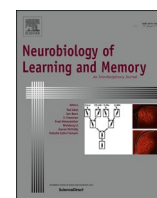


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## The role of hippocampal mossy cells in novelty detection

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## ABSTRACT

At the encounter with a novel environment, contextual memory formation is greatly enhanced, accompanied with increased arousal and active exploration. Although this phenomenon has been widely observed in animal and human daily life, how the novelty in the environment is detected and contributes to contextual memory formation has lately started to be unveiled. The hippocampus has been studied for many decades for its largely known roles in encoding spatial memory, and a growing body of evidence indicates a differential involvement of dorsal and ventral hippocampal divisions in novelty detection. In this brief review article, we discuss the recent findings of the role of mossy cells in the ventral hippocampal moiety in novelty detection and put them in perspective with other novelty-related pathways in the hippocampus. We propose a mechanism for novelty-driven memory acquisition in the dentate gyrus by the direct projection of ventral mossy cells to dorsal dentate granule cells. By this projection, the ventral hippocampus sends novelty signals to the dorsal hippocampus, opening a gate for memory encoding in dentate granule cells based on information coming from the entorhinal cortex. We conclude that, contrary to the presently accepted functional independence, the dorsal and ventral hippocampi cooperate to link the novelty and contextual information, and this dorso-ventral interaction is crucial for the novelty-dependent memory formation.

## 1. Introduction

Imagine that while you drive your everyday route to work, an accident happens. This novel event will first generate an emotional response in your body (Ferrari et al., 2016) reinforcing the memories of the contextual horizon, such as the song you were listening to during the accident or the clothes you wore that day. This popular knowledge has been experimentally addressed by the improved recollection of words presented together with novel scenes (Fenker et al., 2008). Although most of us have direct experience with this phenomenon, the brain mechanisms that cooperate in order to induce the novelty-dependent memory enhancement are just starting to be understood.

The hippocampus has been known to be an essential structure for memory encoding and retrieval since the case of H.M. was first described in 1957 (Scoville & Milner, 1957). From this seminal paper, an extensive amount of research has been dedicated to this structure in relation to its function in memory. Theories about how the hippocampus is related to memory generally proposed a unitary model, where the whole hippocampus is responsible for a single type of general memory (Squire, 1992). Nevertheless, evidence for a hippocampal role in emotional memory started a controversy over its overall function and led to the

idea of possible separated hippocampal functions in the dorsal and ventral poles (Strange et al., 2014).

Moser and Moser collected more than anatomical evidence and reported that the hippocampus is functionally heterogeneous, with different portions of the longitudinal axis having different functional roles (Moser & Moser, 1998). Their idea was mainly based on three previous studies. The first one (Swanson & Cowan, 1977) presented anatomical evidence showing that the output connections to subcortical regions were different for the dorsal and ventral hippocampal formation. Other anatomical studies also demonstrated dorsoventral topographical gradients in entorhinal inputs to the dentate gyrus (Dolorfo & Amaral, 1998) and hippocampal outputs to the lateral septum (Risold & Swanson, 1996). The ventral subiculum, a major target of the CA1 area, has dense projections to the amygdala, bed nucleus of stria terminalis and hypothalamus (Canteras & Swanson, 1992). The second (Moser et al., 1995), showed that spatial memory was solely dependent on the dorsal hippocampus using lesions of different volumes and locations. In contrast, the third study (Henke, 1990) demonstrated ventral lesions that altered stress responses and emotional behavior (also see a review by Bannerman et al., 2004). In more recent years, genetic markers were used to further investigate the division of the hippocampus throughout

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its dorsoventral axis. Genetic-anatomic data together with careful evaluation of connectivity and functional studies led Fanselow and Dong to construct a model showing that CA1 and CA3, the Ammon's horn as a whole, and the dentate gyrus (DG) are divided into three major domains: dorsal, intermediate, and ventral (Fanselow & Dong, 2010). More recent neuroimaging data in humans also support functional differentiation of hippocampal circuits along its long axis (Grady, 2020; Hrybouski et al., 2019; Persson et al., 2018). Thus, it is well established that the dorsal hippocampus mainly mediates cognitive functions, especially spatial memory, while the ventral pole is more involved in emotional responses. For the detection of novelty, the ventral moiety of the hippocampus (Bernstein et al., 2019; Duffy et al., 2013; Floriou-Servou et al., 2018), and its human homologue, the anterior hippocampus (Kafkas & Montaldi, 2018) seem to be more involved.

In this article, we review the literature that deals with the dorsoventral dichotomy of the DG in novelty detection with a special emphasis on the recent data that position mossy cells in the ventral DG as a key node in this operation. We propose that the interaction of the dorsal and ventral moieties of the DG is essential to orchestrate the detection of novelty and the concomitant enhanced memory encoding. We further hypothesize a theta rhythm-mediated mechanism that is likely to act in parallel with other novelty-detection circuits in order to link the ventral and dorsal hippocampi to generate novelty-driven contextual memory.

## 2. What is novelty?

Novelty detection triggers a variety of brain and behavioral responses that lead to exploration and increase of memory encoding of the novel information in humans (Fenker et al., 2008; Kaplan et al., 2014; Knight, 1996; Strange et al., 2005; Tulving & Kroll, 1995; Wittmann et al., 2007) and rodents (Bernstein et al., 2019; Hunsaker & Kesner, 2008; Jeewajee et al., 2008; Larkin et al., 2014; Lee et al., 2005). This novelty response is rapidly lost upon repeated exposure to the same stimuli, with the concomitant adaptation of the neural response (Berke et al., 2008; Davis et al., 2004; Murty et al., 2013; Villarreal et al., 2007). Although novelty detection seems to be well defined, novelty itself is very often not clearly defined in research articles dealing with it. Novelty is sometimes used interchangeably with a surprise for example. Despite the obvious relatedness of these two concepts, they are different, and mixing them can lead to confounding theories about novelty detection. Here we adopt the distinction between novelty and surprise from Barto et al. 2013: "Detecting novelty requires examining (by one means or another) the contents of memory to determine if the stimulus has or has not previously been experienced and attended to. Surprise, on the other hand, is the result of a discrepancy between an expectation and an observed actuality. This comparison of experience with an expectation does not require examination of the contents of memory despite the fact that an expectation is clearly built on previous experience. Something can be unanticipated without being un-experienced" (Barto et al., 2013). We consider it important that this definition is clearly stated, because of the relationship between novelty detection and memory. The requisite of examination of memory contents in novelty detection but not in surprise, explains why the hippocampus is a novelty detector but not a surprise detector (Tobia et al., 2016). This definition also sheds light on the existence of an intrahippocampal mechanism that compares the memory contents with the present event, in order to catalog it as a novel one. Here we propose that hippocampal mossy cells play a key role in this mechanism.

## 3. The hippocampal mossy cell

Although the hippocampus consists of a repeated pattern of mainly excitatory pathways from the DG, CA3, CA1, and subiculum along the longitudinal axis (Andersen et al., 1971), anatomical, behavioral and imaging data strongly support the idea of segregated functions along the

hippocampal axis. Also for the transverse axis, distinct functions have been allocated to the DG and CA areas (Kheirbek et al., 2013). Several reports pointed out the importance of the DG in novelty detection. For instance, Hunsaker et al. showed that lesions of the DG in rats impaired novelty detection, whereas those restricted to the CA3 area did not cause any deficits in the task (Hunsaker et al., 2008).

The DG is considered within the canonical trisynaptic circuit as the entrance of the information flow coming from the entorhinal cortices. In DG, mossy cells (MC) are a large subset of neurons that together with granule cells (GC) and GABAergic interneurons constitute the major cell types of the DG. MCs were first described by Lorente de Nó (1934) as non-principal cells of the hilar region of the hippocampus (Lorente de Nó, 1934). Years later, Amaral's landmark paper of Golgi-stained rat tissue reported these cells as the most impressive and frequently observed neurons in the hilus (Amaral, 1978). The most characteristic feature is the encrustation of the proximal dendrites with thorny excrescences resembling moss, a trait that led him to give the name of mossy cells. These excrescences receive excitatory synapses from mossy fiber terminals of GCs in the DG (Amaral, 1978; H E Scharfman, 1995a). MCs are glutamatergic, shown by immunohistochemical analyses, and confirmed by electrophysiological recordings of individual cells displaying an excitatory postsynaptic action (Buckmaster et al., 1996; Scharfman, 1995b; Scharfman & Schwartzkroin, 1988; Scharfman, 2016). Their axons project to the inner molecular layer of the DG, expanding several hundred micrometers along the septotemporal axis and innervating both GCs and interneurons (Blasco-Ibáñez & Freund, 1997; H E Scharfman, 1995a; Scharfman, 2016). Furthermore, these projections not only reach the ipsilateral but also the contralateral side (Blasco-Ibáñez & Freund, 1997; Buckmaster et al., 1996). The segregation of hippocampus into the dorsal and ventral poles also divides the mossy cell population, and likewise, different functions started to be attributed to each subpopulation.

## 4. Mossy cells in the dorsal DG

Mossy cells in the dorsal DG (dorsal MC) have been shown to be mainly inhibitory on dorsal GCs, by feedforward inhibition. Photostimulation of the commissural pathway (COM), which originates from MCs in the contralateral hilus and innervates the proximal dendrites of GCs within the inner one-third molecular layer, resulted in a greater inhibition than excitation on individual GC recordings (Hsu et al., 2016). It was also shown that diverse interneuron subtypes contribute to the COM-mediated inhibition, including basket cell-like, total molecular layer and molecular layer-like cells (Hsu et al., 2016). We have also recently reached similar conclusions by means of *in vitro* and *in vivo* experiments. By whole cell recordings of dorsal GCs and optogenetic stimulation of dorsal MC axons, we have demonstrated that dorsal MCs display a strong disinhibitory inhibitory component (Fredes et al., 2020). In our *in vivo* studies, we showed that excitation of dorsal MCs during novel environment exploration using designer receptors exclusively activated by designer drugs (DREADDs), leads to a decreased number of c-fos-positive dorsal GCs, supporting the idea that the effect of dorsal MC activation is mainly inhibitory over dorsal GCs (Fredes et al., 2020).

Dorsal MCs are also involved in epileptic seizure control. Activation of these cells, but not MCs in the ventral DG (ventral MC), reduced the duration of electrographic seizures and their inhibition significantly increased the probability of seizure generalization (Bui et al., 2018), also supporting the inhibitory character of dorsal MCs over the dorsal DG. It is important to mention, however, that the definition of ventral DG in this study refers probably to the intermediate DG, following the compartmentalization outlined by Fanselow & Dong (2010).

Finally, dorsal MCs play a crucial role in spatial coding and their joint action with GCs seems critical for pattern separation (Danielson et al., 2017; GoodSmith et al., 2017; Senzai & Buzsáki, 2017). Using two-photon calcium imaging, spatial tuning was observed in dorsal MCs during head-fixed spatial navigation, and importantly, they underwent

robust remapping in response to contextual manipulation. A significant portion of the studied MCs was classified as spatially tuned. Altogether, it was suggested that MCs discriminate contexts based on their spatial tuning profile (Danielson et al., 2017). To study the role in pattern separation and how MCs might shape the sparseness of GC firing, Danielson et al. developed a biologically relevant computational model of the DG. When deleting MCs, there was a higher recruitment of GCs in response to entorhinal input, which led to a reduction in the pattern separation efficacy of GCs. Moreover, specific deletion of MC-basket cell connection significantly increased GC excitability, which affected negatively the pattern separation performance.

Also, GoodSmith et al. showed that dorsal MCs tend to be active in most environments, unlike GCs, and that they can differentiate between environments based on the relative location, spacing, and number of firing fields in distinct environments. They also observed that GCs and dorsal MCs present independent representations of distinct environments, but different coding mechanisms for generating the independent maps. While GCs use independent ensembles of cells, MCs use largely overlapping ensembles, where each neuron displays a different spatial firing pattern in each environment (GoodSmith et al., 2017). Similarly, Senzai and Buzsáki described that dorsal MCs are more active, have multiple place fields and stronger remapping of place fields than GCs. They show a robust sensitivity to environmental changes and they rarely “inherit” place fields from single GC (Senzai & Buzsáki, 2017). Although the conclusions reached by these studies are of paramount importance, none of them have tested dorsal MC function by manipulation experiments. Recently, we have tested the functionality of dorsal MCs in contextual fear conditioning (Fredes et al., 2020). By expressing inhibitory DREADDs in these cells we found that they have an active role in context-dependent fear conditioning and also fear expression. Animals that received a clozapine N-oxide (CNO) injection 30 mins prior to the conditioning session in order to inhibit the activity of dorsal MCs, showed an increased freezing level in the retrieval session in a context-dependent manner, suggesting an inhibitory role of dorsal MCs in contextual memory formation. The interpretation of this increased freezing level, however, is obscured because we also found an acute effect of increased freezing during the conditioning session by the inhibitory DREADD manipulation. Altogether, there have been important advances in understanding the role of dorsal MCs in the DG circuitry and memory formation. However, the function of their ventral counterparts has been kept elusive until recently.

## 5. The role of ventral mossy cells in novelty detection

The ventral MCs have been known to be different from their dorsal counterparts for a long time. The first evidence came from the mouse, where ventral MCs, but not dorsal MCs were found to be Calretinin positive (Fujise et al., 1997). This defining feature of ventral MCs has been further demonstrated using RNA sequencing (Cembrowski et al., 2016). It has been also reported that MCs are activated by novelty signals preferentially in the ventral region, as shown by *c-fos* expression (Bernstein et al., 2019; Duffy et al., 2013). We have further investigated the role of the ventral MC in novelty detection utilizing Calretinin-cre mice (Fredes et al., 2020). MCs are known to have very long axonal processes, reaching the inner one-third of the inner molecular layer. By means of viral tracing and electron microscopy, we found an important difference of ventral MCs compared to their dorsal counterparts. The projections of ventral MCs in the inner molecular layer mostly contact GC spines in the dorsal DG. In comparison with dorsal MCs, they make very few synaptic contacts with parvalbumin (PV)-positive dendrites, making them potentially excitatory over dorsal GCs. We have further verified this hypothesis by *in vitro* and *in vivo* experiments. In contrast to the dorsal MC stimulation, we showed that optogenetic stimulation of ventral MC axons evoked monosynaptic depolarizing currents with little disynaptic inhibitory currents in the dorsal GCs. Furthermore, measuring the activity of dorsal GCs by GRIN lens in freely behaving

animals by calcium imaging, and indirectly by *c-fos* expression, we demonstrated a robust activation of dorsal GCs by ventral MC excitation by DREADDs (Fredes et al., 2020). Then, we have addressed the idea that ventral MCs are sensitive to environmental novelty. The calcium imaging of ventral MCs and dorsal GCs in animals freely exploring a novel environment showed that both cell populations gradually decrease their activity along environmental familiarization, and are reactivated upon exposure to another new environment. Importantly, this novelty-related increase in activity in ventral MCs was accompanied by no apparent increase of locomotion. These results strongly support the hypothesis that ventral MCs are novelty detectors.

## 6. Where the novelty signal comes from?

Probably the first question one asks about the novelty detector would be: Where the novelty signal comes from? We can think of two possible scenarios. One is that ventral MCs work as a simple relay, transmitting the novelty signal from other brain regions. Another more complex possibility is generation of the novelty signal within ventral MCs, based on neuronal computation of multiple presynaptic inputs representing the previous and present states. This mechanism would be equivalent to examining memory contents as stated above. At present anatomical data about the presynaptic inputs to MCs, is restricted to dorsal and intermediate DG (Sun et al., 2017). By using monosynaptic rabies tracing, this study showed that the main inputs to dorsal MCs are local GCs and interneurons, which are unlikely to provide information about previous states or memories, given that GCs are thought to have a pattern separation function and not required for retrieval of memories (Hainmueller & Bartos, 2018; McHugh et al., 2007). Instead, CA3 projection would be a very good candidate to inform MCs about memory contents, given that they are involved in pattern completion and memory storage (Guzman et al., 2016; Nakazawa et al., 2002; 2004). Although Sun et al. reported that CA3 inputs to dorsal MCs are scarce, this could be different for ventral MCs. We hypothesize that ventral MCs may receive a more substantial projection from CA3 and this projection may transfer past contextual information to ventral MCs. In the ventral hilus, this memory content would be compared to the actual contextual horizon. Specifically, ventral MCs receive direct inputs from ventral GCs, which in turn receive contextual information from the caudal entorhinal cortex. This information can be compared in the ventral hilus with memory contents provided by the CA3 projections. The exact nature of the comparator circuit is, however, not easy to predict without the anatomical details of the ventral hilus connectivity. Neuronal comparators are often described as match/mismatch detectors since they determine if actual stimuli agree (match) or disagree (mismatch) with the expected sensorial information (Duncan et al., 2012). For instance, Vinogradova (2001) formulated a comprehensive description of a comparator function for the hippocampus. She suggested that the hippocampal neurons that responded to a new stimulus with excitation were “novelty detectors,” while those that responded with inhibition were “identity detectors.” The identity detectors are active when sensory information matches sensory expectation, and a novel stimulus inhibits the activity of these cells. This activity was thought to inhibit the registration of this stimulus as new. However, under mismatch conditions, these identity detectors are inhibited, allowing the registration of the new stimulus by the novelty detectors leading to memory formation (Vinogradova, 2001). For ventral mossy cells, a solid understanding of the local and long-range connections of the ventral DG circuitry is necessary to construct and test a circuit comparator model.

## 7. Parallel mechanisms for novelty detection in the hippocampus

So far, we have seen that ventral MC projections target the dorsal inner molecular layer, imposing a strong excitatory drive onto dorsal GCs. We have also presented evidence that ventral MCs are responsive to

environmental novelty. The next evident question would be, how these two findings relate to novelty-dependent contextual memory formation? In order to answer this question, we have tested the influence of ventral MC activity on contextual memory formation by chemogenetically inhibiting their terminals in the dorsal DG during the conditioning phase of contextual fear learning in a novel environment. We found that this manipulation significantly reduced the freezing in the retrieval session only if CNO was injected before the conditioning but not after that or before the retrieval (Fredes et al., 2020). This experiment indicates that the excitatory drive from ventral MCs to dorsal GCs is necessary for contextual memory acquisition in novel environments. We then reasoned that if the activity of ventral MCs and dorsal GCs is gradually reduced by familiarization as we found above, the contextual learning would be limited because of the lack of the novelty signal from ventral MCs to dorsal GCs, as previously reported as latent inhibition (Hall et al., 2000). We then tested if an artificial activation of ventral MCs in a familiar environment would mimic the novelty signal to dorsal GCs, and then allow for contextual memory formation. Our experiments showed that a chemogenetic activation of ventral MC during conditioning in a familiar environment, rescues the freezing to control levels in the retrieval session in a context-dependent manner (Fredes et al., 2020), thus confirming our hypothesis.

These results can be interpreted in the light of reported roles of the dorsal GCs in the contextual memory formation. Dorsal GCs change their population activity upon novel environment exploration, forming contextual memory engrams (Bernier et al., 2017; Hainmueller & Barros, 2018; Josselyn et al., 2015; Liu et al., 2012; Ramirez et al., 2013; Redondo et al., 2014). Direct optogenetic inhibition of dorsal GCs block context memory acquisition (Bernier et al., 2017; Kheirbek et al., 2013), which indicates that dorsal GC firing is indispensable for context memory formation. Although they receive major excitatory inputs from the entorhinal cortex, these inputs seem not enough to drive GCs since no changes in firing rate (Burgalossi et al., 2014) or no increase in c-fos-positive cells (Jenkins et al., 2004) with environmental novelty have been observed there. Consistent with this evidence, our data demonstrate that memory acquisition requires ventral MC inputs to dorsal GCs.

Based on the extensive bilateral projection and its excitatory nature, we propose that this ventro-dorsal pathway conveys a novelty signal serving as gain control allowing information relayed from the entorhinal cortex to form contextual engrams in the dorsal GCs (Fredes et al., 2020) (Fig. 1).

Although artificial reactivation of dorsal GCs engram cells has been shown to induce context independent freezing, after contextual fear conditioning (Liu et al., 2012), inhibition of dorsal GCs during the

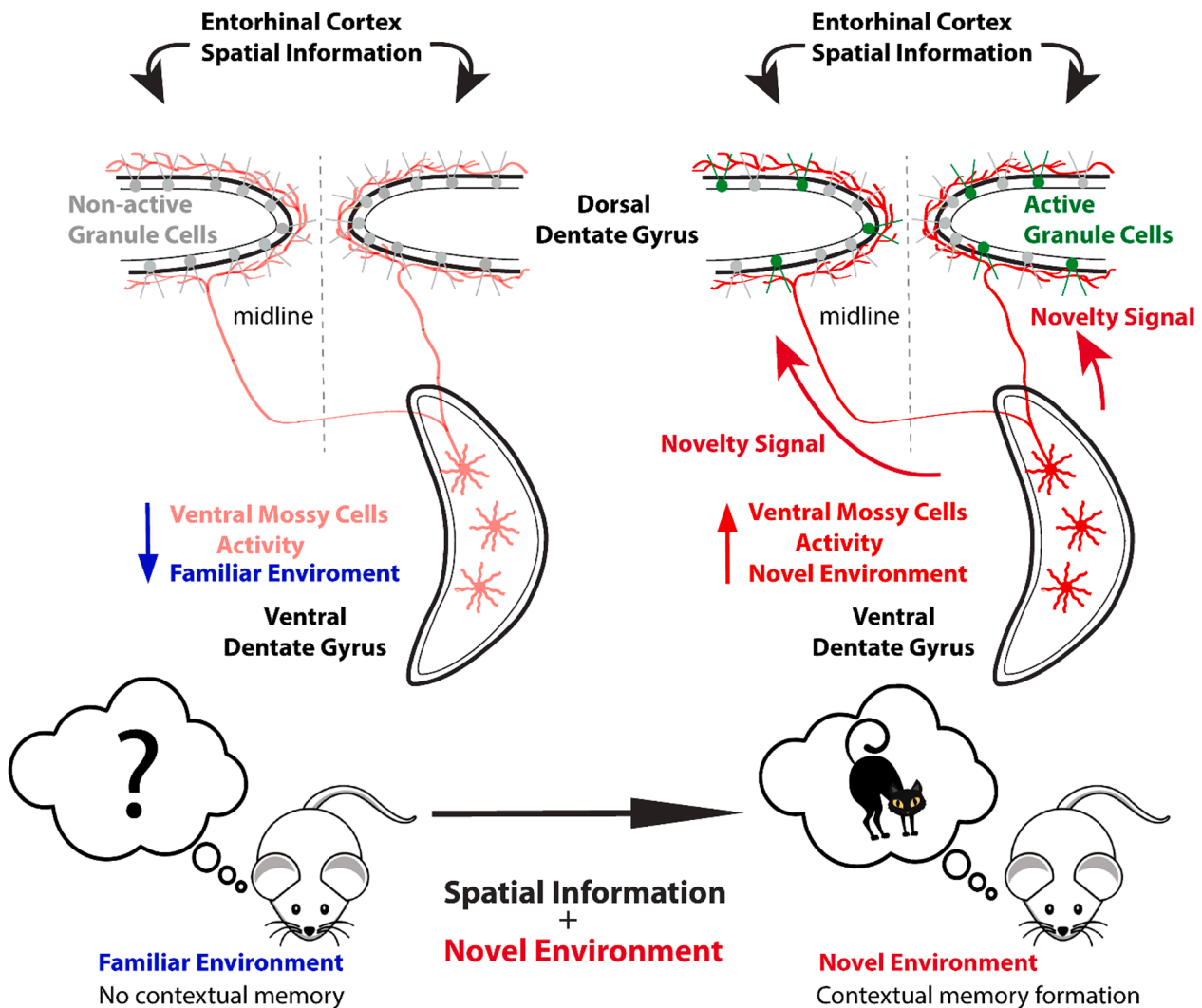


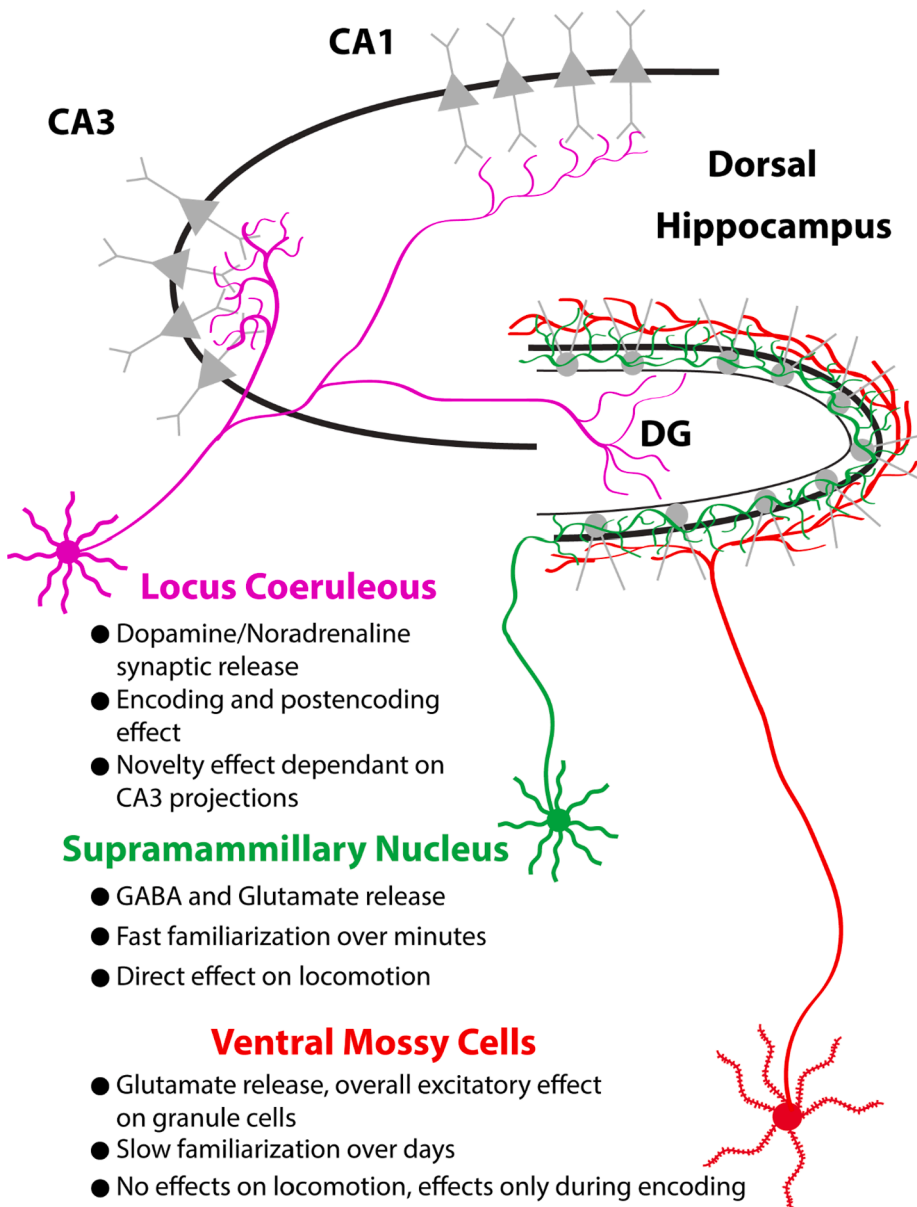
Fig. 1. Ventral mossy cells gate the formation of contextual memory by a widespread depolarization of dorsal granule cells. In a familiar environment (left), ventral MC activity is low, excitatory inputs from the entorhinal cortex are not sufficient to elicit GC firing, so no contextual memory is formed. When animal enters into a novel environment (right), ventral MCs become more active shifting membrane potential of dorsal GCs toward the threshold, now, the spatial information from the entorhinal cortex is sufficient to make a subpopulation of dorsal GCs fire, and thus form contextual memory (Modified from Fredes et al., 2020).

retrieval phase of the same paradigm, does not have any effect on the freezing response (Kheirbek et al., 2013). These results are in line with our data showing that inhibition of ventral MCs or their terminals in the dorsal DG during retrieval phase of contextual fear conditioning, have no effect in the amount of freezing (Fredes et al., 2020), indicating that the reactivation of the engram cells may not be necessary for physiological retrieval.

Other circuits for hippocampal novelty detection have been recently reported (Fig. 2) including the dopaminergic projections from locus coeruleus (LC) to the dorsal hippocampus (Takeuchi et al., 2016; Wagatsuma et al., 2017) and supramammillary nucleus (SuM) to the DG (Chen et al., 2020). Tyrosine-hydroxylase-expressing (TH+) LC neurons were found to be activated by environmental novelty and optogenetic activation of LC TH+ neurons enhances memory consolidation (Takeuchi et al., 2016). However, the LC and ventral MC pathways are apparently independent, because chemogenetic activation of ventral MCs is sufficient to facilitate the formation of contextual memories in familiar environments and, contrary to the post-encoding effect of LC activation (Takeuchi et al., 2016), inhibition of ventral MC right after the conditioning has no effect on memory formation (Fredes et al.,

2020). Also, Wagatsuma et al. 2017 revealed that LC projections to CA3, but not in CA1 or DG, are necessary for novel contextual learning. This evidence further supports the idea that LC-hippocampus pathways work independent of the ventral MC-dorsal GC novelty signaling, probably supporting different stages in contextual memory formation.

A more related pathway was recently discovered by Chen et al., 2020, where SuM neurons projecting to the dorsal DG are responsive to environmental novelty. The authors showed that bidirectional optogenetic manipulation of the SuM terminals in the dorsal DG changed animal locomotion levels associated with habituation when they visited novel and familiar environments. Thus, these results suggest the novelty signal from SuM terminals in the dorsal DG are required for contextual memory. Although the SuM and ventral MC pathways to dorsal DG seem redundant, their kinetics of familiarization/habituation are different. We showed that ventral MCs and dorsal GCs gradually decrease their activity over a period of 6 days of visiting the same environment (Fredes et al., 2020). In contrast, SuM neurons habituate over minutes within the same day (Chen et al., 2020). This striking difference suggests different roles for these pathways in novelty detection. One possibility is that SuM neurons inform about the current environmental novelty to the dorsal



**Fig. 2.** Comparison of known pathways involved in hippocampal novelty detection. Locus Coeruleus (magenta) projects to most of the hippocampus but the manipulation effect is only effective on its projections onto CA3. Terminals release dopamine/noradrenaline and manipulation of its activity have an encoding and post encoding effect on novelty-driven memory. Supramammillary Nucleus (green) projections to the GCs and inner one third molecular layer of the DG have been found to have an effect on novelty-related memory by releasing GABA and glutamate. The novelty-driven activation of this nucleus rapidly decreases within minutes upon repeated exposure to the same environment. Manipulation of the activity of these terminals causes a direct effect on animal locomotion. Ventral mossy cells (red) project bilaterally to the inner one third molecular layer of the DG, releasing glutamate and thus directly activating dorsal GCs. The novelty-driven activation of these cells decreases over the course of days of repeated exposures to the same environment. Manipulation of these terminals have little effects in locomotion and only modulate memory encoding.

DG in order to sustain exploration but do not act as a depolarization drive to dorsal GCs as we have shown for the ventral MC pathway. This idea is supported by the fact that the SuM terminals over the DG release both glutamate and GABA. Also the robust feed forward inhibition observed in dorsal GCs after optogenetic stimulation of SuM terminals, which is similar to the responses in dorsal GCs upon dorsal MC terminal stimulation (Chen et al., 2020; Fredes et al., 2020; Hsu et al., 2016). This way, the novelty signal from the SuM may unchains complex local circuit computations involving many cell types, regulating the continuous update of the context representation and thus, controlling the explorative drive of the animal. This hypothesis is supported by the fact that inhibiting SuM terminals or dorsal MCs have a similar effect: a decreased locomotion during novel environment exploration (Chen et al., 2020; Fredes et al., 2020). On the other hand, as stated above, the increase of ventral MC activity upon novelty exposure is locomotion independent and habituates over the course of days. Furthermore, the manipulation of the ventral MC pathway does not change the locomotion but directly controls dorsal GC activity, affecting the formation of memory engrams for pattern separation necessary for long-term contextual memory encoding (Fredes et al., 2020) (Fig. 2).

## 8. Dorso-ventral segregation of hippocampal theta rhythm and novelty detection

As mentioned above, there are mounting evidences linking the hippocampus to novelty detection and those showing that neurophysiological signals within the hippocampus normally habituate or decrease with repeated experience (Berke et al., 2008; Kemere et al., 2013; Kumaran & Maguire, 2009; Nyberg, 2005; Vinogradova, 2001). Particularly, Penley et al., 2013 have shown that rats navigating across a runway in a novel space, as compared to a familiar environment, exhibit an increase in theta power across electrode sites throughout the entire septotemporal hippocampus including DG and CA1 (Penley et al., 2013). Furthermore, they found an increase in theta coherence across septotemporally distant CA1 electrodes. However, their data shows a dramatic decrease in theta coherence between electrodes placed in the dorsal and ventral DG when the animal explores a novel environment. These findings suggest that environmental novelty synchronizes the CA1 field activity and engages it across the entire septotemporal axis of the hippocampus, but a different mechanism operates in the DG within the theta range during novel spatial experience. In support of this idea, Hinman et al., 2011 reported that theta amplitude decreases as a function of familiarization to the linear track at temporal (ventral) but not septal (dorsal) levels of the hippocampus (Hinman et al., 2011). In the same work the authors also demonstrated that theta power was tightly related to the locomotion speed of the animal in electrodes located in the septal but not temporal part of the hippocampus. As theta power in the hippocampus is dependent on medial septum activity (Wang et al., 2015), and also correlated with the speed (King et al., 1998), we speculate that the ventral DG may have a local theta generator or pacemaker, which is closely modulated by exposure to novelty. This would explain the lack of theta power/speed correlation and the decreased theta power in the ventral hippocampus during familiarization. Having two independent theta pacemakers, one that coordinates and engages the whole longitudinal axis of the hippocampus, and another that is triggered by novelty in the ventral DG, may also explain the decrease of coherence between dorsal and ventral DG observed in the novelty exposure. When the animal gets familiarized with the environment, the theta generator in the ventral DG loses its novelty drive, leading to the concomitant theta power decrease with familiarization, and increase theta coherence between dorsal and ventral DG, which become paced by the same clock, namely, the medial septum (MS) (Vandecasteele et al., 2014; Wang et al., 2015). As novelty also induces arousal, the recent discoveries of the nucleus incertus (NI) control on hippocampal theta rhythm should be also taken into account (Szónyi et al., 2019; Lu et al., 2020). The GABA releasing terminals from NI target somatostatin-positive

interneurons in the dorsal hippocampus and simultaneously glutamatergic neurons in the MS (Szónyi et al., 2019). Optogenetic activation of this subpopulation of NI GABAergic cells, decreases power and frequency of dorsal hippocampal theta. On the other hand, neuromedin B (NMB) expressing neurons in the NI are active during locomotion and promote arousal and increase theta power in the dorsal hippocampus (Lu et al., 2020). Thus, it is possible that upon novelty, the nucleus NMB expressing neurons become active, and the GABAergic subpopulation becomes inhibited, supporting the increase of theta power observed in the dorsal hippocampus during novelty exploration.

For the case of ventral hippocampus increase in theta power, we hypothesize that ventral MCs could be an excellent candidate for the novelty driven theta pace maker. First and most importantly, an *in vitro* study has shown that in the developing mouse DG, that ventral but not dorsal MCs exhibit intrinsic burst firing in the absence of synaptic inputs (Jinno et al., 2003). Also, the authors have shown that the intrinsic bursting firing of ventral MCs was likely dependent on the persistent sodium currents. Their data is clear cut, as none of the dorsal MCs showed intrinsic burst firing, but over 80% of recorded MCs in the ventral pole exhibited these spontaneous firing activities. Although the intrinsic firing of ventral mossy cells in this study were very slow compared to theta (6–9 bursts per min), these intrinsic properties are modulated by synaptic inputs, which may lead to theta phase locking in the intact brain.

Another piece of evidence supporting our hypothesis is the above mentioned increased activity of ventral MCs when the animal explores a new environment and the gradual decrease of their activity when the animal gets familiarized with the environment (Fredes et al., 2020). This pattern of activity follows the same trend of theta power in the ventral hippocampus (Hinman et al., 2011). Further experiments of electrophysiological recordings of the firing in identified ventral MCs coupled with local field potentials in freely behaving animals are needed to disclose these possibilities.

Following our hypothesis that ventral MCs could act as a theta pacemaker in the ventral DG, their projection over dorsal GCs could impose a synchronous rhythm there too. This however, would not be in line with the decrease in coherence between dorsal and ventral DG when the animal is exploring a new environment. Taking the MS projection to the dorsal hippocampus as an example of theta rhythm control, theta-phased-locked neurons in the MS are inhibitory and pace the rhythm in the dorsal hippocampus by inhibiting interneurons (Freund & Antal, 1988). However, it is important to note that MS cholinergic projections have as well, an important effect on hippocampal theta rhythm (Vandecasteele et al., 2014). Thus, although we cannot rule out the possibility that ventral MCs impose the theta timing in the dorsal DG, we think this scenario is unlikely because of the targeting selectivity of the ventral MC axons within the dorsal DG we have shown (Fredes et al., 2020).

Considering all this data, an inevitable question emerges: is there a causal role of the theta anti-coherence observed upon novelty exposure in memory encoding? Dealing with this question would be a challenging enterprise, because manipulation of theta rhythm synchrony leaving overall firing activity unchanged is essential in order to selectively dissect the effect of synchrony.

## 9. Conclusions

The anatomical segregation of the hippocampus is based on its differential connectivity and gene expression that supports segregated functions along the dorso-ventral hippocampal axis. However, novelty detection has been reported to take place in the whole hippocampal axis, especially in the DG. MCs in the ventral DG are responsive to environmental novelty and project to the dorsal DG. We propose that this novelty signal through the ventro-dorsal pathway acts as a gate for the spatial information coming from the entorhinal cortex in order to form contextual memory. Other novelty detection pathways in the

hippocampus including those from the locus coeruleus to CA3 and the supramammillary nucleus to the DG seem to support different aspects and mechanisms of novelty-related memory formation, and work independently from the ventral MC pathway. Novelty-related synchrony in the theta frequency along the dorso-ventral DG axis can be another mechanism involved in novelty-driven memory formation. The recent discovery of parallel novelty detection pathways to the hippocampus opens many questions about how they relate each other during novelty-driven memory formation. Future studies need to address the electrophysiological activity of multiple novelty detection systems simultaneously, at the cellular and regional levels in order to provide a more complete understanding of how novelty primes the hippocampus to enhance memory.

### Credit Author Statement

Felipe Fredes and Ryuichi Shigemoto conceived the idea and wrote the manuscript.

Felipe Fredes made the figures.

Felipe Fredes is the corresponding author.

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