a modular and flexible organizational scheme in the hippocampus, enabling one region to mediate distinct behavioral outcomes depending on outputs and contextual demands.

Overall, these findings emphasize that the ventral hippocampus is not a homogeneous emotion-processing hub but rather a highly specialized and adaptable region that orchestrates complex behavioral responses. By delineating how different subclasses of interneurons selectively regulate pyramidal neuron activity to drive either anxiety or fear behaviors, this work furthers our understanding of the microcircuit dynamics underlying emotional regulation.

Dissecting vHPC circuits in the regulation of approach avoidance conflict

Building on this foundation, others have begun to investigate how vHPC interactions with downstream targets regulate approach avoidance (AA) conflict, a type of conflict where animals must weigh potential rewards against the risk of aversive outcomes. Seminal lesion studies from the 1950s and 1960s demonstrated that hippocampal damage leads to disinhibited behavior in the face of competing motivational drives (Kimura, 1958; Isaacson et al., 1961; Kimble, 1963; Jarrard et al., 1964), laying the foundation for the Behavioral Inhibition System (BIS) theory (Gray and McNaughton, 2003). According to BIS theory, the hippocampus detects AA conflicts, amplifies negative or conflicting information, engages risk assessment, and subsequently biases behavior toward avoidance.

A non-spatial, mixed-valence Y-maze conflict task has been instrumental in modeling these learned forms of conflict (Ito and Lee, 2016). In this paradigm, rats learn to associate visuotactile

cues with positive (sucrose), negative (footshock), or neutral outcomes (Fig. 1B). When appetitive and aversive cues are presented together, rats with global vHPC lesions exhibit a pronounced approach bias toward the conflict-paired arm of the maze, a behavioral pattern not observed in rats with dHPC lesions (O'Neil et al., 2015; Ito and Lee, 2016; Schumacher et al., 2016; Duc et al., 2025). Subsequent studies have identified distinct subfield-specific functions within the vHPC that exert bidirectional control over conditioned AA behaviors, showing that vCA3 and DG subfields suppress approach, while vCA1 promotes approach during AA conflict (Schumacher et al., 2018; Yeates et al., 2020).

To clarify the pathways through which these vHPC subfields influence AA behavior under conflict, key efferent projections from vCA3 and vCA1 were selectively inhibited. The caudodorsal region of the lateral septum (LS) is a major and possibly exclusive output of the vCA3 (Risold and Swanson, 1997; Bienkowski et al., 2018). Using the same Y-maze cued conflict task, chemogenetic inhibition of the vCA3→LS circuit resulted in a pronounced approach bias toward the conflict-associated cue and a reduction in retreat behaviors (Yeates et al., 2022). Interestingly, inactivation of vCA1 projections to the LS led to a non-specific increase in the exploration of, and decreased retreat behaviors in, both conflict and neutral arms. The effect of manipulating these LS-projecting vHPC circuits diverged in the novelty suppressed feeding task: vCA3→LS inactivation decreased latency to approach familiar food in a novel environment, while vCA1→LS inactivation increased this latency. Together, these findings suggest that the vCA3→LS circuit plays a central role in suppressing approach towards motivationally salient stimuli under conflict. In contrast, the vCA1→LS circuit contributes to the inhibition of general approach or exploratory drive under conflict, potentially to direct approach to salient stimuli.

Chemogenetic inactivation of vCA1 projections to the nucleus accumbens (NAc) also caused distinct behavioral alterations in the AA conflict test (Patterson et al., 2025). vCA1→NAc inactivated rats displayed decision making deficits and an overall avoidant phenotype. These animals spent more time in the central compartment, engaged in prolonged risk-assessment before choosing an arm, and retreated more frequently in both conflict and neutral arms. In line with previous reports of disrupted social memory (Bagot et al., 2015; Okuyama et al., 2016; Muir et al., 2020), vCA1→NAc inactivated animals consistently avoided interaction with an unfamiliar conspecific. Together, these data suggest a role for vCA1→NAc in regulating risk assessment behavior and approach decisions under AA conflict, extending to socially relevant contexts.

Together with prior findings, these results suggest a functional division of labor within vHPC circuits: the vCA3→LS circuit appears to implement a core BIS function, suppressing approach when approach avoidance conflict is high. In contrast, vCA1 circuits may act as a BIS override mechanism when approach becomes adaptive. Specifically, the vCA1→LS circuit may suppress environmental scanning under AA conflict to enable approach, whereas the vCA1→NAc circuit may inhibit risk assessment behavior to promote approach decisions. In sum, parallel vHPC subcircuits exert dissociable and complementary control over behavior during conflict, enabling dynamic resolution of competing motivational drives.

Neuromodulatory and sex-dependent tuning of vHPC circuit function

Approach-avoidance conflict tasks provide powerful behavioral assays for probing how animals resolve competing drives. While these tasks primarily index decision making under conflict, they also robustly elicit anxiety like behaviors: hesitation, risk assessment and behavioral inhibition. The functional output of vHPC pathways, whether suppressing or promoting approach, depends critically on the animal's internal state. Neuromodulatory systems, particularly serotonergic tone, provide a flexible mechanism for dynamically tuning vHPC activity in response to arousal, novelty or perceived threat.

These influences act in part through modulation of local network excitability and oscillatory dynamics. Hippocampal theta oscillations (4-12 Hz), prominent across the entire dorso-ventral axis of all hippocampal subfields (Buzsáki, 2002; Colgin, 2013), play a central role in coordinating long range communication (Fries, 2005; Buzsáki and Vöröslakos, 2023), for example between the vHPC and PFC during anxiety (Adhikari et al., 2010; Jacinto et al., 2016; Padilla-Coreano et al., 2016), and amygdala during fear (Likhtik et al., 2014).

Theta frequency increases systematically with running speed (Rivas et al., 1996; Maurer et al., 2005; Jeewajee et al., 2008), but this relationship is mediated by behavioral state: novelty flattens the slope (Jeewajee et al., 2008; Wells et al., 2013; Hines et al., 2023), and anxiolytics shift the intercept downward (McNaughton and Gray, 2000; McNaughton et al., 2007; Engin et al., 2008; Siok et al., 2009; Yeung et al., 2012, 2013). These parameters serve as sensitive readouts of hippocampal computation under varying internal states (Korotkova et al., 2017). Serotonergic input from the median raphe nucleus (MnR) has long been recognized as a potent regulator of hippocampal theta activity. Early studies showed that disrupting MnR input enhances hippocampal theta (Maru et al., 1979; Yamamoto et al., 1979), while increasing serotonin (5-HT) tone suppresses it (Kudina et al., 2004; Jackson et al., 2008).

Recent work has expanded this framework by identifying a population of serotonergic neurons in the median raphe region that targets the vHPC (5-HT^{vHP}). *In vivo* fiber photometry recordings confirmed functional sex differences in these neurons during anxiety-related behavior. During exploration of the elevated plus maze (EPM), a classic assay of approach-avoidance conflict, 5-HT^{vHP} neurons from male mice showed a decrease in their activity upon the animal entering the closed arm, whereas cells from female mice showed an attenuated decrease, suggesting prolonged engagement of 5-HT^{vHP} neurons when transitioning from aversive to safe.

To directly test whether 5-HT^{vHP} neurons modulate hippocampal activity, optogenetic activation was used during open field exploration while recording local field potentials from the ventral hippocampus. In female mice, activation of 5-HT^{vHP} neurons flattened the theta frequency-speed relationship, suggesting impaired familiarization to the environment, whereas no such effect was observed in males. Behaviorally, this manipulation increased anxiety-like behaviors and decreased risk-assessment, predominantly in females. Electrophysiological recordings revealed that 5-HT^{vHP} neurons in the median raphe region from female mice exhibit more depolarized resting membrane potentials and higher firing rates than those from males.

Consistent with longstanding models implicating serotonergic modulation in behavioral inhibition (McNaughton and Gray, 2000), these findings position 5-HT^{vHP} neurons as key modulators of

state-dependent hippocampal network activity. These sex-specific differences in circuit function are especially relevant given the marked disparity in anxiety disorder prevalence and expression between males and females (Kessler et al., 2009). Understanding how serotonergic modulation interacts with projection-specific vHPC circuits could shed light on the neural basis of anxiety and its possible dysregulation in psychiatric conditions.

Reward Integration in vCA1-NAc circuits

The rich heterogeneity of the vHPC is further exemplified by its involvement in functions beyond behavioral inhibition, with growing evidence implicating the vHPC as a key structure in reward-guided behavior and motivational salience (Ciocchi et al., 2015; Lafferty et al., 2020; Yoshida et al., 2020; Hamel et al., 2022; Nguyen et al., 2024; Iyer et al., 2025; Patterson et al., 2025). Both the dorsal and ventral hippocampus project to the NAc, where they modulate goal-directed navigation, influence hedonic processing, and contribute to the regulation of feeding behavior (Ciocchi et al., 2015; Reed et al., 2018; Trouche et al., 2019; Yang et al., 2020; Sosa and Giocomo, 2021; Wee et al., 2024; Iyer et al., 2025).

Alterations in the function of the vHPC→NAc projection have been implicated in a range of disorders involving disrupted reward processing. vHPC→NAc has been implicated in stress-induced deficits in reward processing (LeGates et al., 2018; Pignatelli et al., 2021). Stress modifies activity within this pathway, and pathway-specific manipulations bidirectionally modulate susceptibility to depression-like behavior (Bagot et al., 2015; Muir et al., 2020; Williams et al., 2020). Individual differences in vHPC→NAc activity also predict differential adaptation to chronic stress in male and female mice (Muir et al., 2020), suggesting functional importance in understanding differential vulnerability. Moreover, exposure to various addictive substances, known to ‘hijack’ reward systems and recognized as risk factors for depression (Covington et al., 2011), modulate synaptic and structural plasticity within the vHPC→NAc pathway (Bossert et al., 2016; Marchant et al., 2016; Barrientos et al., 2018; Kircher et al., 2019; Pascoli et al., 2014). Additional evidence points to a functional contribution of this pathway in integrating information about threat to modulate reward motivated behavior, particularly in male mice (Muir et al., 2024).

Taken together, these findings suggest that the vHPC→NAc may play a role in reward processing, a function most often associated with medial prefrontal cortical inputs to NAc (mPFC→NAc) inhibition (Bagot et al., 2015; Otis et al., 2017; Barker et al., 2019; Muir et al., 2020; Yoshida et al., 2020; Spellman et al., 2021; Hamel et al., 2022; Lindenbach et al., 2022; Parker et al., 2022; Wenzel et al., 2023). Pathway-specific in-vivo fiber photometry recordings have demonstrated that population-level calcium dynamics in vHPC→NAc, as well as mPFC→NAc, are robustly suppressed by reward outcomes in a two-armed bandit task (Iyer et al., 2025); Fig. 1B). This suppression persists beyond a single trial, with subsequent non-reward gradually increasing activity such that the relative degree of suppression represents an integrated history of recent outcomes. Intriguingly, vHPC→NAc pathway preferentially encodes outcomes under conditions of variable reward, suggesting this neural signal may be tuned to reward omission or loss.

Contextual modulation further differentiates these two pathways: vHPC→NAc encoding is sensitive to behavioral context, preferentially encoding outcomes contingent upon actions. When

outcomes are delivered passively, the vHPC→NAc shifts encoding toward representing surprising rewards, further suggesting its role is anchored in signaling loss or deviations from expectations. In contrast, the mPFC→NAc consistently encodes reward outcomes, irrespective of trial history or task demands. Despite these differences, activity in both pathways similarly predict task engagement. Optogenetic activation of either pathway—alone or in combination—suppresses task engagement in an additive manner. These findings suggest that while mPFC→NAc conveys stable reward value, the vHPC→NAc acts as a dynamic signal of recent reward history.

While the NAc's involvement in reward processing has long been recognized (Xu et al., 2024), the specific neural mechanisms remain incompletely understood. Probing encoding across trial histories and varying task demands suggests that while both mPFC→NAc and vHPC→NAc serve this function, they are engaged in distinct settings such that the vHPC-NAc may serve to amplify surprising rewards. Previous work established that stimulating glutamatergic inputs to the NAc broadly suppresses reward-motivated behavior (Millan et al., 2017; Reed et al., 2018; Lafferty et al., 2020). A temporally integrated reward-induced neural signal may harness this inhibitory mechanism to finely adjust ongoing behavior. Thus, vHPC→NAc translates recent reward history to tune behavioral engagement to prevailing environmental conditions.

As the most robust glutamatergic input to the medial shell of the NAc, the vHPC→NAc pathway plays a critical role in regulating behavioral engagement. Failure to appropriately disengage this circuit may suppress reward-driven behavior, potentially manifesting as anhedonia. Indeed, disruption of input balance is observed following chronic stress (Bagot et al., 2015; Muir et al., 2020; Williams et al., 2020; Pignatelli et al., 2021), as well as after exposure to substances such as alcohol (Kircher et al., 2019; Griffin et al., 2023) and cocaine (Pascoli et al., 2014; Cahill et al., 2016; Barrientos et al., 2018; Zinsmaier et al., 2022), all of which are associated with aberrant reward processing. Together, these findings position the vHPC→NAc circuit as a flexible integrator of motivational history, adjusting behavioral engagement based on recent outcomes and environmental demands.

Ensemble representations in vHPC

While lesion, inactivation and anatomical tracing studies have established the vHPC as central to controlling diverse behaviors, recent research has begun to uncover the precise neural codes within vCA1 that underlie these functions. A model has emerged that suggests that vCA1 neurons encode stimuli with immediate behavioral relevance, forming a 'map' that integrates sensory information from the environment with internal drive states (Turner et al., 2022). This organization is akin to the spatial mapping function of dorsal CA1 (dCA1), where ensembles exhibit location-stimulus- and temporal specific firing patterns that generate a cognitive map of space (O'Keefe and Nadel, 1978; McNaughton et al., 2006). The vCA1 map represents stimuli not only for where or when they occur, but for what they mean to the animal - whether they signal potential threat, opportunity for reward, or even social salience.

Electrophysiological and calcium imaging studies have consistently shown selective engagement of vCA1 neurons, but not those in dCA1, during exploration of threatening environments like the elevated plus maze (Ciocchi et al., 2015; Jimenez et al., 2018). The activity of these neurons

correlates with individual differences in baseline anxiety and with the aversiveness of contextual cues (Ciocchi et al., 2015; Jimenez et al., 2018). Within vCA1, functional heterogeneity is organized along projection-defined output channels (Fig. 1B): neurons projecting to the lateral hypothalamus (LH) and medial prefrontal cortex (mPFC) are preferentially activated during threat exposure, whereas populations targeting the nucleus accumbens (NAc) exhibit comparatively reduced engagement by aversive stimuli (Adhikari et al., 2010; Ciocchi et al., 2015; Padilla-Coreano et al., 2016; Jimenez et al., 2018, 2020; AlSubaie et al., 2021).

Moreover, distinct aversive cues, such as footshocks and predator odor, are represented by separable ensembles in vCA1, indicating that this region encodes the specific identity of threatening stimuli rather than a generalized valence signal (Biane et al., 2024). This specificity persists even when stimulus relevance is altered through learning: in a conditioned taste aversion paradigm, the vCA1 representation of an initially appetitive stimulus does not converge with those of innately aversive stimuli following its pairing with malaise. These findings suggest that vCA1 encodes the unique identity of salient stimuli, with valence-specific generalization perhaps occurring downstream, particularly within the amygdala, a region densely innervated by vCA1 and well-known for encoding and transforming valence-related information (Felix-Ortiz et al., 2013; Gore et al., 2015; Beyeler et al., 2016; Namburi et al., 2016; Tye, 2018; Zhang et al., 2019; O'Neill et al., 2024; Xia et al., 2025).

Beyond its role in threat processing, vCA1 ensembles also contribute to reward-related learning displaying pronounced plasticity during associative learning. For instance, a recent imaging study (Biane et al., 2023) demonstrated that vCA1 neurons initially showed minimal responsiveness to neutral cues but rapidly reorganized their activity to represent odor stimuli predicting reward. These representations were stable across days, after extinction and reinstatement, and even after reversal of the valence of the outcome paired with the odor, indicating the formation of a persistent neural code for salient stimuli (Biane et al., 2023).

Together, these data raise the intriguing possibility that the discrimination observed in vCA1 between stimuli of similar valence may reflect the encoding of the distinct internal bodily or behavioral states elicited by these stimuli.

Latent state inference in vHPC

Building on this framework, we explore the hypothesis that the vHPC, and vCA1 in particular, supports latent state inference: the construction of abstract internal models that guide decision-making under uncertainty, analogous to how dorsal hippocampal circuits distinguish between spatial contexts (O'Keefe and Nadel, 1978; Komorowski et al., 2013; Hartley et al., 2014; Kubie et al., 2020; Courellis et al., 2024).

To investigate this possibility, a recent study employed a dynamic two-armed bandit task in mice (Mishchanchuk et al., 2024); Fig. 1D). In this task, mice choose between two levers with probabilistic reward schedules that reverse unpredictably (Tai et al., 2012; Parker et al., 2016). Mice could be solving this task using one of two main strategies: a subject might rely on simple reinforcement (e.g. increasing the likelihood of repeated a rewarded action, a common

implementation of this is called Q-learning) or alternatively, a subject can instead aim to form an understanding of the underlying environment that produces such outcomes – a strategy known as hidden state inference (SI) (Costa et al., 2015; Adams et al., 2016; Qü et al., 2024). Computational modelling showed that SI models consistently outperformed Q-learning models in explaining mouse behavior, suggesting that animals use latent, contextual representations to solve the task (Costa et al., 2015; Vertechi et al., 2020; Qü et al., 2024).

To assess the contribution of vCA1 to this process, targeted lesions of excitatory neurons in vCA1 were performed. These lesions impaired the use of SI strategies while sparing reinforcement learning, providing causal evidence that vCA1 is required for the formation and use of latent context representations during decision-making.

Microendoscopic calcium imaging was used to examine how vCA1 neurons represent different aspects of the task. It was found that individual neurons in vCA1 encoded not just choices and outcomes, but also the latent context of each trial. Strikingly, these context representations were abstracted across specific actions and outcomes, suggesting a high-level, generalisable state representation. At the population level, neural activity in vCA1 reliably decoded choice, outcome and latent context with high accuracy, even before the outcome was known.

Together, these findings show that vCA1 supports decision-making by forming stable, abstract representations of latent task contexts (Gershman et al., 2010; Duvelle et al., 2023; Mishchanchuk et al., 2024). These representations are necessary for optimal behaviour and are also reflected downstream. These findings may have implications for understanding psychiatric conditions, such as depression and schizophrenia, where contextual inference is often impaired (Servan-Schreiber et al., 1996; Holmes et al., 2005).

More broadly, this role for the vHPC in hidden state inference role may reflect a general computational principle of the hippocampus, potentially offering a unified framework for understanding the dramatic differences in function across the dorsal-ventral axis with one overall circuit computation. For example, a circuit optimized for hidden state inference would be ideally suited for estimating the likelihood of future negative outcomes, a key function of vCA1 models of anxiety. At the same time, this same computational framework can account for the role of dorsal hippocampus circuits in spatial inference, where animals estimate location through the integration of self-motion and visual cues. Viewing hippocampal functions through this framework may open new avenues for understanding how diverse hippocampal functions emerge from a shared underlying mechanism of latent state inference.

Conclusion

Together, the studies reviewed here show the ventral hippocampus as a modular and computationally dynamic structure that integrates emotional, motivational and contextual information to shape behavior. Once thought to function as a uniform center for anxiety, the vHPC is now understood to comprise anatomically distinct microcircuits and projection-defined pathways that differentially regulate fear, anxiety and reward learning. These circuits are embedded within neuromodulatory and oscillatory networks that flexibly tune vHPC output

according to internal states. At the population level, vCA1 ensembles form behaviorally relevant representations that support not only emotional discrimination but also latent state inference during uncertainty.

This reconceptualization of vHPC function has broad implications for understanding psychiatric vulnerability, particularly disorders characterized by impaired threat evaluation, behavioral inhibition, or reward sensitivity. Emerging evidence suggests that dysregulation within specific vHPC subcircuits—rather than global dysfunction—may underlie selective cognitive and affective symptoms across conditions such as anxiety, depression, and PTSD (Abdallah et al., 2017; Lazarov et al., 2017; Kirkby et al., 2018; Hu et al., 2021). This perspective opens new avenues for targeting circuit-specific vulnerabilities, informed by projections, ensemble activity, neuromodulatory tone, and sex-specific dynamics.

Future work will tease out how vCA1 integrates information related to stimulus identity, meaning and the internal state of the animal when these stimuli were encountered and learned. In addition, the functional interactions between vCA1 ensembles encoding opposing behavioral states, such as approach and avoidance, remain to be fully understood. It is still unclear whether these ensembles act independently, competitively, or in coordination and how their dynamics align with vCA1's projection-defined architecture (Jin and Maren, 2015; Jimenez et al., 2018, 2020; Gergues et al., 2020; Wee and MacAskill, 2020). In parallel, recent studies are beginning to reveal how altered emotional states, such as those induced by chronic stress, reshape the encoding properties of anatomically defined vCA1 circuits (Bagot et al., 2015; Anacker et al., 2018; Hultman et al., 2018; Xia et al., 2025). Although vHPC activity shifts under these conditions are well documented, how these changes affect stimulus coding, ensemble recruitment, and behavioral output in vCA1 remains largely unexplored.

Finally, because anxiety often involves anticipation of uncertain or future threats, it is critical to understand how prospective coding in vCA1 contributes to this process. Human imaging studies have implicated the anterior hippocampus in constructing imagined future scenarios (Schacter et al., 2008; Addis and Schacter, 2012), and rodent studies have shown that dorsal CA1 exhibits rapid alternation between potential future paths (Kay et al., 2020). Whether and how vCA1 may support analogous prospective coding, distinguishes safe from aversive outcomes, or may differentially replay past experiences based on the emotional significance, remain open and important questions. Pursuing these lines of inquiry will not only further refine fundamental models of hippocampal processing but also advance translational pathways for developing targeted interventions aimed at restoring adaptive computation in disrupted vHPC networks.

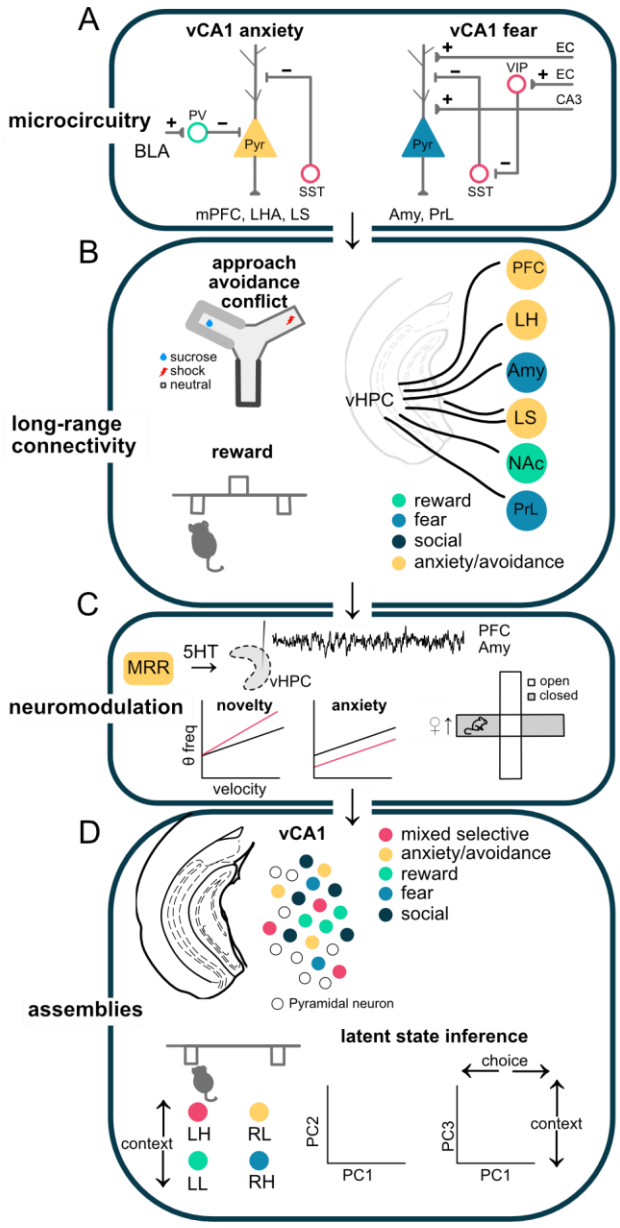

Figure 1: Multi-level organization of vHPC computations supporting adaptive behavior. Schematic overview illustrating the multi-level organization of vHPC function, providing an insight in how anatomically and functionally distinct vHPC circuits interact to orchestrate behavior.

A Within vCA1, distinct inhibitory microcircuits gate the expression of fear and anxiety. A disinhibitory circuit involving VIP and Sst interneurons support fear, whereas PV interneurons regulate anxiety-related activity through strong perisomatic inhibition of pyramidal neurons. Modified from Li et al., 2024.

B Representation of anatomically segregated outputs from vHPC, color coded for behavioral function this projection underlies. Notably, vHPC sends output to several downstream targets not depicted here. Examples of this scenario include vCA1→LS role in approach avoidance behavior (Yeates et al., 2022) and vHPC→NAc in adaptive, reward guided behavior (Iyer et al., 2025).

C Serotonergic input from the MRR modulates vHPC activity and anxiety in a sex-specific manner. **D** Single-unit recordings and calcium imaging reveal that vCA1 pyramidal neurons encode diverse emotionally salient stimuli through stable and selective ensemble activity. Schematic representation of these anatomical-functional relationships, with circles depicting vHPC pyramidal neurons. vCA1 ensemble activity supports the formation of abstract representations that guide decision making under uncertainty. Modified from Turner et al., 2022; Mishchanchuk et al., 2024; 5-HT: serotonin; Amy: amygdala; BLA: Basolateral amygdala; EC: entorhinal cortex; LH: lateral hypothalamus; LS: lateral septum; PFC: prefrontal cortex; PrL: prelimbic cortex; Pyr: pyramidal neuron; MRR: median raphe region, Sst: somatostatin; vHPC: ventral hippocampus; VIP: vasoactive intestinal peptide; θ: theta;

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