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REVIEW ARTICLE

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The complexity of ventral CA1 and its multiple functionalities

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Abstract

The hippocampus is one of the most widely investigated brain regions with its massive contributions to multiple behaviours. Especially, the hippocampus is subdivided into the dorsal and ventral parts playing distinct roles. In this review, we will focus on the ventral hippocampus, especially the ventral CA1 (vCA1), whose role is being actively discovered. vCA1 is well known to be associated with emotion-like behaviour, in both positive (reward) and negative (aversive) stimuli. How can this small region in volume mediate such variety of responses? This question will be answered with technologies up to date that have allowed us to study in-depth the specific neural circuit and to map the complex connectivity.

KEYWORDS
anxiety, autism, fear conditioning, hippocampus, learning and memory, reward, ventral CA1

1 | INTRODUCTION

Hippocampus is known to be the most critical brain region in learning and memory. The substantial hippocampus, which physically takes up a large portion of the brain, was primarily subdivided into septal and temporal poles simply to categorize domains. However, studies revealed differentiating roles within the hippocampus allowing for categorization according to the function – dorsal and ventral hippocampus (vHip). Anatomical and electrophysiological studies have demonstrated long-axis gradients, whilst gene expression studies showed that demarcated functional domains are superimposed.[1]

Early studies have led to a strong belief in the critical role of the dorsal hippocampus (dHip) in learning and memory, resulting in concentrated research in this region.[2,3] As for the vHip, the study of this specific region began in an attempt to better understand emotion-related behaviour, especially those that are associated with anxiety.[4–7] Especially, understanding how emotions are generated from the vCA1 can further provide information related to various diseases such as addiction, autism and anxiety. Neuroscience began with the observation of human brain anatomy which permitted defining its structure; thus, it was limited to defining the function. Since hippocampus is a relatively conserved brain structure among mammals, studying hippocampus in animal models like rodents can indirectly provide information about human phenotypes.

This review is focused on studies primarily performed in rodents to define the role of vCA1 participating in different behaviours with multiple neural projections-starting from the earliest studies of the vHip to more in-depth studies focused on social memory, fear, anxiety and reward-related behaviours.

2 | HIPPOCAMPUS, THE PREMISE OF MEMORY

Before understanding the role of the hippocampus, it is necessary to mention the most relatable H.M case – over hundreds of hippocampal studies were originated from this patient. The subject was treated with bilateral medial temporal lobectomy to cure epilepsy. The treatment resolved epileptic symptoms, however, the subject suffered from severe side effects that led to the inability to form new memories. This severity of H.M's memory impairment has inspired scientists to further investigate the role of the hippocampus in learning and memory.[8] H.M's case has intrigued many scientists to work on the

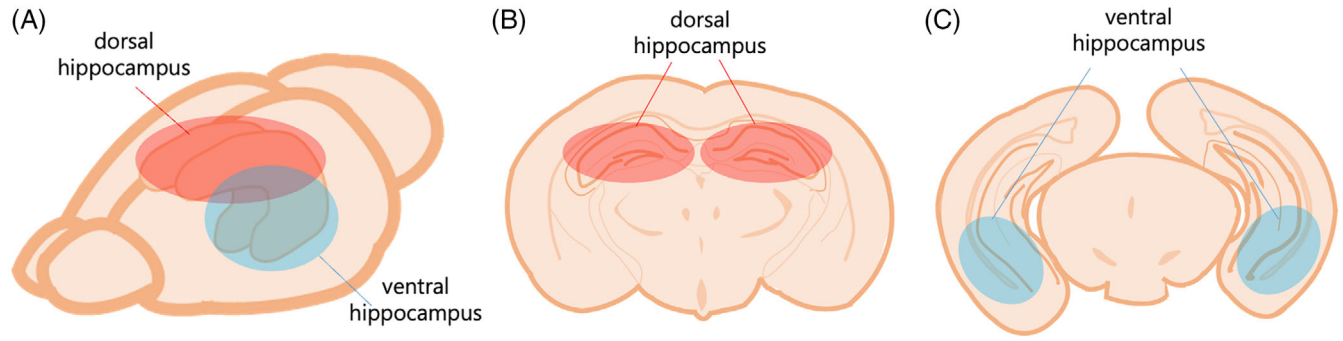

FIGURE 1 Illustration of the hippocampal section (A) Mouse brain with the hippocampus along its longitudinal axis. (B) Coronal section of the dHip. (C) Coronal section of the ventral hippocampus

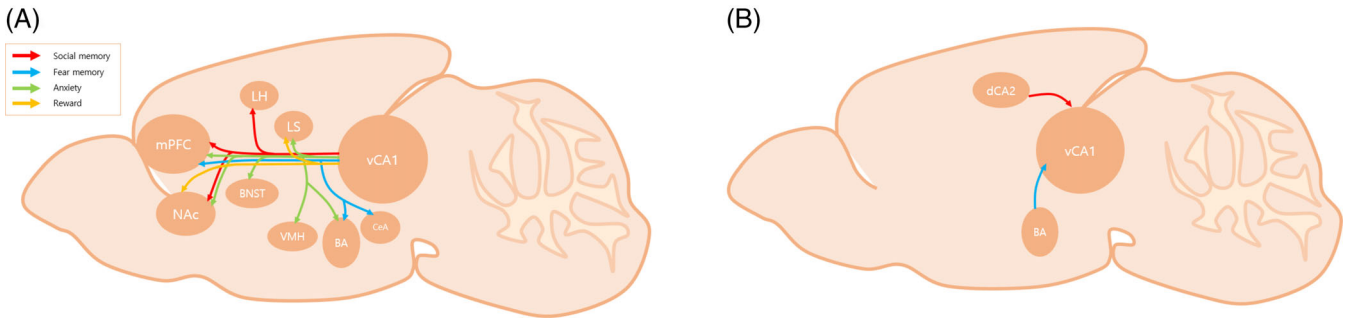

FIGURE 2 Input and output pathways of the vCA1 (A) efferent pathway and (B) afferent pathway

hippocampus from its anatomical structure to its function. Similar to the study of other brain sites, research of the hippocampus was initially focused on lesion studies. However, the advancement of molecular biology, chemogenetics and optogenetics has allowed the experiment to proceed in more detail – in a cell-type and a circuit-specific manner.

Since the beginning of the hippocampal research, the subdivision into the dorsal and vHip was clear, whereas there has been an active debate on the individual role and function of the two regions[9] (Figure 1). Discovering the roles of each subdivision has been a critical step for further understanding how the hippocampus affects our memory system. The clarification of each subdivision with each specific role and its mechanism will be the first clue to provide a breakthrough for various clinical treatments on mental disorders (Figure 2).

3 | THE EARLIEST STUDIES OF THE vHip

Studies on the two subdivisions have allowed for a clear and further in-depth understanding of the hippocampus. The spatial information is processed by the dHip with its connection to the cortical regions, whilst the vHip is more related to emotion due to its projection towards the amygdala and hypothalamus.[3,10–14] Lesion studies have historically been a fundamental technique in neuroscience to investigate the necessity of the brain region under behavioural observation.

Preliminary neuroscientific studies were less focused on the vHip, but rather, mostly focused on the dorsal regions as considered important for spatial learning.[3,10,11] Male Long-Evans rats were tested for a double dissociation between dHip and vHip lesions, and the only dHip-lesioned mice showed impairment of spatial memory.[11] Subsequent studies have shown controversial results[10,15,16] as vHip *N*-methyl-D-aspartate (NMDA) lesions affected the ability to rapidly acquire a new context during the Morris water maze in male Long–Evans rats.[10]

vCA1 and vCA3 are subregions in the vHip that play distinct roles in learned approach-avoidance conflict processing.[17] Both are also well-known regions that encode spatial information. In CA3, place cells are particularly distinct, especially along the longitudinal axis, wherein the ventral axis has a larger spatial map than the dorsal axis.[18]

Also, the vCA1 participating in spatial navigation further led to the basic study of fear memory. Ventral hippocampus lesions disrupt exquisite surroundings, which impacts the impairment of contextual or spatial navigation (i.e. defence-like behaviour).[12–14] Furthermore, a decrease in the rate of habituation of exploratory responses, retarded retention and extinction of fear conditioning were discovered in the vHip lesioned mice.[13,19]

Lastly, there are many studies related to the cause of the anxiolytic effect. It has been reported that the selective temporal hippocampal lesions decrease anxiety, exhibiting an anxiolytic effect by the failure of avoidance in the open arm task. Also, a decreased

neuroendocrine stress response was observed during confinement to a brightly lit chamber,[12] which was not found in the lesion of the septal pole. As for the dHip, its lesion failed to drastically change any defensive behavioural measure. Opposing results were obtained in the vHip, which was conducted to fade defensive behaviour.[14,20]

4 | LIMITATIONS OF THE LESION STUDY

Lesion studies have provided the first idea that these subdivisions play a different role, in an independent manner. Yet, as there cannot be a fine line in lesion specification, studies that claimed to be conducted under the same conditions showed conflicting results.[6,21,22] Controversies on the distinction of the hippocampal subregions were raised from the results of lesion studies.[10,15,16] One explanation could be that these differences were derived from the ambiguity of the 'dorsal' and the 'ventral' hippocampus.[6] Bannerman et al.[23] defined the dorsal part as 50% of the whole hippocampus from the septal pole, and the remaining half as the ventral part.[7] Whilst studies from the Moser group fixated on 20% of each pole, which was more restricting but did not cover the lesion of the whole hippocampus.[3,12]

Furthermore, recently another subdivision of the hippocampus was defined – the intermediate hippocampus.[24] This is evidence that partition of lesion is a limited method as it lacks accuracy. This imprecision could possibly affect other regions than the region of interest. For more intricate hippocampal research, recent technology has allowed for more accuracy. The hippocampus has been categorized beyond the dorsal and ventral – the region has been further subdivided within. The ventral and the dHip both are independently subdivided into CA1, CA2 and CA3. This review will be mainly focusing on the vCA1 subregion, which is actively being studied among other vHip subdivisions.

5 | vCA1 AND THE EFFECT ON SOCIAL MEMORY

The term 'social memory' was first implicated by Thor and Holloway in 1982, by observing rodents that possess the ability to discriminate conspecifics proving the capability of social recognition.[25,26] This is important for rodents as it gives the ability to forage, mate and create a social hierarchy. The absence of sociability may even lead to negative emotions, as it was reported that once mice were isolated, they showed impaired social memory[27] and displayed depressive-like behaviour.[28,29] Preceding studies, which were simply focused on observations of lesions, proved that the hippocampus plays a critical role in sociability, but there was controversy on which specific part of the hippocampus needs to be explored.[21,22,26,30]

It has been reported that the sociability of rodents can be reproduced in the laboratory by observing social interaction or social memory.[30,31] Under this kind of setting, researchers could elaborate neural pathways related to social behaving in rodents. Rodents show curiosity towards a never-before-met mouse, thus showing higher investigating time to the "novel" mouse compared to the 'familiar' mouse. By artificially inhibiting and stimulating activated vCA1 neurons through optogenetics, Okuyama et al.[32] proposed that the 'engram cells' among the Nucleus Accumbens (NAc)-projecting vCA1 pyramidal cells are the key to storing social memory. Moreover, Tonegawa's group showed social memory recall via optogenetically reactivating the 'engram cells', vCA1 neurons responding to the familiar mouse, after a certain amount of time from the first exposure. Rao's study extends to monitoring regions of the brain and concluded that the vHip specifically responds to the presence of conspecifics with elevated sharp-wave ripple activities,[33] indicating that the vCA1 is the core for memory and recognition, thus, discriminating familiar and novel mice.

Additionally, recent research has connected social memory to the dorsal CA2 (dCA2)-vCA1-NAc circuit.[32,34–37] The input of dCA2 towards the vCA1 is required for memory processing including memory encoding, consolidation and recall. Then, social memory is stored in the vCA1.[35,37,38] The experimental mice tended to show less interest towards familiar mice and interacted more with the novel mouse. Such behaviour is mediated by the Nac that receives inputs from the vCA1.[32]

In parallel, another pivotal pathway is rising from the vCA1 to medial prefrontal cortex (mPFC). Chemogenetic activation and inactivation were performed chronically with continuous clozapine-N-oxide via water delivery to observe the participation of the vCA1-mPFC circuit in social memory- in both cases, social memory was impaired. Philips et al. have further demonstrated that this vCA1-mPFC pathway mediates hyperactivation in *Mecp2*-mutant mice, with overrepresented vHip fibres in the mPFC. The phenotype of this Rett syndrome mouse model was similar to autistic-like behaviour, resulting in the loss of ability to discriminate against familiar mice.[39]

6 | AUTISM AND SOCIAL MEMORY

A key characteristic of autism is the deterioration of social function; therefore, observing mice with gene mutations associated with autism is a textbook condition for observing sociability.[40–43] Affected regions of the brain can be identified through gene knockout (KO), and this technique has been adopted by many studies to explore the influence of autism on the brain.[27,39,41,43] Once the importance of vCA1 in social memory was discovered, studies can precisely define which phenotype is the result of social memory in mouse model of autism.

The first target phenotype that creates autistic conditions is X-linked heterozygous mutations in methyl CpG binding protein 2 (*MeCP2*). This has been proven by human studies that show patients suffering from autism between 6 and 18 months specifically carry phenotypes with deteriorated cognitive and social functions.[44] The deletion of *MeCP2* made differences between the *MeCP2* KO and wildtype mice evident, as basal Fos activity was higher in the vHip of the *MeCP2* KO mouse.[39] The three-chamber test and unrestricted paradigms have proven that *MeCP2* KO mice are incapable of storing social memory. Owing to the superiority in number of activated mPFC

projecting neurons compared to that of the lateral hypothalamus (LH) projecting-vHip neurons, Phillips et al.[39] have focused on the identification of the vHip-mFPC neurons. The long-term potentiation was not induced and chemogenetic inhibition via hM4Di has rescued the social deficit of *MeCP2* KO mice.

Various ex vivo and in vivo recordings have shown the connection between pyramidal neurons of vCA1 to the mPFC mainly located in layers 2/3 and 5.[39,45,46] Additionally, recent studies revealed that the vCA1 pyramidal neurons also innervate PV^+ neurons in the mPFC.[47] Phillips et al.[39] performed wheat germ agglutinin (or WGA) transsynaptic labelling with immunohistochemistry to determine the pattern of innervating vHip axons in the mPFC. In WT mice, WGA-labelled neurons were mainly excitatory pyramidal neurons whereas *MeCP2* KO mice showed an articulated fraction of PV^+ neurons -expressing inhibitory γ-aminobutyric acid (GABAergic) interneurons.[39] It had been previously reported that the PV^+ neurons are required for social discrimination,[27,47] but in excess, these neurons may cause an imbalance between excitation and inhibition in the mPFC, which can affect the social memory formation.[39]

Shank3, a gene known to cause neurodevelopmental and neurobehavioural deficits in 22q13 deletion syndrome, is another clear feature associated with autism.[48] *Shank3* KO in mice resulted in reduced levels of proteins, which are believed to function as scaffolds in the postsynaptic density of glutamatergic synapses.[48,49] Moreover, it is reported that by deleting *Shank3* gene in mice resulted in higher levels of self-grooming alongside social behaviour and novel object recognition impairment.[50,51] Impairment in long-term social memory (24 h) was observed in *Shank3* KO mice, whilst the social memory was maintained in the short term (30 min). The connection of mPFC with the hippocampus was observed earlier in *Shank3* mice by Harony-Nicolcas et al.[52] describing that the dorsal CA1 (dCA1)-prelimbic mPFC circuitry displayed attenuated synaptic plasticity. In *Shank3* KO mice, reduced sociability has led to observed disruption of sharp-wave ripples. Neurons activated during social behaviour underlying in the vCA1 were minor in *Shank3* KO mice, which resulted in an inability to socially discriminate.[53]

Defining the synaptic bases related to social behaviour would provide an insight to understand psychiatric disorders such as schizophrenia or depression, as this phenotype is articulated in a mouse model of autism.[53] Among the hippocampal subregions, dysfunction in CA1 is specific to schizophrenia, whereas dysfunction in CA2/CA3 is attributed to schizophrenia and bipolar disorder. Given that the vCA1 has a strong projection to the mPFC and ventral subiculum (vSUB) which are both involved in schizophrenia it is a suitable region to study psychiatric disorder.[39,54]

7 | vCA1 AND THE EFFECT ON FEAR MEMORY

Fear conditioning being simple yet compelling acts as the premise of a behavioural paradigm allowing in-depth study of circuit mechanisms. For a whilst, research was mainly focused on the dorsal hippocampal CA1 as a key region of contextual fear memory.[2,56,57] Early studies based on the lesion studies demonstrated that the vHip was not involved in contextual fear memory. Beginning with ibotenate lesion studies in the 1990s, the role in fear memory of the vCA1 was first mentioned.[3,10–14] However, these lesion studies showed some discrepancies over the functions and even were not enough to study in circuit levels. New approaches not only allowed to discover the role of vCA1, but also its circuit and its underlying mechanism.

To elucidate the importance of vCA1 in encoding contextual information, various manipulations were performed both in vivo and ex vivo. Recent studies remarkably empowered the role of vCA1 by using miniscope calcium imaging, electrophysiology and optogenetics. Memory retrieval was the primarily well-known role of the vCA1 during contextual fear memory with projections towards both mPFC and basal amygdala (BA) pathways.[13,19,57–62] It has been reported that a subset of vCA1 neurons send dual projections to mPFC and BA.[57,59–61,63] Furthermore, as vCA1 neurons are important for context acquisition, it is also important to mention its role in the memory encoding process.[62] Jimenez et al.[58] recently revealed that activated vCA1 neurons during fear conditioning were necessary for memory encoding, and another subset of neurons activated during memory retrieval are correlated to the shock-encoding neurons. However, there still are discrepancies to defining vCA1 neurons between the shock-encoding neurons and contextual neurons.[58,62,64]

As the amygdala is the core region of fear responses, vCA1 neurons also project into the central amygdala (CeA), inspite of having a weaker response.[65,66] A further studies by Xu et al.[67] added that the central amygdala is required for context-dependent retrieval of cued fear memory.

Furthermore, the connection between the vHip and mPFC in fear memory is also being actively investigated. Both PL and IL receive input from the vHip that are uniquely involved in fear renewal rather than the suppression of fear extinction. Maren et al.[56] have several works on this subject,[56,59,60,68,69] from which they have asserted that fear renewal is driven by vHip neurons by fostering fear expression with PL activation and limiting fear suppression by inhibiting IL.[70] Also, inhibition of the vHip-PL during memory acquisition disabled memory recall, suggesting that the vHip updates any current spatial information to the PL.[71] In a behavioural paradigm in which mice learn to discriminate between a safety cue and foot shock cue, vCA1 neurons projecting to the prelimbic cortex showed higher population activity when exposed to safety cues. This suggests a possible role for this circuit in inhibiting fear expression.[72] In addition, Val 66 Met, a human variant of the brain-derived neurotrophic factor (BDNF) gene, is known to be associated with impaired fear extinction. Giza et al.[73] demonstrated that the BDNF Met prodomain reduces dendritic spines and eliminates synapses in the hippocampus. Their study was prolonged to an in vivo study, where they confirmed similar morphological changes (reduction of dendritic spine density and prelimbic projections) were observed in the vCA1 of periadolecent mice, coupled with impaired fear extinction. In adolescent $Bdnf^{Met/Met}$ mice, the similar spine and prelimbic innervation deficits were found. Also, fibre photometry experiment has proven that vCA1 neurons

projecting to the prelimbic encode extinction. As with relapse of fear memory, vCA1 neurons projecting to the CeA is known to mediate this process as inhibiting this pathway abolishes fear renewal response.[67] vCA1 neurons projecting to the infralimbic cortex was shown to recruit PV^{+} interneurons thereby applying feed-forward inhibition to mediate fear relapse.[74]

8 | VCA1 AND THE EFFECT ON ANXIETY

A strong connectivity between the mPFC and vCA1 has been reported in many previous studies, yet it was unknown whether vCA1-mPFC neurons are related to anxiety.[39,57,59–61,63,72,75] Neurons residing in the mPFC are able to differentiate safe and aversive locations during elevated plus maze (EPM).[75] Also, the high correlation between theta-frequency activity of the mPFC and vCA1 in an anxiogenic environment strengthens the importance of this circuit.[75,76] Anxiety-related behaviour can be examined by inhibiting vCA1-mPFC circuit by hyperpolarising ion pumps, known as Archaerhodopsin (ArchT). Moreover, observation of live cell recording of vCA1 neurons projecting to various regions shows inputs towards the mPFC exhibit higher neuronal activity than other brain regions during EPM.[77]

However, a different claim also exists – the work by Kheirbek's lab proposed a conflicting result concluding that showed a different result, that the activation of vCA1 axon terminals projected to the LH increases anxiety-like state.[78] Both electrophysiology and miniature miniscope recordings have revealed that the vCA1 neurons were selectively activated in the open-arm session during the EPM, in which the neurons exhibited a significantly higher rate of $Ca2^{+}$, and especially neurons projecting from the LH are responsible for inducing anxiety-like behaviour and avoidance.[78] The authors suggest that this inconsistency was found in line with the theory of LeDoux, who proclaimed that thalamic 'low' and cortical 'high' roads are both critical to auditory fear processing. [79]

Accordingly, a similar paradigm was performed in the vCA1-NAc, vCA1-lateral septum (LS) circuit demonstrating that the input of the vCA1 towards NAc and LS also impacts anxiogenic behaviour.[80,81] Glangetas et al.[82] added that this anxiolytic behaviour is driven by NMDA receptors dependent long-term potentiation of vCA1/vSUB to BNST (bed nucleus of the stria terminalis) pathway. This was proven as the inhibition with NMDA receptors antagonist in BNST blocked (disrupted) anxiolytic effect mediated by high frequency stimulation of vSUB and vCA1.[82]

The last downstream target is the ventromedial hypothalamus (VMH), and the social interaction was observed to see the influence on aggressive behaviour. Unlike the previously reviewed studies, this report focuses on maximized aggressive behaviour manipulated by post-weaning social isolation, which is followed by foot shock-induced stress then exposure to a stranger mouse. This setting increased attacking behaviour which was the mainly observed response. By suppressing the activity of vCA1-VMH neurons with hM4Di the attacking behaviour was decreased, contrary to when the activated attacking behaviour was restored. These findings show connectivity between attacking behaviour and vCA1-VMH. Open field test (OFT) testing was also conducted by artificially activating VMH-vCA1 projecting neurons resulting in anxiogenic behaviour in rats depict by the preferred periphery positioning compared to centred positioning.[84]

Projections from the posterior BLA are well-known for the afferent pathway involved in anxiogenic behaviour.[78,84–88] Pi et al.[86] have subdivided BLA in anterior–posterior, and vCA1 with deep layer (calbindin1-negative), and superficial layer (calbindin1-positive). These subregions are specifically connected to the corresponding subregion: anterior BLA (aBLA) innervating deep layer whereas posterior BLA (pBLA) is innervated in the outer layer of vCA1. Photostimulation of the pBLA-vCA1 has led the mice to exhibit anxiolytic behaviour, whilst aBLA-vCA1 mediated anxiety-like behaviour.[86] Anxiety can also cause such symptoms when a subject experiences unpredictable chronic mild stress.[85,87] Decreased phosphorylation of GluA1 affecting AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor) function due to chronic stress can weaken the connectivity of pBLA-vCA1, inducing depressive-like state and anxiety.[85]

Chronic restraint stress (CRS), which mediates social avoidance and anxiety-like behaviours also has an effect on the increase in acetylcholine muscarinic receptor (mAChR) in vHip. This social avoidance behaviour was further rescued by mAChRs antagonist, by suppressing excitatory synaptic transmission.[89] Furthermore, unlike male subjects, anxiety behaviour was unnoticed in females. Fos immunohistochemistry shows stronger enrolment of vHip in innate anxiety in male mice.[90] This anxiety-like behaviour was shown to be specifically associated with the activation of vCA1 among other subregions in the vHip.[17]

9 | REWARD-RELATED BEHAVIOUR, A GUIDE TOWARDS ADDICTION

Motivational behaviour can lead to two opposing consequences – either extremely strong (addiction) or practically absent (depression). This is due to how the subject inputs the surrounding environment and interprets them. The subjects' interpretation of surrounding input is then behaviourally shown as the subjects' deportment. Studying motivational behaviour can be replicated in two ways; either exhibiting approached seeking behaviour or oppositely avoiding punishment.

Between the two different motivational behaviours, an avoidance mediated paradigm requires only simple and straightforward tasks, whilst rewarding rodents take a lot longer for training due to complex behavioural tasks. Seeking behaviour is the most common behaviour of rodents to translate their motivation – thus, most of the experimental animals undergo food or water deprivation before the experiment. Nucleus accumbens (NAc) has always been the core region mediating social behaviour, commonly known to generate goal-directed behaviour.[91–93] In reward-related behaviour, the NAc is the most observed region of the brain as it is considered as the neural interface between motivation and action with its dynamic dopaminergic effect.[92,94] Especially, the connectivity between ventral tegmental areas, another source of dopamine, is well studied.[95,96]

Recent studies have yielded strong evidence that the role of the hippocampus is important, as much as NAc, which is necessary and sufficient to modulate seeking behaviour during reward.[97,98] The subregions of the hippocampus are known to encode differently during reward; dCA1 is more likely to encode reward proximity, whilst vCA1 neurons are more likely to predict reward.[99] To understand the connectivity of the vCA1 to the NAc, Zhou et al.[100,101] investigated the labelling of engram cells in each region during cocaine-conditioned place preference (CPP). Their chemogenetic inactivation data revealed that the non-cocaine control engram cells in the vCA1 affect the retrieval of cocaine CPP memory, suggesting that the vCA1 engram cells are involved in only contextual information for a specific reward memory. Activation of the NAc core was sufficient for CPP, whilst vCA1 neurons were silenced, suggesting that the NAc core engram cells projecting from the vCA1 are important for memory recall.[100,101] Moreover, by using D1-cre driver line, Zhou et al.[100,101] reported that the main cell type of vCA1 to NAc core engram cells were D1 cells, rather than D2 cells.

Due to the diverse connectivity of vCA1, not only the NAc but other regions are also connected to the vCA1. A symbolic region is a lateral septum and this region plays an essential role in feeding behaviour. The LS connection to the vHip (mainly targeted ventral CA3 [vCA3] and dentate gyrus) was previously discovered and showed that optogenetic activation of the vHip-LS reduces food intake.[103] As for the vCA1, during the goal-directed food-seeking lever-press behaviour task, vCA1-LS neurons exhibited a higher rate of calcium activity, especially during the food intake.[81] Reward omission reduced the activity of LS-projecting vCA1 neurons, suggesting that vCA1-LS neurons are specific to the food reward.[103]

Interestingly, another study by Yoshida et al.[104] demonstrated that decreased calcium activity of vCA1 pyramidal neurons promotes the sustainment of goal-directed lever pressing. Here, goal-directed behaviours not only include the obtention of a reward but also the avoidance of punishment, wherein such behaviour was enhanced when vCA1 neuron activity decreases due to suppressed aversive emotional states as mediated by serotonergic neurons from the median raphe region.[104]

Motivated behaviour can be observed simply by providing direct 'reward' to the subject, but it can also be observed indirectly by inducing 'hopefulness (HF)' or 'helplessness (HL)'-modulated behaviour. The two notions were respectively introduced to the subject by anticipated avoidance training and foot shocks. HF animals appeared to carry potentiation of spatial learning with strengthened posterior BLA-vCA1 connectivity since this connection was faded in HL mice accompanied with memory deficit. Optogenetic modulation has allowed to artificially potentiate pBLA-vCA1 connections in the HL mice, and this was sufficient to mimic the phenotype of HF mice.[105] Another very interesting study was recently carried out by Lin's group showing that the inputs to dCA3 from vCA1 are crucial in spatial memory.[106] This was proven as silencing of vCA1-dCA3 circuit impaired spatial learning and memory during the object location memory test and the object recognition memory test.[106]

10 | COMPLEX CONNECTIVITY

Various studies have been conducted to show the diversity of vCA1 neurons; studies focusing on behavioural, circuit specificity, cell type and its relying molecular mechanisms.[64,78,79,82] Recent techniques have allowed accurate investigation of neural projections in a cell-, circuit- and time-specific manner. A subset of vCA1 neurons can be activated in multiple behavioural tasks, and several projections play multiple roles.

In recent years, active interest of interneurons has risen supporting the idea that these neurons are as critical as excitatory neurons. Furthermore, through mapping technology, we are now able to visualise the connectivity of vCA1 neurons into different regions. The question of whether the vCA1 neurons are necessary or sufficient to trigger such phenotype will be the next confronted question. Similar to the importance of pyramidal neurons in social memory, among interneurons, PV^+ neurons residing in the vCA1 region have been the focus of research as a key cell type that mediates social memory.[27,32,35] It has been reported that hippocampal GABAergic interneurons exhibit greater cellular diversity compared to pyramidal neurons. This firing action potential of the theta cycle, which are interacted with glutamatergic inputs that are necessary for synaptic temporal dynamics and network oscillations.[106,107] Moreover, among different types of interneurons, PV^+ neurons have been shown to control the activity of their target cells.[107,108]

Pyramidal neurons and PV^+ neurons both play an important role in social memory retrieval and recognition of conspecifics, yet it is still unclear whether and how these neurons are interrelated. Along with the importance of PV^+ neurons in social memory, the plasticity of PV^+ neurons critically mediates long-term consolidation of spatial memory. It is partially influenced by D1/5 dopamine receptor signals, which causes DARPP-32 and ERK phosphorylation in the PV^+ interneurons.[110] Studies that define cell types remain lacking, hence, molecular approaches will be an upcoming challenge.

In addition to the studies that were previously mentioned above, mapping axonal projections enabled visualizing neural projections deriving from the vCA1. It has been studied that vCA1 are connected to various distinct brain regions – projecting to the NAc, mPFC, LS, LH, BNST, VMH and amygdala. These findings were first performed by observing neural alterations in a specific behaviour task and adding to this recently, reconstruction and mapping of long-range projections consolidated the information regarding the heterogeneity of vCA1 neurons. The manoeuvre of juxtacellular labelling permitted tagging single neurons with neurobiotin. By determining soma location and dendritic arborization, the author identified three major distinct routes of vCA1 pyramidal neurons.[110] To analyse how various types of information are controlled in these diverse pathways, Ciocchi et al. manipulated tetrode recordings and antidromic spiking analysis with an optic stimulus in vCA1, whilst performing different behavioural tasks – spatial memory, reward and anxiety.[77] vCA1 neurons seemed to be selective to each task with its selective pathways, but triple projecting neurons which are responsive to the overall task were exigent exhibiting a high firing pattern. More recently, the assessment of high-

throughput sequencing of genetically barcoded neurons (MAPseq) enabled axonal tracing of thousands of vCA1 neurons. Distinct pathways selectively receiving the vCA1 inputs and outputs were identified via molecular profiling in support with the viral tracing of vCA1.[63]

The transcriptional profiles of vCA1 and dCA1 are distinct from each other.[112] Although most of the inputs of the former come from the intrahippocampal regions, which are stronger along the rostral-caudal axis and are distinct from those of dCA1, both have regions that still receive similar inputs from the amygdala nuclei and olfactory areas.[113]

To understand the heterogeneity of vCA1, researchers focused on tracing vCA1 neurons in distinct pathways over time and achieved to define multi-projecting neurons. Nonetheless, several neural projections participate in multiple behavioural features, such as the vCA1-mPFC pathway engaged in the social memory and fear memory. In addition, between vCA1 and BLA, the projection is not unilateral but rather bidirectional. Understanding how neurons interplay within the same pathway whilst the subject is exposed to different behaviours seems to be prominent in the future.

11 | CONCLUSION

The hippocampal complex is one of the most important fields of neuroscience. Hippocampal research has been mostly centred on the dorsal region, thus, only recently ventral region studies focusing on the role of the vCA1 as a pre-region has become a topic of interest. The recent study driven by Tao et al.[113] has proposed that unlike the dCA1, vCA1 receives inputs from the subregions of olfactory areas and amygdala nuclei. Even though several afferent regions are known, studies focusing on the inputs towards the vCA1 with its specific role would be prominent.

Also, unlike the dHip, subregions other than the vCA1 in the vHip require further investigation. vCA3 and the vSUB are progressively being investigated, but there are still many questions to be answered. Recent papers still use the term 'vHip' rather than specifying the subregion.[88,114] It has been suggested that the inner layer and the outer layer within the vCA1 play different roles. The rise of the technology will provide an insight of heterogeneity in the vHip.

The connections of vCA1 are complex, most of the neurons are projected towards two distinct regions, and some neurons exhibit even triple connectivity. It has been proved that vCA1-BA and vCA1-mPFC have individual projections during fear-related memory, whilst some mPFC-projecting vCA1 neurons were indirectly projecting to the BA.[62] The interpretation of these overall task-activated cells would be the next challenge.

To enclose, the hippocampus has remained largely unfamiliar to neuroscientists, and through the exploration of its role in memory and spatial processing and navigation, we can understand how memory is formed and stored. Rodents were used in this study as they have genetic similarities with humans. Human episodic memories have been proven to be analogous to those of rodents and both also have similar heterogeneity functions along the anteroposterior axis.[73,115] However, there are still discrepancies in the frequency of theta between the two species[116]; hence, it is necessary to perform further investigation to graft our findings to human behaviour.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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