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Pathway specific interventions reveal the multiple roles of ventral hippocampus projections in cognitive functions

Abstract: Since the 1950s study of Scoville and Milner on the case H.M., the hippocampus has attracted neuroscientists' attention. The hippocampus has been traditionally divided into dorsal and ventral parts, each of which projects to different brain structures and mediates various functions. Despite a predominant interest in its dorsal part in animal models, especially regarding episodic-like and spatial cognition, recent data highlight the role of the ventral hippocampus (vHPC), as the main hippocampal output, in cognitive processes. Here, we review recent studies conducted in rodents that have used advanced *in vivo* functional techniques to specifically monitor and manipulate vHPC efferent pathways and delineate the roles of these specific projections in learning and memory processes. Results highlight that vHPC projections to basal amygdala are implicated in emotional memory, to nucleus accumbens in social memory and instrumental actions and to prefrontal cortex in all the above as well as in object-based memory. Some of these hippocampal projections also modulate feeding and anxiety-like behaviours providing further evidence that the "one pathway-one function" view is outdated and future directions are proposed to better understand the role of hippocampal pathways and shed further light on its connectivity and function.

Keywords: chemogenetics; cognition; efferent pathways; memory; optogenetics; ventral hippocampus.

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1 Introduction

The hippocampus (HPC) lies bilaterally in the medial temporal lobe of the mammalian brain (Vijayakumar and Vijayakumar 2013). In humans, HPC volume has been positively correlated to memory performance (Pohlack et al. 2014), while its reduction has been observed in a number of neurodegenerative diseases, such as Alzheimer's, neuropsychiatric disorders, including depression (Campbell et al. 2004), and other conditions such as stress, hypoxia, trauma and obesity (Cooper et al. 2015; Di Paola et al. 2008; Humphreys et al. 2019; McEwen 1994, 1999; Mestre et al. 2017).

In rodents, the HPC is divided into a dorsal (dHPC) and ventral (vHPC) part (corresponding to posterior and anterior HPC, respectively, in primates and humans) mainly based on anatomical connections and functional properties (Fanselow and Dong 2010; Fogwe et al. 2022; Moser and Moser 1998; Papatheodoropoulos 2018; Trompoukis and Papatheodoropoulos 2020). Both dHPC and vHPC are composed of four sub-regions, the 3 *Cornu Ammonis* (CA1, CA2 and CA3) and the dentate gyrus (DG), in addition to the subiculum, which provides the main output pathways (DeKraker et al. 2020). The HPC includes predominately pyramidal excitatory (glutamatergic) neurons, found in the granular layer of DG and pyramidal layer of CA3, CA2 and CA1, and a smaller network of inhibitory interneurons representing 10–15 % of HPC cells (Aika et al. 1994; Bezaire and Soltesz 2013; Pelkey et al. 2017). Regarding the extensive intraHPC network, connections are mainly established in each subdivision, i.e., the dorsal CA1 receives inputs mainly from dorsal CA2 and CA3, whereas input to the ventral CA1 (vCA1) is predominately from ventral CA3 through Schaffer collaterals (Amaral and Witter 1989; Tao et al. 2021). Some dorsoventral connections are also present, including projections from dorsal CA2 to vCA1 (Meira et al. 2018; Raam et al. 2017) or longitudinal DG projections from mossy cells, located in the hilus of the DG (Houser et al. 2021).

While dHPC and vHPC share some common inputs, such as the main input provided by the entorhinal cortex, their organisation appears to vary along the dorsoventral axis (Tao et al. 2021). Moreover, some inputs are specific, such as cortical inputs to the dHPC and subcortical inputs to the vHPC (Bannerman et al. 2014). The main output neurons of

dHPC and vHPC are the pyramidal excitatory neurons of CA1 and subiculum (Graves et al. 2012) and the two parts also project to common target areas, such as the lateral septum (LS; Fanselow and Dong 2010; Besnard et al. 2020). However, there are important distinctions regarding the output of the two hippocampal parts; the dHPC projects mainly to the cortex (particularly, entorhinal and retrosplenial cortices), whereas the vHPC projects to multiple subcortical and cortical target areas, including the lateral hypothalamus (LH), bed nucleus of the stria terminalis (BNST), basal amygdala (BA), shell part of the nucleus accumbens (NAc), anterior olfactory nucleus (AON) and the medial prefrontal cortex (mPFC; for reviews: Fanselow and Dong 2010; Moser and Moser 1998; O'Leary and Cryan 2014).

Regarding the vHPC projections to mPFC, recent evidence suggests a distinct anatomical and functional profile between the ventral and dorsal part of the mPFC [vmPFC and dmPFC corresponding to infralimbic (area 25) and prelimbic (area 32) cortices, respectively], which could be missed if mPFC is examined as a single region (Heidbreder and Groenewegen 2003; Liu and Carter 2018; Marek et al. 2018). Recent studies also indicate that the vast majority of vHPC neurons project to one single target area and less than 10 % project to two or three areas (Ciocchi et al. 2015; Gergues et al. 2020; Kim and Cho 2017; Kosugi et al. 2021; Parfitt et al. 2017; Wee and MacAskill 2020). Moreover, the gene profile of certain pathways (e.g. vHPC-to-vmPFC) is distinct from other vHPC pathways and the different vHPC neurons may be distinctly innervated. For instance, LH-projecting vHPC neurons receive major input from the paraventricular nucleus of the thalamus, whereas BNST-projecting vHPC neurons receive extensive input from the amygdala (Gergues et al. 2020).

Taking into consideration this anatomy, it is not surprising that the dorsal and ventral subregions are proposed to mediate different behaviours (Ciocchi et al. 2015; Jimenez et al. 2018; Parfitt et al. 2017). Although the dHPC has been extensively studied for years, less is known about the functional role of the vHPC in cognition. For instance, in rodents, lesions of the dHPC, but not vHPC, lead to spatial memory deficits (Moser et al. 1993; Pothuizen et al. 2004) reinforcing the idea that the dHPC, and not the vHPC, is important for memory processing. Traditionally, it is the dHPC that has been implicated in cognitive functions, mainly episodic-like and spatial memory, while the vHPC has been primarily linked to emotional and motivational processes (Bannerman et al. 2014; Fanselow and Dong 2010; McHugh et al. 2011). However, this dHPC/vHPC functional dichotomy does not seem to hold true as more recent studies have showed that the vHPC participates in learning and memory processes, even when emotional status is not linked to these functions

(Loureiro et al. 2012; Naneix et al. 2021; Phillips et al. 2019). In addition, the recent development of *in vivo* correlational and causal virus approaches such as fiber photometry, optogenetics and chemogenetics have been crucial in monitoring and manipulating specific vHPC efferent pathways allowing to more precisely delineate the role of vHPC in learning and memory but also the extent to which distinct vHPC efferent pathways contribute to a range of cognitive processes.

To achieve this, one strategy is to infuse in vHPC a virus carrying the gene coding for different proteins, such as GCaMP (a calcium sensor for photometry), designer receptors exclusively activated by designer drugs (DREADDs) or opsins and either to monitor terminals of these vHPC neurons in a target structure by implanting optic fibers or to manipulate these vHPC terminals through local photostimulation (optogenetics) or local infusion of specific DREADD ligands (chemogenetics) (Smith et al. 2016). These approaches can also benefit from intersectional viral approaches using the Cre-Lox system, which consists of a Cre recombinase enzyme that recombines a pair of target DNA sequences called Lox sequences. Using this strategy, a double-loxed inverted open reading frame (DIO) system, also called Cre-dependent system, can include the gene coding for GCaMP, DREADD or opsins, in an antisense configuration which prevents expression in the absence of Cre. In presence of Cre recombinase, DIO-GCaMP, DIO-DREADD or DIO-opsin is flipped allowing its expression (Atasoy et al. 2008; Patel et al. 2020). The intersectional viral approach consists of infusing a retrograde virus carrying the Cre in a particular vHPC projecting area allowing the retrograde transport of the Cre from the terminals to the vHPC cell bodies, where a second virus carrying a Cre-dependent GCaMP, DREADD or opsin is infused. Implantation of the optic fiber above these GCaMP-expressing vHPC neurons will allow monitoring them and photostimulation of vHPC neurons (optogenetics) or systemic injection of the DREADD exogenous ligand (chemogenetics) will lead to specific activation or silencing of the pathway of interest. The optimization of these techniques is still undergoing, including the development of wireless optogenetics (Yang et al. 2021) or more specific sensors for fiber photometry or receptor ligands for chemogenetics. Here, we will not cover the limitations of these techniques which have been extensively described elsewhere (Urban and Roth 2015; Vlasov et al. 2018).

The aim of the current review is to highlight the complex and understudied role of vHPC and its efferent pathways in cognition through the presentation of recent data combining specific vHPC pathway monitoring or manipulations with behavioural paradigms. Of particular interest are the role of vHPC projections to BA, NAc and vmPFC, but also to AON and LS in different cognitive functions, including fear memory,

social and non-social recognition memory, and instrumental behavior.

2 Fear memory

Fear conditioning is a form of associative learning in which an organism learns to associate a neutral conditioned stimulus (e.g. a tone or a context) with an aversive unconditioned stimulus (e.g. a mild electrical foot shock) and, on subsequent presentations of the conditioned stimulus alone, the organism presents a conditioned response (expressed as freezing; Shechner et al. 2014). Contextual fear conditioning (CFC), through its spatial component, is highly dependent on a functional HPC and several studies have shown that manipulation of the vHPC neurons projecting to basal amygdala (BA) affects CFC. For instance, optogenetic inhibition or stimulation of the vHPC-to-BA pathway reduces both the encoding and retrieval of CFC (Jimenez et al. 2018; Kim and Cho 2020; Xu et al. 2016) and opto-stimulation of this pathway during retrieval also rescues CFC deficits in *Il1rapl1* knock-out mice, a model of intellectual disability (Zhang et al. 2015). Given that optogenetic stimulation of vHPC-BA pathway reduced CFC in normal conditions but rescued a pre-existing CFC deficit suggests that a balanced level of activity in this pathway is required for CFC, with an inverted U-shaped functional relationship. The vHPC-to-BA pathway is also required for other context-related aspects of fear behaviour such as generalization and observational fear. Indeed, inhibition of this pathway decreases CFC generalization, i.e., fear responses in a context different from the conditioning context, at remote intervals after conditioning (Ortiz et al. 2019), and also observational fear, the ability to experience other's fearful situation (Terranova et al. 2022). Altogether, these studies implicate the vHPC-to-BA pathway in the contextual regulation of fear, including memory generalization and observational memory.

vHPC neurons projecting to vmPFC and dmPFC are also important for fear memory. Regarding vHPC-to-dmPFC, a recent study investigated the pattern of neural activity during fear conditioning in both rodents and humans and found that this pathway is more active when safety cues are presented than with threat cues are presented, and its activity correlated with freezing behaviour in rodents (Meyer et al. 2019). Interestingly, inhibition of this pathway also reduces CFC encoding in rats (Twining et al. 2020). By contrast, the vHPC-to-vmPFC pathway appears to be required for fear extinction. Indeed, brain-derived neurotrophic factor (BDNF), a growth factor crucial for brain plasticity, is increased in the vHPC following fear extinction and BDNF infusion into the vHPC reduces conditioned freezing and increases the firing rate of vmPFC, but not dmPFC, neurons in fear conditioned rats (Peters et al. 2010; Rosas-Vidal et al. 2014). Blocking BDNF in the vmPFC restored fear following vHPC BDNF infusion, and BDNF infusion in vmPFC, but not dmPFC, induces fear extinction (Peters et al. 2010; Rosas-Vidal et al. 2014). These studies show that the vHPC-BA and vHPC-dmPFC pathways control encoding and retrieval of CFC, while the vHPC-vmPFC pathway seems to regulate fear extinction. Taking into account that the vmPFC and dmPFC receive projections form the BA, these structures together with the vHPC may participate in fear memory regulation (Adhikari et al. 2015). Specifically, the amygdala-dmPFC-vHPC circuit may modulate fear expression, while fear extinction is likely mediated by an amygdala-vmPFC-vHPC circuit (Sierra-Mercado et al. 2011). However, the extent of the frontal network involved in fear extinction may also depend on the use of active (avoidance) versus passive (freezing) coping. A recent study has shown that avoidance extinction increases BDNF expression in both vmPFC- and dmPFC-projecting vHPC neurons and blocking BDNF in either vmPFC or dmPFC delays recall of avoidance extinction (Rosas-Vidal et al. 2018).

Other vHPC efferent pathways may also participate in CFC. For example, a recent study using *in vivo* calcium imaging suggested that activity in the vHPC-to-LS pathway (vCA3 to LS) is associated with suppressed CFC responses, whereas activity in an intra-hippocampal pathway, vCA3-to-vCA1, is associated with elevated CFC responses (Besnard et al. 2020). By contrast, manipulating projections from vHPC to central amygdala or LH does not affect CFC retrieval (Jimenez et al. 2018; Xu et al. 2016). Interestingly, vHPC projections to central amygdala, but not to BA, are required for contextual gating of cued fear memory retrieval after extinction (Xu et al. 2016). A summary of the aforementioned studies examining the effect of manipulating vHPC efferent pathways on fear behaviour is shown in Table 1.

3 Social memory

Since the first lesion work of Kogan and colleagues (Kogan et al. 2000), the hippocampus has been reported to have a critical role in social learning and memory, i.e., remembering an interaction with a conspecific. More recent studies have highlighted the specific role of the dorsal CA2 area in social memory (Hitti and Siegelbaum 2014) and of its projection to ventral CA1 (Meira et al. 2018; Raam et al. 2017). Indeed, in vCA1, both pyramidal projecting neurons and parvalbumin interneurons have been implicated in social memory (Deng et al. 2019; Okuyama et al. 2016). Using calcium imaging, these studies revealed that vCA1 parvalbumin interneurons showed

Table 1: Effects of manipulating vHPC efferent pathways on contextual fear memory.

vHPC target area	Approach species	Effect on contextual fear memory	References
BA	Opto **Mice**	Inhibition ↘ retrieval *Laser during retrieval*	Xu et al. (2016)
BA	Chemo **Mice**	Inhibition ↘ encoding *CNO 30 min before conditioning*	Kim and Cho (2020)
BA	Opto **Mice**	Stimulation ↘ encoding/ retrieval *Laser during conditioning or retrieval*	Jimenez et al. (2018)
BA	Opto **Mice**	Stimulation ↗ retrieval in KO *Laser 1 h before retrieval*	Zhang et al. (2015)
BA	Chemo[a] **Mice**	Inhibition ↘ generaliza- tion *CNO 5 min before test*	Ortiz et al. (2019)
BA	Opto **Mice**	Inhibition ↘ observa- tional fear *Laser during conditioning*	Terranova et al. (2022)
dmPFC	Opto **Rats**	Inhibition ↘ encoding *Laser during conditioning*	Twining et al. (2020)
LS	Opto **Mice**	Inhibition ↗ freezing *Laser after conditioning*	Besnard et al. (2020)
CeA	Opto **Mice**	No effect on retrieval *Laser during retrieval*	Xu et al. (2016)
LH	Opto **Mice**	No effect on encoding/ retrieval *Laser during conditioning or retrieval*	Jimenez et al. (2018)

Studies reporting an increase (↗), a decrease (↘) or no effect after chemo- or optogenetic manipulation of vHPC neurons projecting to the basal amygdala (BA), the dorso-median prefrontal cortex (dmPFC), the lateral septum (LS), the central amygdala (CeA) or the lateral hypothalamus (LH). [a]CNO was infused into the BA.

a higher level of activation when mice were exposed to novel mice than to familiar mice (Deng et al. 2019), whereas vCA1 pyramidal cells demonstrated the opposite pattern with more cells activated in response to a familiar mouse than to a novel mouse (Okuyama et al. 2016). Moreover, specific optogenetic manipulation of either of these neuronal populations affected social memory retrieval (i.e., discrimination between familiar and novel mice), and optogenetic reactivation of vCA1 pyramidal neurons that responded to the familiar mouse elicited memory retrieval, which suggests that vCA1 pyramidal cells encode a social engram, e.g. physical traces of social memory (Okuyama et al. 2016).

Okuyama and colleagues also revealed that projections from vCA1 pyramidal cells to NAc shell (but not BA or olfactory structures) mediate social memory (Okuyama et al. 2016). In particular, opto-inhibition of the vHPC-to-NAc

pathway disrupted whereas opto-stimulation of this pathway improved social memory (Okuyama et al. 2016), suggesting these NAc-projecting vHPC neurons store the memory of familiar conspecifics. It was also reported that optogenetic stimulation of vHPC projections to anterior olfactory nucleus (AON), a forebrain olfactory structure, impaired social discrimination (Aqrabawi et al. 2016) but control experiments revealed it was related to olfactory processing rather than social memory. More recently, it was shown that chronic chemogenetic activation or inhibition of the vHPC-to-vmPFC pathway impairs social recognition (Phillips et al. 2019). Similar social memory deficits were obtained with acute chemogenetic activation of vHPC-to-vmPFC, but not vHPC-to-NAc projections (Phillips et al. 2019). These results are in contrast with those of Okuyama et al. (2016), showing modulation of social memory after opto-manipulation of vHPC-to-NAc pathway which may be due to the use of different techniques to manipulate this pathway (local optogenetic inhibition/stimulation versus intersectional viral approach for chemogenetic activation) or more likely due to some redundancy between the two pathways (vHPC-to-vmPFC and vHPC-to-NAc). Indeed, two recent papers indicate that vmPFC projections to NAc control social recognition memory (Park et al. 2021a; Xing et al. 2021), especially during retrieval (Xing et al. 2021), highlighting the possibility that, in addition to vHPC-to-NAc circuit, the vHPC-vmPFC-NAc circuit is also essential for social memory. A summary of the studies examining the effect of manipulating vHPC efferent pathways on social memory is shown in Table 2.

4 Recognition memory

Rodents are able to recognize objects or (non-social) odours previously encountered based on either recollection (precise retrieval of information about a specific episode) or familiarity (Eichenbaum et al. 2007). In rodents, this memory is based on the natural tendency of rodents to more extensively explore what is new, as demonstrated in several tasks including novel object or odour, familiar object or odour in novel location, novel object-location or odour-location association, novel object-context or odour-context association, and object or odour temporal order memory. The vHPC has been shown to play a key role in object-based and odour-based recognition memory (Martin et al. 2007; Naneix et al. 2021). For instance, we recently showed that obesogenic diet impairs long-term novel recognition memory through vHPC overactivation, since chemogenetic inactivation of vHPC projection neurons (achieved using virus carrying CaMKII promoter) rescued

Table 2: Effects of manipulating vHPC efferent pathways on social memory.

vHPC target area	Approach species	Effect on social memory	References
NAc	Opto **Mice**	Inhibition ↘ retrieval Stimulation ↗ retrieval	Okuyama et al. (2016)
AON	Opto **Mice**	Stimulation ↘ olfactory processing	Aqrabawi et al. (2016)
vmPFC	Chemo **Mice**	Chronic stimulation or inhibition ↘ Acute stimulation ↘ retrieval	Phillips et al. (2019)
Olfactory bulb	Opto **Mice**	No effect *Laser during retrieval*	Okuyama et al. (2016)
BA	Opto **Mice**	No effect *Laser during retrieval*	Okuyama et al. (2016)
NAc	Chemo **Mice**	No effect *CNO before retrieval*	Phillips et al. (2019)
vmPFC	Opto **Mice**	No effect on olfactory processing *Laser during retrieval*	Aqrabawi et al. (2016)

Studies reporting an increase (↗), a decrease (↘) or no effect after chemo- or opto-genetic manipulation of vHPC neurons projecting to the nucleus accumbens (NAc), the anterior olfactory nucleus (AON), the ventro-medial prefrontal cortex (vmPFC) or the basal amygdala (BA).

diet-induced deficits in recognition memory (Naneix et al. 2021).

The number of studies that have assessed the impact of vHPC pathway manipulation on object-based recognition memory is quite limited and most focus on vHPC-to-vmPFC pathway. Recently, Morici and colleagues showed that coherence and synchronisation of vHPC-vmPFC activity is increased during exploration of contextually mismatched objects and that pharmacological disconnection of vHPC and vmPFC abolished the retrieval of object-in-context memory (Morici et al. 2022). Another study proposed that vHPC-to-vmPFC pathway inhibition specifically impairs object in-place memory (based on object-location association), without affecting temporal order memory, location memory, or novel object recognition memory (Barker et al. 2017; see also Phillips et al. 2019). Regarding the vHPC projections mediating the effect of obesogenic diet on object-based memory, we recently demonstrated that specific inactivation of the vHPC-to-vmPFC, but not vHPC-to-NAc, pathway alleviated impairments of object location memory induced by obesity, whereas inactivation of the vHPC-to-NAc, but not vHPC-to-vmPFC, pathway during training rescued obesity-induced deficits of long-term object recognition memory (Bakoyiannis et al. 2022). Therefore, in addition to its role in fear and social memory, the vHPC-to-vmPFC pathway is also implicated in some object-based memory, such as object-in-context, object-in-place and object location memory.

The impact of vHPC pathway manipulation on olfactory recognition memory has also been evaluated, with a focus on vHPC projections to the AON (Aqrabawi and Kim 2018b; Aqrabawi et al. 2016). Opto-stimulation of vHPC-to-AON, but not vHPC-to-vmPFC, impairs olfactory-guided behaviours (Aqrabawi et al. 2016) and chemogenetic inhibition of the vHPC-to-AON pathway leaves novel odour recognition memory intact but impairs retrieval in odour-context association and temporal order memory tasks (Aqrabawi and Kim 2018b). Both of these effects are still observed when the inhibition is restricted to vHPC neurons that project to the medial part of the AON (mAON), whereas similar manipulation of projections to the lateral AON (lAON) disturbs odour-context associations but not temporal order memory (Aqrabawi and Kim 2018b). Table 3 summarizes the results of these studies on the role of vHPC projections to vmPFC and AON in recognition memory.

5 Instrumental actions

Instrumental actions, established via instrumental conditioning, allow organisms to acquire new behavioural strategies and exert control over their environments. It was originally proposed, based on lesion studies, that vHPC was not required for the performance of instrumental actions or for the acquisition and expression of goal-directed actions, as assessed by contingency degradation and outcome devaluation tasks (Corbit et al. 2002; Macedo et al. 2008). Indeed, instrumental behaviour was shown to be unaffected in rats with neonatal vHPC lesions (Macedo et al. 2008) or in rats with lesions of the ventral subiculum performed at adulthood, prior to behavioural testing (Corbit et al. 2002). It was argued that the deficits in goal-directed behaviour that had previously been observed following vHPC lesions were actually due to damage to fibres passing through vHPC en route to entorhinal cortex (Corbit et al. 2002). However, Gourley et al. (2010) later challenged this position. Using a deterministic reversal task, they showed that mice with vHPC lesions were able to correctly shift their responding to a newly reinforced nose-poke aperture but showed impaired response inhibition on the previously reinforced nose-poke. These mice also showed increase break-points in a progressive ratio task (Gourley et al. 2010). The authors observed a similar pattern of results in mice with lesions of medial orbitofrontal cortex (mOFC), suggesting that vHPC may send information to mOFC regarding the current motivational properties of a rewarding outcome (Gourley et al. 2010).

Table 3: Effects of manipulating vHPC efferent pathways on object/odour-based memory and instrumental actions.

Functions investigated	vHPC target area	Approach species	Effects	References
Object in-place memory	vmPFC	Chemo **Rats**	Inhibition ↘	Barker et al. (2017)
Object location memory	vmPFC	Chemo **Mice**	Inhibition rescues obesity-induced ↘ *CNO before acquisition*	Bakoyiannis et al. (2022)
Object recognition, temporal order memory	vmPFC	Chemo **Rats**	No effect	Barker et al. (2017)
Object recognition memory	vmPFC	Chemo **Mice**	No effect	Phillips et al. (2019)
Object recognition memory	vmPFC	Chemo **Mice**	No effect in obese mice	Bakoyiannis et al. (2022)
Object recognition memory	NAc	Chemo **Mice**	Inhibition rescues obesity-induced ↘ *CNO before acquisition*	Bakoyiannis et al. (2022)
Object location memory	NAc	Chemo **Mice**	No effect in obese mice	Bakoyiannis et al. (2022)
Odour-context association	mAON lAON	Opto **Mice**	Inhibition ↘ retrieval	Aqrabawi and Kim (2018a)
Olfactory temporal order memory	mAON	Opto **Mice**	Inhibition ↘ retrieval	Aqrabawi and Kim (2018b)
Novel odour memory	AON	Both **Mice**	No effect *CNO or laser before retrieval*	Aqrabawi and Kim (2018a, 2018b)
Instrumental conditioning	OFC	Chemo **Mice**	Inhibition ↘ sensitivity to changes in contingency	Barfield and Gourley (2019)
Instrumental conditioning	OFC	Opto **Mice**	Inhibition ↘ sensitivity to changes in contingency	Wikenheiser et al. (2017)
Instrumental conditioning	NAc	Chemo[a] **Mice**	Inhibition ↗ sensitivity to changes in contingency	Barker et al. (2019)

Studies reporting an increase (↗), a decrease (↘) or no effect after chemo- or optogenetic manipulation of vHPC neurons projecting to the ventro-medial prefrontal cortex (vmPFC), the nucleus accumbens (NAc), the anterior olfactory nucleus (AON, the medial part; mAON, the lateral part; lAON) or the orbitofrontal cortex (OFC). [a]CNO was infused into the NAc.

More recent studies have also reported changes in instrumental actions following temporary activation or inhibition of vHPC and its efferent pathways (see Table 3). For example, Yoshida and colleagues (2019) observed that calcium activity in ventral CA1 (but not dorsal CA1) was suppressed during lever pressing to obtain a reward or to avoid an aversive footshock. Optogenetic activation of ventral CA1 (vCA1) also impaired ongoing lever pressing for reward, whereas opto-inhibition increased the latency to complete a sequence of lever presses and increased the break point in a progressive ratio task (Yoshida et al. 2019). These effects were shown to be mediated by serotonin in vCA1 as serotonin receptor antagonist increased vCA1 activity and reduced lever pressing (Yoshida et al. 2019).

Stress-induced modulation of vHPC activity can also affect instrumental actions. Chronic social defeat stress decreases motivation on a food-seeking lever-press task and suppression of vCA1 activity rescues this stress-induced motivational impairment (Yoshida et al. 2021). Moreover, overexpression of the stress sensitive tyrosine kinase B in vHPC impaired instrumental contingency degradation and reduced progressive ratio breakpoints (Barfield et al. 2017). Interestingly, this effect may be mediated via vHPC efferents to lateral orbitofrontal cortex (lOFC; Barfield and Gourley 2019), as corticosterone-induced stress reduces vHPC axon terminals in lOFC and inactivation of lOFC-projecting neurons in vHPC impairs instrumental contingency degradation (Barfield and Gourley 2019). Others have also argued that the vHPC-lOFC pathway is critical for adapting to changes in action-outcome contingencies. Using a nose-poke reversal task in rats, Wikenhaiser et al. showed that suppression of ventral subiculum output slows behavioural adaptation to changes in reward contingency and attenuates encoding of response information in OFC (Wikenheiser et al. 2017). While vHPC pathways to prefrontal cortex appear necessary for goal-directed behaviour (i.e., behaviour that is sensitive to changes in action-outcome relationships), vHPC projections to ventral striatum may support habitual behaviour. Indeed, chemogenetic silencing of the vHPC-to-NAc shell pathway results in maintained sensitivity to changes in the action-

outcome contingency under conditions that would normally result in a behaviour that is insensitive to these changes, i.e., habitual behaviour (Barker et al. 2019). That is, habitual behaviour can be prevented in rats by inhibiting vHPC neurons that project to the shell region of the NAc. Together, these studies support a dissociable role for hippocampo-cortical versus hippocampo-striatal pathways in instrumental behaviours (Table 3). Specifically, activity in the vHPC-to-OFC pathway favours goal-directed control whereas activity in the vHPC-to-NAc pathway impairs this control and promotes habitual responding. These distinct efferent pathways may therefore be required to maintain the balance between goal-directed and habitual action control. The contrasting effect of inhibition of these pathways may explain why non-specific lesions of vHPC failed to affect instrumental behaviour. Acute neural interventions may also have more severe effect than chronic interventions, due to the compensation that can occur following brain lesions (Otchy et al. 2015; Wolff and Ölveczky 2018).

6 Appetitive memory and feeding behaviour

Amnesic patients suffering from hippocampal damage show enhanced consumption of successive meals (Higgs et al. 2008). In rodents, lesions of the vHPC also increase food consumption (Davidson and Jarrard 1993; Davidson et al. 2009; Hock and Bunsey 1998) suggesting that the vHPC controls feeding behaviour both in humans and animals (Kanoski and Grill 2017).This seems to be related to role of vHPC in both food-related memory and food intake *per se.* Indeed, data in rodents indicate that vHPC regulates energy intake through memory of meal episodes. Pharmacological or optogenetic vHPC silencing after the end of a meal accelerated the onset of the next meal, suggesting that vHPC is required for the inhibitory effect of memory on future intake (Hannapel et al. 2017, 2019). In addition, opto- and chemogenetic inhibition of vHPC increased food intake, while stimulation of vHPC reduced it (Sweeney and Yang 2015).

Various vHPC efferent pathways have been proposed to mediate these alterations of feeding-related behaviours (Kanoski and Grill 2017). A recent study indicated that vHPC-to-vmPFC communication flexibly encodes new spatial rules that predicts future food reward (Park et al. 2021b), and a fiber photometry study showed that the vHPC-to-LS pathway is activated during food-seeking behaviour (Kosugi et al. 2021), suggesting the vHPC could participate in spatial exploration/memory related to food.

Indeed, inhibition of vCA3-LS pathway accelerates food exploration during environmental uncertainty, while silencing the vCA1-to-LS increased the latency to initiate food exploration (Yeates et al. 2022) without affecting anxiety-like behaviours (see below and Table 4). Another study revealed that chemogenetic inactivation of the vHPC-to-LS pathway impairs location memory of food reinforcement, without affecting aversive spatial memory, food-motivated operant responding, or non-spatial HPC-dependent appetitive memory (Décarie-Spain et al. 2022).

Using fiber photometry, it has also been revealed that the vHPC-to-LS pathway is activated during the consummatory phase (Kosugi et al. 2021) and opto-stimulation of the vHPC-to-LS pathway reduces food consumption (Sweeney and Yang 2015). Similarly, stimulation of the vHPC-to-BNST pathway decreases food intake while silencing this pathway increases food intake (Sweeney and Yang 2015). This suggests that vHPC projections to LS and BNST regulate food intake by impeding overconsumption.

The vHPC is under the influence of hormones controlling food intake such as ghrelin, leptin or glucagon-peptide 1 (GLP-1). Indeed, ghrelin, a gut derived hormone that augments feeding (Tschöp et al. 2000), has many receptors in vHPC. Infusion of ghrelin in the vHPC increases food intake and the proposed mechanism involves vHPC-to-LH pathway (Suarez et al. 2020). In contrast to ghrelin, leptin and GLP-1 inhibit hunger (Brennan and Mantzoros 2006) and leptin administration in the vHPC has been shown to reduce food intake (Kanoski et al. 2011). There are also numerous GLP-1 receptors (GLP-1R) in the vHPC and administration of a GLP-1R agonist in the vHPC leads to decreased food intake (Holst 2007; Hsu et al. 2015). Interestingly, chemogenetic inhibition of the vHPC-to-vmPFC pathway blocks the GLP1R-induced reduction of food intake (Hsu et al. 2018). These studies indicate that hormonal signalling in the vHPC can increase or reduce feeding behaviour and suggest these opposite effects involve specific efferent pathways (LH and vmPFC, respectively). A summary of the studies examining the effect of manipulating vHPC efferent pathways on feeding behaviour is shown in Table 4.

7 Anxiety-like behaviour

The link between vHPC and emotional processes, including anxiety, has been well established. Increased activity has been observed in the vHPC when animals explore the anxiogenic open arms of the elevated-plus maze (Ciocchi et al. 2015; Jimenez et al. 2018; Yoshida et al. 2019) and lesions, chemo- or optogenetic silencing of vHPC decrease anxiety-

Table 4: Effects of manipulating vHPC efferent pathways on feeding and anxiety-related behaviours.

Functions	vHPC target area	Approach species	Effects	References
Appetitive flexible memory	vmPFC	Opto **Mice**	Activation ↘ updating	Park et al. (2021a, 2021b)
Appetitive spatial memory	LS	Chemo **Rats**	Inhibition ↘ CNO before retrieval	Décarie-Spain et al. (2022)
Food exploration	LS	Chemo[a] **Rats**	Inhib vCA3-LS ↗ approach Inhib vCA1-LS ↘ approach	Yeates et al. (2022)
Food intake	LS	Both **Mice**	Stimulation ↘	Sweeney and yang (2015)
Food intake	BNST	Chemo **Mice**	Stimulation ↘ Inhibition ↗	Sweeney and yang (2015)
Food intake	vmPFC	Chemo[a] **Rats**	Inhibition blocks ↘ induced by vHPC GLP1R	Hsu et al. (2018)
Anxiety (EPM)	vmPFC	Opto **Mice**	Inhibition ↘	Padilla-Coreano et al. (2016)
Anxiety (EPM, OFT)	vmPFC	Chemo **Mice**	Stimulation ↗	Parfitt et al. (2017)
Anxiety (**EPM**)	vmPFC	Opto **Mice**	Stim deep vHPC layer ↗ Stim superficial layer ↘	Sánchez-Bellot et al. (2022)
Anxiety (EPM, OFT)	LH	Opto **Mice**	Stimulation ↗ Inhibition ↘	Jimenez et al. (2018)
Anxiety (OFT)	BA	Opto **Mice**	No effect	Jimenez et al. (2018)
Anxiety (EPM, OFT)	LS	Chemo **Mice**	Stimulation ↘ Inhibition ↗	Parfitt et al. (2017)
Anxiety (EPM, Conflict task)	LS	Chemo[a] **Rats**	No effect in EPM inhib vCA3-LS ↗ conflict Inhib vCA1-LS ↗ approach	Yeates et al. (2022)
Depression (CSDS)	NAc	Opto **Mice**	Stimulation ↗	Bagot et al. (2015)
Depression (FST)	NAc	Chemo[a] **Mice**	Inhibition rescues obesity-induced ↗	Tsai et al. (2022)

Studies reporting increase (↗) or decrease (↘) effect after chemo- or optogenetic manipulation of vHPC neurons projecting to the lateral septum (LS), the ventro-medial prefrontal cortex (vmPFC), the bed nucleus of the stria terminalis (BNST), the lateral hypothalamus (LH), the basal amygdala (BA) or the nucleus accumbens (NAc). [a]CNO was infused into LS, vmPFC or vHPC (after retrograde DREADD virus into the NAc). EPM, Elevated-plus maze; OFT, Open-field test; Conflict task, approach-avoidance conflict resolution; CSDS, chronic social defeat stress; FST, forced swim test.

like behaviours (Bannerman et al. 2003; Jimenez et al. 2018; McHugh et al. 2004; Parfitt et al. 2017).

Recent studies have also highlighted the critical role of the vHPC efferent pathways in anxiety (see Table 4). vHPC neurons projecting to the mPFC are enriched with information about anxiety (Ciocchi et al. 2015) and inhibition of the vHPC-to-vmPFC pathway reduces anxiety (Padilla-Coreano et al. 2016) while its stimulation increases anxiety (Parfitt et al. 2017). A recent study also revealed that vHPC projection to vmPFC is composed of two parallel circuits located in the superficial or deep pyramidal layers of the CA1/subiculum border (Sánchez-Bellot et al. 2022). These circuits show opposing activity during exploration of the closed and open arms of the elevated-plus maze and optogenetic activation of superficial vHPC-to-vmPFC population reduces anxiety-like behaviours, promoting open arm exploration; while activation of the deep circuit is

anxiogenic, reducing open arm exploration (Sánchez-Bellot et al. 2022).

Other vHPC efferent pathways are also important for regulating anxiety-like behaviours. For example, stimulation of the vHPC-to-LH, but not vHPC-to-BA, pathway augments anxiety behaviour (Jimenez et al. 2018). This absence of effect of vHPC-to-BA manipulation is surprising as it is well established that direct glutamatergic input from the basolateral amygdala to the vHPC mediates anxiolytic effects (Felix-Ortiz et al. 2013; Pi et al. 2020). vHPC-to-LS pathway is also activated during an aversive or anxious-like state (Kosugi et al. 2021). In addition, stimulation of the vHPC-to-LS reduces anxiety whereas inhibition of this pathway elevates anxiety-like behaviours assessed using elevated-plus maze and open-field tests (Parfitt et al. 2017). Another recent study compared the effects of inactivation of discrete sub-populations of vHPC neurons projecting to

LS (vCA3-LS and vCA1-LS), in the elevated-plus maze, as a measure of approach-avoidance "anxiety", and in a learned approach-avoidance conflict resolution task (Yeates et al. 2022). While inhibition of each sub-circuit has no effect on the elevated-plus maze, it did affect performance in the learned conflict task. Silencing the vCA3-LS increased conflict approach and suppressed avoidance responses, whereas inactivation of vCA1-LS increased non-specific approach responses (Yeates et al. 2022). This demonstrates the differential effect of chemogenetic inhibition of the whole versus discrete vHPC projections to LS on anxiety-like behaviours (Yeates et al. 2022). These results indicate that the vHPC-LS pathway plays an opposite role to the vHPC-vmPFC and vHPC-LH pathways in anxiety-like behaviour, with the former exhibiting an anxiolytic-like effect (Table 4).

Some vHPC pathways have also been shown to regulate other emotional behaviours. Chronic stress, a model of depression, induced increased activity in the vHPC-to-NAc pathway (Muir et al. 2020) and opto-stimulation of this pathway enhanced stress susceptibility after chronic social defeat stress (Bagot et al. 2015), whereas chemogenetic inhibition of the vHPC-NAc pathway rescued obesity-induced depressive-like behaviour (Tsai et al. 2022; Table 4). Finally, activation of the vHPC promotes, while its inhibition reduces, aggressive behaviour induced by stress and this behaviour is modulated by projections to the ventromedial hypothalamus (Chang and Gean 2019).

8 Conclusions and perspectives

The role of the vHPC in cognitive functions has recently received a great deal of attention. Indeed, the availability of new tools in animal models in the last decade has allowed researchers to activate or inhibit specific subpopulations of this major output region of the hippocampus, based on their projections. In particular, studies using these tools have revealed that the vHPC-BA pathway is implicated in emotional memory, the vHPC-NAc in social memory and instrumental actions, while the vHPC-vmPFC in all the above as well as in object-based memory (Figure 1). Even this simplified scheme highlights that the concept of "*one pathway – one function*" is outdated.

It should be noted that many studies claiming to specifically manipulate activity in vHPC (or dHPC) also include the intermediate part of the HPC (iHPC) in their area of interest. This region of the hippocampus is considered a relay for integrative information rather than an intermediate transitional region (Bast et al. 2009; Cembrowski et al. 2016; Levone et al. 2020) and has been proposed to be functionally independent to dHPC and vHPC, thanks in particular to specific efferent projections (Aqrabawi and Kim 2018a, 2018b; Bast 2007; Barker et al. 2017; Strange et al. 2014). As such, it is not entirely clear the extent to which some of the effects on cognitive behaviour reported above can be solely attributed to vHPC pathways and not iHPC pathways.

This review highlights that one vHPC pathway can support many cognitive functions. For instance, as mentioned above, the vHPC-vmPFC pathway is involved in CFC, social memory and object-based memory (Figure 1; Barker et al. 2017; Ciocchi et al. 2015; Parfitt et al. 2017; Park et al. 2021a; Phillips et al. 2019) but the specific vHPC sub-populations remain to be characterized, including whether they receive distinct inputs from other structures (see Sánchez-Bellot et al. 2022; Gergues et al. 2020). To address this question, an important strategy would be to combine transgenic and viral approaches in order to tag vHPC-to-vmPFC neurons based on neural activity markers (such as c-Fos) during different experiences (e.g. CFC training, social interaction and object exploration). This will reveal if segregated or overlapping vHPC cell populations respond to different experiences, as recently reported for vHPC neurons activated by aversive and appetitive stimuli (Shpokayte et al. 2022).

This review also highlights that several vHPC efferent pathways may be required to support a single cognitive function. For instance, it has been shown that vHPC projections to NAc, vmPFC, and potentially AON, modulate social memory (Figure 1). The specific and complementary roles of these different pathways in social memory remain to be clarified. Future research may determine the temporal involvement of these pathways; that is, during memory encoding, consolidation and/or retrieval (Jimenez et al. 2018; Kosugi et al. 2021; Okuyama et al. 2016). It would also be important to refine the behavioural tasks in order to clarify the role of each pathway. For instance, vHPC projections to BA and central amygdala are both involved in context-dependent regulation of fear behaviour. However, they regulate different aspects of this function with one pathway mediating contextual fear memory retrieval and the other controlling contextual gating of cued fear memory retrieval after extinction (Xu et al. 2016).

Specifically manipulating terminals of activity-dependent tagged vHPC neurons would also provide an interesting perspective to distinguish the role of different pathways in one particular function, as recently described (Shpokayte et al. 2022). In this report, vHPC neurons were tagged with aversive or appetitive experiences which also drove opsin expression in these neurons and their terminals. Opto-stimulation of tagged vHPC terminals in BA and NAc,
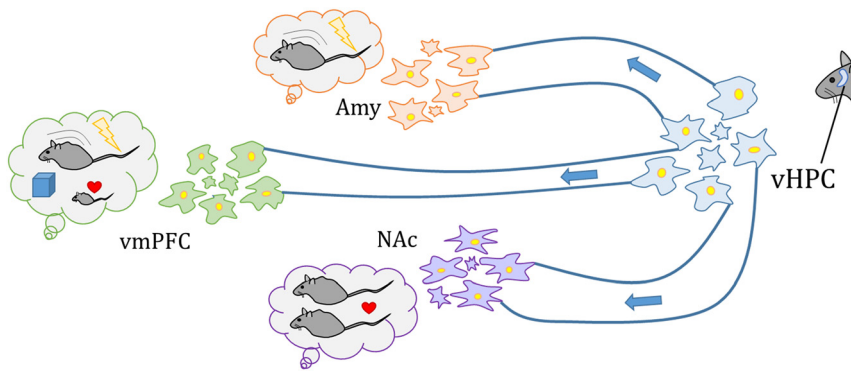
Figure 1: Ventral hippocampus (vHPC) specific pathway manipulation and their possible effects on different types of memory: fear (lightning), social (heart) and object (blue square) memory. Amy: amygdala, vmPFC: ventro-medial prefrontal cortex; NAc: nucleus accumbens. Considering vHPC-to-Amy manipulation does not affect social memory, more investigation is requested to fully characterize the role of this pathway in object-based memory and of the vHPC-to-NAc pathway in fear and object-based memory.

but not vmPFC, were able to elicit the behavioral output of the tagged experience, that is, avoidance or preference (Shpokayte et al. 2022). Therefore, it would be possible to tag vHPC neurons activated by social experience (see Okuyama et al. 2016) and to manipulate terminals of these tagged neurons in the NAc, vmPFC and AON to clarify their respective roles. The use of different DREADDs, such as the muscarinic and κ-opioid receptors-derived DREADD in combination with different ligands (such as clozapine-N-oxide and salvinorin B; Vardy et al. 2015) may also be useful to simultaneously manipulate two vHPC pathways (in the same or opposite directions) during behaviour.

Defining the possible role of vHPC pathway collaterals may also be particularly useful as their role remains largely unknown. Indeed, 5–10 % of vHPC neurons project to two or three areas (Ciocchi et al. 2015; Gergues et al. 2020; Kim and Cho 2017; Kosugi et al. 2021; Parfitt et al. 2017; Wee and MacAskill 2020) and collateral projections to vmPFC, NAc and BA have been reported to be more active during a variety of behaviors, including fear renewal (Jin and Maren 2015), and during sharp wave/ripples (Ciocchi et al. 2015). Therefore, it would be useful to specifically manipulate neurons projecting to two targets, using for instance intersectional viral approaches, to evaluate the specific role of collateral vHPC projections in behaviour.

Finally, as the gene profile of certain vHPC pathways is distinct from other pathways (Gergues et al. 2020), the exact cellular and molecular mechanisms via which the vHPC can orchestrate and modify these cognitive behaviours also remains to be determined.

Overall, future research in this field will be beneficial to our understanding of HPC function and its related circuitry, which may boost therapeutic research against disorders characterized by impaired HPC homeostasis.

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