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Linking external stimuli with internal drives: A role for the ventral hippocampus

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Abstract

The ventral hippocampus (vHPC) has long been thought of as the "emotional" hippocampus. Over the past several years, the complexity of vHPC has come to light, highlighting the diversity of cell types, inputs, and outputs that coordinate a constellation of positively and negatively motivated behaviors. Here, we review recent work on how vCA1 contributes to a network that associates external stimuli with internal motivational drive states to promote the selection of adaptive behavioral responses. We propose a model of vHPC function that emphasizes its role in the integration and transformation of internal and external cues to guide behavioral selection when faced with multiple potential outcomes.

Introduction

The ventral hippocampus (vHPC) is a key node in the extended network that generates emotional and motivated behavior. In recent years, there has been growing interest in vHPC function, the mechanisms by which it contributes to specific behaviors, and how its properties differentiate vHPC networks from the well-studied dorsal hippocampal network. This has led to numerous studies delineating the circuits and cell types in vHPC, specifically within the vCA1 subregion, identifying their unique wiring patterns and their diverse functional properties. The complexity of vCA1 has come to light, with distinct components of its structure (cell types, inputs, and outputs) hypothesized to differentially encode features of an explored environment and ongoing internal drive states to promote adaptive behavioral outputs. The field has progressed considerably since lesion and manipulation studies identified the dorsal HPC (dHPC) as a controller of cognitive functions and vHPC as a regulator of unconditioned fear and anxiety responses [1–4], and human studies established corresponding roles in the posterior and anterior HPC [5]. Given the new findings, it is time to refine the current abstract model of vCA1 into one that highlights the rich heterogeneity of the region.

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In the following sections, we discuss recent progress and put forward a more mechanistic model for vCA1 function. We propose that vCA1 neurons encode stimuli that have immediate significance for the animal, generating a map that links external stimuli with internal drive states. This is analogous to the well-described properties of assemblies of dCA1 neurons that exhibit location-, stimulus-, and time-specific discharge patterns to generate a map of space ([6,7], among many others). We suggest that ensembles of vCA1 neurons store experiences imbued with the motivation to avoid danger, eat, find mates, and gain or maintain social status. These ensembles of vCA1 neurons are largely anatomically segregated (Box 1) and, therefore, able to route specific information to distinct downstream targets and drive the selection of appropriate adaptive behavioral responses.

Here, we review recent circuit-based studies in rodents that provide support for this important aspect of HPC function. In addition, we discuss how dysfunction in this process may contribute to mood and anxiety disorders. Owing to the focused nature of this review, we will limit our analysis to the primary output of vHPC, the vCA1/vSub subregions.

vCA1 in motivation to avoid

One of the most well-described properties of vCA1 has been its ability to generate representations of innately anxiogenic or fearful environments and and enable an animal to react accordingly. Single-unit electrophysiological recordings and calcium imaging data from rodent models have demonstrated that neurons in vCA1, but not dCA1, have stable responses across anxiety-provoking areas of the elevated plus maze (EPM) and open field test (OFT) [8,9]. In the EPM, activity in vCA1 both correlates with baseline anxiety state and scales with the aversive nature of the cues in the task [9]. In addition, optogenetic silencing of vCA1 in mice during exploration of the anxiety-provoking areas of these assays reduces avoidance [9]. Silencing vHPC, but not dHPC, also impedes an animal's ability to associate a specific context with a fearful experience, as measured by the context specificity of tone-signaled active avoidance behavior [10]. These data demonstrate a role for vCA1 in encoding salient spatial stimuli, scaling these representations based on anxiety state and the aversiveness of the environment, and transforming these representations into an output signal that can be decoded by a downstream area for appropriate action selection (Figure 1).

While vCA1 as a whole is clearly involved in the integration of anxiogenic stimuli and the transformation of this information into appropriate behavior, sub-populations of vCA1 neurons have been implicated in specific aspects of this process. vCA1 cells encoding anxiogenic features of mazes are more abundant in populations projecting to the medial prefrontal cortex (mPFC) or lateral hypothalamus (LH), but not in neurons projecting to the nucleus accumbens (NAc) or the amygdala [8,9]. Optogenetic stimulation of vCA1-LH projection neurons decreases the exploration of anxiogenic portions of the EPM and OFT and drives avoidance in a real-time place preference assay, while inhibition reduces open arm avoidance in the EPM [9]. Similarly, when vHPC inputs to mPFC are inhibited either optogenetically or pharmacologically, open arm avoidance decreases [11,12]. Thus, vHPC projections to mPFC and LH play a role in transforming representations of anxiogenic stimuli into actions that promote avoidance. Furthermore, mPFC neurons that encode anxiety-related information in the EPM also synchronize their firing with theta-frequency

(4–12 Hz) oscillations in vHPC [12–14]. Interestingly, vCA1 neurons that project to either mPFC or LH do not tend to collateralize [9,15,16], raising the interesting possibility that these distinct output streams from vCA1 may encode specific features of a fearful environment that drive diverse classes of behavior not captured by the gross assessments used in previous studies. Recent experiments indicate that, even within the projection to mPFC, there exists functional heterogeneity, with deep and superficial layer projection neurons differentially responding to safe versus anxiogenic areas of the EPM [17]. Active areas of investigation include how distinct subclasses of projection neurons encode features of an anxiogenic environment and how local circuits contribute to the transformation of this information into an output signal that is decoded by mPFC and LH to initiate appropriate approach/avoidance decisions.

Unlike the projections to mPFC and LH, vCA1-basal amygdala (BA) projecting neurons do not seem to encode anxiogenic features of anxiety-based assays but do respond to footshocks in a contextual fear conditioning assay and are necessary for encoding context-fear associations [9,18–20]. Meanwhile, vCA1 projections to the central nucleus of the amygdala (CeA) have been implicated in context-dependent fear renewal [20], which has also been shown to recruit vCA1 outputs to prelimbic (PL) and infralimbic cortex (IL) [21]. This leads to the hypothesis that certain vCA1 projections, like vCA1-LH, may link external stimuli with internal drives to avoid more distal/diffuse threats, while other vCA1 projections, like vCA1-amygdala, vCA1-PL, and vCA1-IL, may create relationships between contextual stimuli and internal drives to avoid more proximal and immediate threats. More recently, a role for vHPC has been identified in observational fear learning. This study found that a subset of vHPC neurons responds to a familiar demonstrator mouse during observational fear by reactivating previously learned context-fear ensembles in the BLA [22].

Another area involved in the processing of diffuse threats, the BNST, receives dense input from vCA1 and has been less well studied. High-frequency electrical stimulation of vHPC can induce anxiolysis in rats, an effect blocked by intra-BNST NMDA antagonists [23]. In addition, vCA1 may exert its inhibitory control of the stress response [24] through the BNST; the BNST sends a GABAergic projection to the paraventricular hypothalamic nucleus (PVN) of the hypothalamic-pituitary-adrenal (HPA) axis [25–27]. With respect to other projection outputs, mice susceptible to chronic stress show increased activity in vHPC-NAc projection neurons [28], and individual differences in the activity of this pathway predict vulnerability to stress [29]. In addition, excess corticosterone in adolescence weakens vHPC inputs to the orbitofrontal cortex [30]. Finally, chronic stress produces a reduction in synaptic strength at vHPC-NAc synapses, specifically on D1-receptor containing medium spiny neurons, an effect that can be reversed by chronic antidepressant treatment [31]. These studies are only a few of the many that have attempted to understand how vHPC activity may be impacted in chronic stress, and future functional mapping studies can uncover how stress modulates vCA1 during related behavioral phenotypes, including avoidance and anhedonia [32]. Together, these results demonstrate the dual roles these vHPC projections play in both the integration of information and the translation of this information into a behavioral response.

vHPC and motivation to seek reward

Recent studies have highlighted the role of reward in modifying representations of diverse stimuli in the hippocampus [33,34]. In addition, place-reward representations have been well studied in HPC, and there are many excellent recent reviews on this topic (e.g., [35,36]). Both dHPC and vHPC project to and functionally interact with NAc during navigation for reward [37,38]. In the vHPC, antidromically identified vCA1-NAc projection neurons are activated during the approach to a goal location in maze-based tasks [8].

Independent of place, recent work has identified a role for this vHPC-NAc circuit in connecting the hedonic value of food with the internal drive to seek food (Figure 1). Low-frequency photostimulation of this pathway, but not other inputs to the NAc, increased the palatability of a sugar reward (as measured in licks per bout) and drove preference to a flavor paired with the stimulation, while inhibition reduced innate preference for a high-value reward [39]. In addition to the role vHPC-NAc plays in encoding palatability, vHPC-NAc activity has been implicated in the transition from anticipatory-feeding behavior to consumption. This occurs when the hunger-promoting hormone ghrelin inhibits vHPC-NAc neurons via GHSR1a receptors [40]. In line with this, optogenetic inhibition of vHPC-NAc stimulated greater eating in animals given free access to food [41]. Ghrelin may also exert its effects via the vHPC-LH pathway, where it can attenuate satiety signals by generating an interoceptive energy-deficient state [42]. Ghrelin infusion into vHPC promotes sated sucrose seeking and increases meal size. These effects are driven by vHPC outputs to LH orexin neurons that in turn project to the lateral dorsal tegmental nucleus (LDTg) [42]. These experiments highlight the rich heterogeneity of vHPC, demonstrating that vHPC engages distinct pathways involved in at least two different aspects of feeding: palatability and consumption. Future studies identifying how distinct targets of vHPC modulate these different components of feeding will shed new light on the role of vCA1 in food approach and consumption.

The vHPC has been implicated in modulating adaptive learning in pursuit of reward. For example, a recent study using odor-guided learning found that vCA1 neurons do not represent odorants at baseline and only gain representations after odor-reward learning. Odor-reward learning rapidly reorganized ensembles of neurons in vCA1 and stored these rewarded odor representations for days after learning [33]. In addition, recent work has indicated that these outputs from vCA1 can be modified via novelty—mice that explored a novel arena prior to testing in a reward-guided T-maze showed weakened vHPC-mPFC functional connectivity and were better able to learn the task. This indicates that one function of vCA1 (specifically vCA1-mPFC) is to recognize novelty and use it to modify encoded representations so that animals are better able to successfully seek reward [43].

While these studies indicate that distinct pathways may encode stimuli of specific valences, this specification is most likely plastic. For example, a recent study found that vCA1-BLA and vCA1-NAc projections could drive either preference or avoidance behavior depending on whether the neurons were associated with a positive or negative engram [44]. Such data suggest that these projections do not have fixed roles, and that context is extremely important when understanding the function of vCA1 projections in motivated behavior.

vCA1 in motivation to seek social interaction

In recent years, vHPC has been linked to social behavior, social interaction, social memory, and the representation of social hierarchy [45–48]. An animal may be motivated to approach, avoid, or ignore another animal based on characteristics of both social partners such as sex or relative social standing and by the familiarity or novelty of the other moiety. vCA1 neurons can distinguish between a familiar and novel mouse, and targeted inhibition of either whole vCA1 or CA1-NAc projection neurons (but not vCA1-BLA) reduces discrimination between novel and familiar mice [47]. In addition, vCA1 social memory neurons are reactivated during sharp-wave ripples (SWRs) offline, with a similar temporal pattern to that observed during online social interaction [49]. Interestingly, in a mouse model for autism (Shank3 KO), the number of vCA1 social memory neurons is reduced, and the sequence of neurons reactivated during offline SWRs was disrupted, suggesting a role for vCA1 in social deficits of autism-related mouse models [49]. In rats, vCA1 cells that respond when a rat interacts with a conspecific are sensitive to whisker touch interactions and ultrasonic vocalizations but show little response to an inanimate object [50]. The vCA1-mPFC projection has also been implicated in social behavior—chemogenetic excitation of this pathway or overactivity (in a mouse model of Rett syndrome) produces deficits in discriminating a novel and a familiar mouse [51]. Local silencing of PV-expressing interneurons in vCA1 can impair social discrimination, revealing an important role for local circuit dynamics in vCA1 storage of social memories. CA2 plays a central role in encoding social information [52] and projects to vCA1, creating a local circuit known to be important for social memory [45]. Other ventral hippocampal subregions, such as CA3, have also been linked to social memory [53]. In contrast, the inhibition of dCA1 or the pathway from vCA1 to BLA does not affect social discrimination [47]. Thus, specific pathways from vCA1 to NAc and mPFC are important for integrating external social cues with the internal motivation to interact with conspecifics (Figure 1).

Human studies have hinted at the importance of the hippocampus in social relationships and interactions. In a game where power and affiliation were modeled as two dimensions of social distance, the left hippocampus represented social distance between the participant and virtual characters in the game [54]. This signal was also influenced by the participant's personality traits—participants who reported less social avoidance and neuroticism showed stronger hippocampal tracking of the relative social standing. Future studies are needed to address the contributions of specific hippocampal subregions to social interaction.

Anterior hippocampus in psychiatric illness and mood

The human hippocampus has been studied for decades in relation to psychiatric illness, and the region plays an important role in the motivations to avoid danger, pursue reward, and seek social interaction, and to the formation of internal models of these three drives. Foundational work has shown decreased overall hippocampal volume in psychiatric mood disorders [55]. More specifically, mood disorders have been associated with a decrease in the number of neurons of the anterior hippocampus (aHPC) which was reversible with antidepressant treatment [56].

The primate aHPC, while analogous to vHPC in rodents, is typically larger than the posterior hippocampus, features unique extensions like the uncus, and carries more hippocampal commissural connections [57,58]. Bulk sequencing shows transcriptional similarities and functional covariance between aHPC and brain networks active during social and emotional cognition and motivational tasks [59]. Single-nucleus sequencing of the human hippocampus has demonstrated that genes identified in gene-wide association studies and linked to major depression and bipolar disorder are significantly upregulated in the aHPC [60],

Depressed patients show reduced functional connectivity between the anterior/intermediate hippocampus and the insula/NAc, and symptoms of depression are positively correlated with aHPC-NAc connectivity [61]. Similarly, patients diagnosed with post-traumatic stress disorder (PTSD) display alterations in hippocampal functional connectivity. Resting-state functional connectivity of the hippocampus as a whole is not detectably different between PTSD patients and trauma-exposed controls without PTSD. However, separating the anterior and posterior hippocampus reveals differences in anterior-posterior connectivity between the hippocampus and the precuneus and posterior cingulate cortex in trauma-exposed controls, whereas PTSD patients lack these differences [62]. In another study, veterans with PTSD showed an inverse correlation between PTSD symptoms and the anatomical and functional connectivity of the aHPC, with symptoms of hypervigilance being positively associated with reduced anatomical connectivity between the aHPC and the prefrontal cortex [63]. At the functional level, a meta-analysis of fMRI activation in the brains of PTSD patients revealed greater aHPC activity during each of the phases of fear conditioning: conditioning, extinction, and recall [64]. Finally, in a human intracranial EEG study, increased variance in HPC-amygdala coherence at the beta frequency range could predict a worsening in the subjective mood of a patient subset [65].

Together, these studies show predispositions and alterations in aHPC structure and activity that correspond to alterations in human behavior and motivational drives. Future studies linking these changes to actionable biomarkers could be used to pinpoint the early stages of psychiatric disorders when symptoms and changes in hippocampal structure are less pronounced and potentially more treatable.

Conclusion

In recent years, there has been an increasing interest in the vHPC's role in motivated and emotional behaviors. This paper reviews several important studies that have dissected the principles of the inputs and outputs of vCA1 and highlighted how distinct output streams may represent diverse features of an explored space to drive adaptive behaviors. However, a number of questions remain. First, how ensembles of vCA1 neurons interact to encode divergent behavioral states remains unknown. How these dynamics map on to the well-described anatomy of vCA1 also remains understudied (Figure 2 and Box 1). Second, it is not well understood how emotional state (such as chronic stress, antidepressant treatment, and exercise) impacts the encoding properties of anatomically and functionally defined ensembles described here. Finally, as anxiety is fundamentally a response to diffuse and unknown threats that may elicit harm in the future, it remains important to understand how prospective coding in the vHPC relates to its role in anxiety-related

behavior. Functional MRI studies in humans have suggested that the aHPC can recombine details from past experience to construct an imagined future [66]. In dCA1, there is a rapid alternation between the representation of possible future goal locations [67]; in vCA1, future research will determine how prospective coding represents safe versus aversive options. Understanding these phenomena may explain why individuals with mood and anxiety disorders generate less positive and less detailed imagined futures [68–70]. Together, future studies dissecting the cell types, population activity patterns, and behavioral functions of CA1 circuits will undoubtedly enrich our understanding of emotional and motivated states in health and disease.

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BOX 1.

Anatomical organization of vCA1

As described in detail, in this review and elsewhere, vCA1 neurons project to several cortical and subcortical areas implicated in mood/anxiety-related behavior, reward seeking, social approach, and neuroendocrine responses to stress. These include (but are not limited to) outputs to the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), lateral hypothalamus (LH), lateral septum (LS), bed nucleus of the stria terminalis (BNST), and basal and central amygdala (BA, CeA). Retrograde tracing studies and single neuron reconstructions have indicated that these outputs are non-overlapping [9,20,21,71,72]. A recent study using high-throughput sequencing of genetically barcoded neurons (MAPseq) to map the axonal projections of vCA1 neurons found that while many vCA1 neurons show a one-to-one connectivity with downstream areas, as predicted by retrograde tracing, a significant portion of neurons broadcast to multiple downstream areas in a non-random fashion [15]. This indicates that vCA1 contains a mix of single-target neurons and neurons that send highly collateralized outputs. For example, neurons that project to the LS were found by both MAPseq [15], and single neuron tracing studies [71] to send collaterals to multiple downstream areas, including the NAc, BNST, LH, and mPFC. The specialized function of these and other collateralized neurons remains to be fully delineated, but their existence suggests that information in a subclass of vCA1 neurons is relayed to many downstream areas. An active area of research is whether these collateralized neurons exhibit information coding properties that are distinct from those of neurons with a single target. One study addressing this question found that vCA1 neurons with trifurcating (or more) projections to the NAc, mPFC, and amygdala were preferentially activated during sharp-wave ripples and during approach/avoidance and reward learning [8]. Input-output tracing using rabies virus approaches has revealed that vCA1 neurons targeting distinct areas receive similar upstream input, suggesting that vCA1 integrates incoming information and sends it to multiple downstream areas [15]. Some subtle biases to input patterns were found that warrant future investigation, such as the preferential targeting of PVT inputs to vCA1-LH neurons versus vCA1-mPFC/vCA1-BA neurons, and the denser innervation of vCA1-BNST neurons by inputs from the amygdala. A recent study also demonstrated that inhibitory and excitatory input from the amygdala to vHPC can differentially modulate projection neurons to the amygdala, mPFC, and BA [73]. Further investigation is needed to elaborate how different inputs to vCA1 shape the region’s outputs in a projection-specific way. In addition, it is important to build an understanding of how long-range inputs interface with local vCA1 microcircuits to fine-tune the vCA1 output in the control of behavior. As recently described, PV local interneurons preferentially target vCA1-BA output neurons and receive innervation from vCA1-mPFC neurons [74].

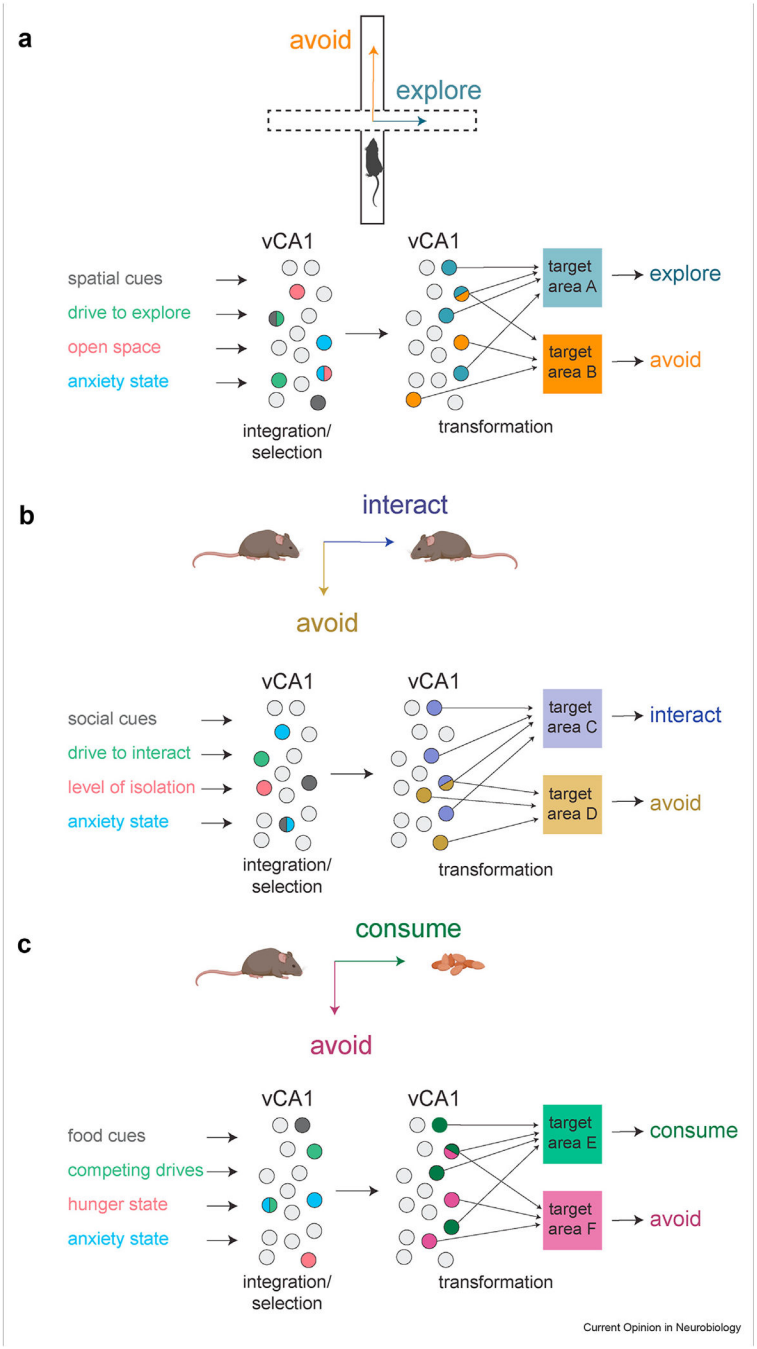

Figure 1. Hypothesized model for vCA1 encoding properties and engagement of downstream targets.

First, vCA1 integrates diverse external and internal stimuli and then shapes output signals to engage downstream areas for appropriate behavioral selection. This is a shared feature among a number of approach/avoidance behaviors such as in the elevated plus maze (a), social interaction (b), and food approach/consumption (c). The circuit mechanisms and local computations in vCA1 that integrate inputs to tune output signals remains an area of active investigation.

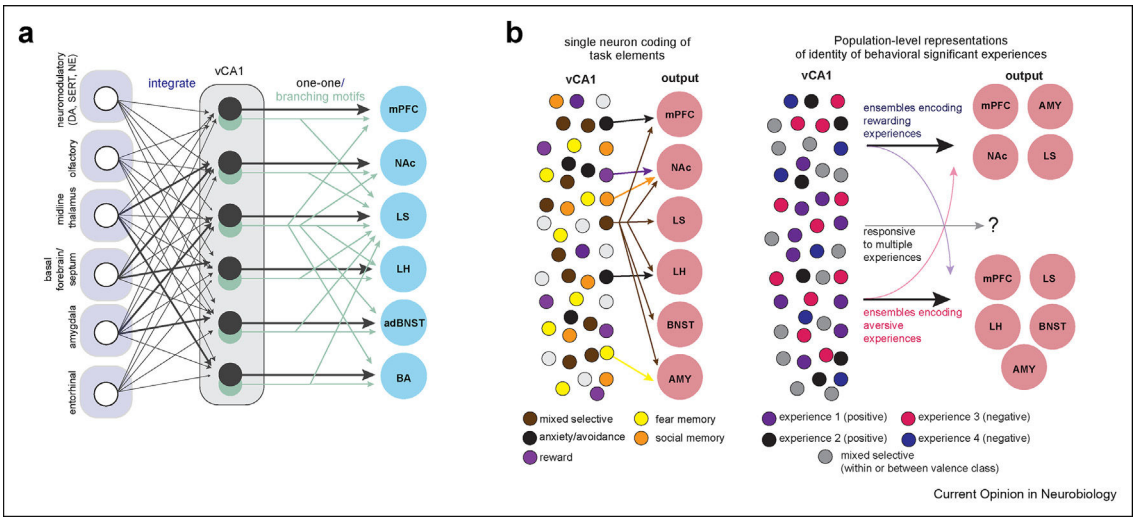

Figure 2. Functional anatomy of the vCA1 circuit.

a. Input-output organization of a subset of vCA1 connections. Modified from Ref. [15]. Based on the analysis of six projection targets of vCA1, it is believed that vCA1 largely integrates input, with some biases in the proportion of upstream input. Output to downstream areas is either via one-to-one connections (black) with a given target or connections that branch to multiple downstream areas (light green). It is important to note that this anatomical map is incomplete, as vCA1 receives input from other areas and sends output to several downstream targets not depicted here, and organizational principles to these areas remain unclear. **b.** Potential anatomical-functional relationships in vCA1. *Left*. In this well-studied scenario, single neurons encode diverse stimuli and serve different behavioral functions, and this is parcellated into distinct projection streams. Examples of this scenario include the finding that social memory is encoded in vCA1-NAc projections [47] while vCA1-LH neurons encode anxiety-related stimuli [9]. *Right*. In an alternate, non-exclusive situation, populations of vCA1 neurons encode behaviorally significant experiences [33], and vCA1 ensembles discriminate based on whether the experience is one that promotes approach or avoidance. Then, these ensembles interact with appropriate downstream areas for action selection. Whether different stimuli of the same valence class are encoded by distinct ensembles of neurons, and how different ensembles that encode different salient stimuli route this information to downstream areas remains an open area of investigation.