Review

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Sharpening the blades of the dentate gyrus: how adult-born neurons differentially modulate diverse aspects of hippocampal learning and memory

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Abstract

For decades, the mammalian hippocampus has been the focus of cellular, anatomical, behavioral, and computational studies aimed at understanding the fundamental mechanisms underlying cognition. Long recognized as the brain's seat for learning and memory, a wealth of knowledge has been accumulated on how the hippocampus processes sensory input, builds complex associations between objects, events, and space, and stores this information in the form of memories to be retrieved later in life. However, despite major efforts, our understanding of hippocampal cognitive function remains fragmentary, and models trying to explain it are continually revisited. Here, we review the literature across all above-mentioned domains and offer a new perspective by bringing attention to the most distinctive, and generally neglected, feature of the mammalian hippocampal formation, namely, the structural separability of the two blades of the dentate gyrus into "supra-pyramidal" and "infra-pyramidal". Next, we discuss recent reports supporting differential effects of adult neurogenesis in the regulation of mature granule cell activity in these two blades. We propose a model for how differences in connectivity and adult neurogenesis in the two blades can potentially provide a substrate for subtly different cognitive functions.

Keywords adult neurogenesis; dentate gyrus; hippocampus
Subject Category Neuroscience
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See the Glossary for abbreviations used in this article.

Introduction

A fundamental question in Neuroscience is how the brain processes sensory information to achieve cognition. In this regard, one of the most extensively studied brain region is the hippocampus, which is considered as the brain's seat for learning and memory. Over the past several decades, experimental approaches including lesions, electrophysiological (ephys) recordings, pharmacological or genetic manipulations, and computational modeling have led to several hypotheses on the mechanisms underlying hippocampal cognitive function and, more specifically, information processing within its sub-regions.

The hippocampus is implicated in various cognitive functions, including contextual learning, navigation, novelty discrimination, and memory processes that emerge as a result of integration, separation, and completion of information projected to, and relayed through, its distinct anatomical sub-regions (Eichenbaum *et al*, 1992; Lisman *et al*, 2017). As an example, navigating a new environment requires several computational processes, such as attending to the landmarks, mapping their spatial organization relative to the agent, fixating onto a target location and charting the best trajectory to reach it. A prevalently accepted notion after years of hippocampal research is that its sub-regions play key distinct roles in such computational processes.

Anatomically, the term hippocampal formation usually refers to the dentate gyrus (DG), the cornu ammonis (CA) and the subicular cortex. Furthermore, CA is divided into four sub-regions, with CA1 and CA3 being the most prominent, CA2 forming a small intermediate zone between these two, and CA4 being considered as a polymorphic sub-region of the DG (Amaral, 1978; for these reasons, CA2/4 will not be considered further for this review). Despite intensive research, understanding the role of each hippocampal sub-region in specific computational processes, and the result of their integration in achieving complex cognitive functions, has been challenging and currently only partially understood.

Historically, most efforts in the study of hippocampus have focussed on CA1, mainly due to easier accessibility of this region. While preparing this manuscript, nearly two million entries came up on Google Scholar when we searched for 'hippocampus', of which ca. 60% remained with the combination 'hippocampus CA1', and only ca. 10% and 15% when combined with 'CA3' and 'dentate gyrus', respectively. Furthermore, the arrowhead-shaped DG anatomically comprises of two characteristic sub-regions, referred to as

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Glossary

Encoding
Borrowed from programming, this term describes the action of converting human-entered inputs (e.g., key presses on the keyboard) into computer's digital form. In neuroscience, this term is used under multiple situations to describe (i) how a stimulus is represented in the neuronal language (see population and rate encoding) or (ii) the process of storing a memory in the neuronal language (see memory encoding).

Population Encoding
Refers to the encoding of a stimulus in the on/off activity of a set of neurons. For example, in a population of 5 neurons (1 if active, 0 if inactive), stimulus A might be encoded as 10110, while stimulus B might be encoded as 10011. For the encoding to be reliable and robust, the same neurons would be active or inactive every time the same stimulus is presented.

Rate Encoding
Encoding of a stimulus in the firing rate activity of neurons. For example, in a population of 5 neurons (1 if active, 0 if inactive), stimulus A might be encoded as 10110 with cells 1 and 3 firing at 1 Hz, and cell 4 firing at 0.5 Hz, while stimulus B might also be encoded as 10110, but with cells 1 and 3 firing at 0.5 Hz, and cell 4 firing at 1 Hz.

Memory Encoding
This is the first phase of memory processing, which is defined as the transformation and short-term storage of a memory into the neuronal language. The representation of a memory can be stored through population encoding, rate encoding, or even population overlap. Also referred to as memory acquisition.

Memory Consolidation
This can be thought of as the second phase of memory processing, which is defined as long-term storage of memory in the neuronal language. This is thought to occur during sleep after memory encoding. While widely studied and known to involve sharp-wave ripples, this process is still not well understood.

Memory Retrieval
Considered as the third phase of memory processing, this term refers to the recall of a memory to modulate behavior accordingly. For example, pairing of a context with a foot-shock would cause the animal to freeze in that same context the next day. Also, after learning a rewarded location, the animals are quicker to find the same location after sleep the next day.

Sleep Replay
This term is used to describe the repetition of the neuronal activity that occurred during memory encoding, while sleeping. This phenomenon of repetitious firing of the same neurons (see STDP) is thought to aid with memory consolidation by strengthening and/or weakening of synapses between neurons.

Spike-time dependent plasticity (STDP)
Colloquially phrased as 'neurons that fire together, wire together' in which the timing between the firing of the neurons is critically important. Research has shown that repeated firing of a presynaptic neuron within a few tens of milliseconds before a postsynaptic neuron strengthens a synapse. In contrast, if a presynaptic neuron repeatedly fires after the postsynaptic neuron within a few tens of milliseconds the synapse gets weakened.

Recurrence
Indicates neurons synapsing onto other neurons within the same neural layer, along with the existence of other input and output synapses. In the hippocampal circuit, CA3 is known to have a high number of recurrent synapses which, as suggested by computational models, promotes pattern completion.

its infra- and supra-pyramidal blades (IP and SP, respectively). In spite of the DG and its structural organization being considered one of the most distinctive features of the hippocampal formation and unique to mammals (Box 1), less than 0.1% of the above-mentioned articles have looked at the differences between its two blades. More so, to the best of our knowledge, not one of the two million Google Scholar entries on 'hippocampus' have looked into any potential IP/SP-blade specific roles in information processing. As Borzello *et al* (2023) very recently pointed out in a comprehensive review on DG function, "little is known about the functional differences between the upper and lower blades of the DG, and this is an area ripe for investigation".

Notably, and as an additional hallmark, DG is one of the only two neurogenic niches in the mammalian brain within which neural stem cells (NSC) reside that generate newborn neurons over the course of life (Altman & Das, 1965). These newborn neurons, generated through a process usually referred to as 'adult neurogenesis', are thought to be critical for fine-tuning hippocampal function and cognitive behavior (Leuner *et al*, 2006; Gonçalves *et al*, 2016; Denoth-Lippuner & Jessberger, 2021), but their contribution to specific computational processes is not well understood. While historically considered homogeneous in cellular composition and function, differences between the IP and SP blades of the DG with regard to the physiology of newborn neurons have only recently begun to emerge (Luna *et al*, 2019). Whether these differences in the physiology of IP/SP newborn neurons provide a substrate for different roles of the two blades in specific cognitive functions has not been investigated.

In this review, we focus our attention on the DG and, specifically, structural and functional differences between its two blades. While doing so, we will briefly summarize the current understanding of the whole hippocampal network, its sub-regions, and afferent and efferent connections, which have been very well reviewed in many previous works (Amaral & Witter, 1989; Strange *et al*, 2014). Also, for the purpose of this review, we will limit our focus to the dorsal hippocampus due to its preferential purported role in cognitive, rather than emotional, behavior (Fanselow & Dong, 2010). To begin with, we will present evidence supporting the existence of parallel circuits in the hippocampus carrying different types of information and expand on the potential participation of the IP and SP blades in these parallel circuits. Next, we will propose a hypothesis based on very recent reports from our group and others', suggesting a distinct role of newborn neurons generated over the course of life within the IP and SP blades in the processing of information carried through the above-mentioned parallel circuits. Through these observations, we outline a new framework to understand how anatomical compartmentalization and adult neurogenesis within the hippocampus cooperate not only in differential transmission but also in differential processing of information to ultimately promote different aspects of learning and memory.

Structure of the mammalian hippocampus

In the mammalian brain, the primary cortical areas are activated by sensory stimuli including vision, odors, touch, etc. The responses of these regions undergo preliminary processing in the secondary and tertiary cortical areas, which respond to higher-order sensory information. These cortical areas have been a subject of study for many decades, and some regions, such as the visual cortex, are now quite well understood (Felleman & Van Essen, 1991; Nassi & Callaway, 2009). For example, say we are watching a child and a cat walking toward each other in front of a fence (Fig 1). While watching this scene, neurons in our primary visual cortical layers V1/V2 would respond to oriented edges in the visual field and light/dark contrasts, with further processing of colors, geometric shapes and movement occurring in neurons of deeper layers, such as V4 and V5 (Fig 1A–H). Subsequent computations occur in the association cortices, such as parietal, restrosplenial, and temporal association areas, where information from multiple sensory modalities is also combined. In our example, the neurons in the inferior temporal gyrus continue the processing of the visual stimuli and respond to objects, faces, and places, such as the moon, cat, or the child's face (Fig 1E). Projections from multiple such association areas then get routed to the hippocampus through the parahippocampal region (perirhinal, postrhinal, and entorhinal cortices), where information converges and is redistributed in a permanent cortico-hippocampal conversation (Eichenbaum, 2000; Fig 1G). With all sensory signals being routed through it, the hippocampus processes this multi-level information and encodes rapid associations between experienced events (Henke, 2010). This places the hippocampus in an ideal position to perform its major recognized role as centre for learning and memory.

In spite of its highly complex afferent, efferent, and internal connectivity (Hainmueller & Bartos, 2020), the hippocampus is traditionally depicted as having a relatively simple trisynaptic internal circuit (DG – CA3 – CA1), with entorhinal cortex as its major input (Fig 2A). Since late-1990s, research began to consider this internal circuit as being comprised of two segregated, yet partially overlapping, parallel streams derived from the medial and lateral entorhinal cortex (MEC and LEC, see below; Burwell, 2000; Fyhn *et al*, 2004; Knierim *et al*, 2006; Eichenbaum *et al*, 2012; Lee *et al*, 2020). Here, we extend on this notion of parallel processing streams in the hippocampus with special emphasis on structural and functional specialization within the IP and SP blades of DG, downstream from MEC and LEC, respectively.

Entorhinal Cortex (EC)

The EC provides the main input to the hippocampal gateway (Ramón y Cajal, 1893; Witter, 2012), and is cytoarchitecturally differentiated into 6 layers, of which layers 2 and 3 send efferent projections to DG/CA3 and CA1, respectively, while layers 5 and 6 receive back projections from CA1 (Valero & de la Prida, 2018; Fig 2A). EC projections to the hippocampus provide a good criterion to define its two main subdivisions, the MEC and LEC (Steward, 1976; Witter *et al*, 2017) whose segregation is thought to begin with the connections coming from the cortical areas (Witter *et al*, 2000). The rodent MEC (parahippocampal cortex in primates) receives more cortical projections from the postrhinal cortex and presubiculum, whereas the LEC receives more cortical projections from the perirhinal cortex (see below for functional implications). Keeping the focus on DG, the two EC subregions connect differentially with it, potentially forming two distinct output streams (Canto *et al*, 2008; Witter *et al*, 2017). In specific, thicker bands of projections innervate the MEC with the IP, while relatively thinner bands are observed between MEC-SP. Conversely, projections between LEC-SP are thicker relative to those between LEC-IP (Fig 2B; Tamamaki, 1997; Witter, 2007a; Luna *et al*, 2019). As discussed below, these and other studies highlight differences in cellular composition and connectivity of the EC and show that the EC receives input, and provides output, in two different, albeit partially overlapping, streams of information.

DG

The DG is a hallmark of the mammalian hippocampus (Box 1) which mostly receives all its input from the EC. Traditionally considered homogeneous in cellular composition, connectivity, and function, differences between the two blades of the DG had only been briefly investigated (Claiborne *et al*, 1986; Woodson *et al*, 1989; Scharfman *et al*, 2002). These studies showed a greater synaptic density and dendritic complexity of granule cells in the SP, as compared to those in the IP (Desmond & Levy, 1985; Gallitano *et al*, 2016), as well as heterogeneity at the level of intrinsic ephys properties (Mishra & Narayanan, 2020) and distinct transcriptome signatures even within the same blade (Erwin *et al*, 2020). Projections from the EC to the DG are essentially divergent, with EC neurons targeting granule cells of the DG at a ratio of 1:10 (Amaral *et al*, 1990). This feature is considered critical for DG function (see below). These projections reach the DG through the medial and lateral perforant path originating from MEC and LEC, and primarily target the IP and SP blades respectively, as mentioned above (Amaral & Witter, 1989). However, if and how the IP/SP blades further expand anatomical differences in connectivity and propagation of two parallel streams of information has not been thoroughly investigated. To the best of our knowledge, differential processing within these parallel streams and its functional implication within the DG has also never been considered.

Figure 1. Visual cortical processing and cortico-hippocampal communication.

(A) Say we are watching a movie scene with a child walking toward the right, and a cat walking in the opposite direction, with a backdrop of a fence in a night-like setting. As we are watching this scene, our visual cortical layers additively process it in steps. (B) Layers V1 and V2 would start by processing edges and boundaries in the scene, along with light/dark contrasts, such as the moon being lighter than its background. (C) V3 would process motion in the scene and provide a sense of some light spots moving to the right, others to the left, while some others being stationary. (D) V4 would further bring in some color to the scene and break it down into basic geometric shapes, while V5 would bring the sense of movement speed in it. (E) Further processing of the visual scene happens in temporal association areas, after which the viewer would start recognizing faces and objects, while other abstract parts of the environment might still stay ambiguous. (F) Now say at a specific location, the child trips over the cat and falls. Taking the child's perspective, this moment might get stored as an episodic memory in the child's hippocampus. (G) Sensory signals from different brain regions (shown as colored geometric shapes) in the child's brain, such as the visual cortex (turquoise, within dashed circle), and olfactory cortex (purple), are routed through (black arrows) and assimilated in the EC/hippocampus circuit (blue/orange) aiding in episodic memory formation and recall. (H) The visual cortical layers occupy topographically distinct areas in the occipital lobe of the brain.

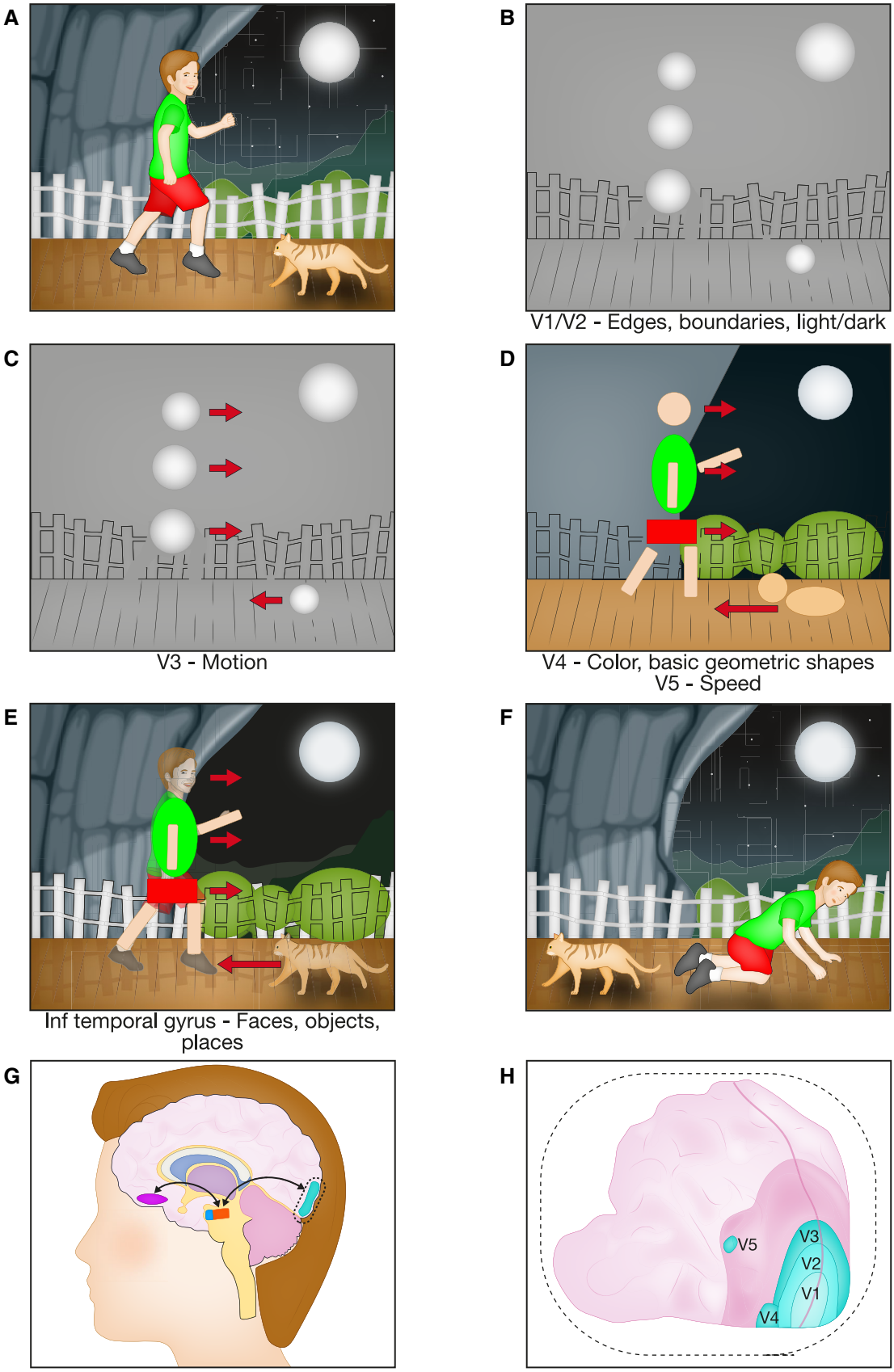

Figure 1.

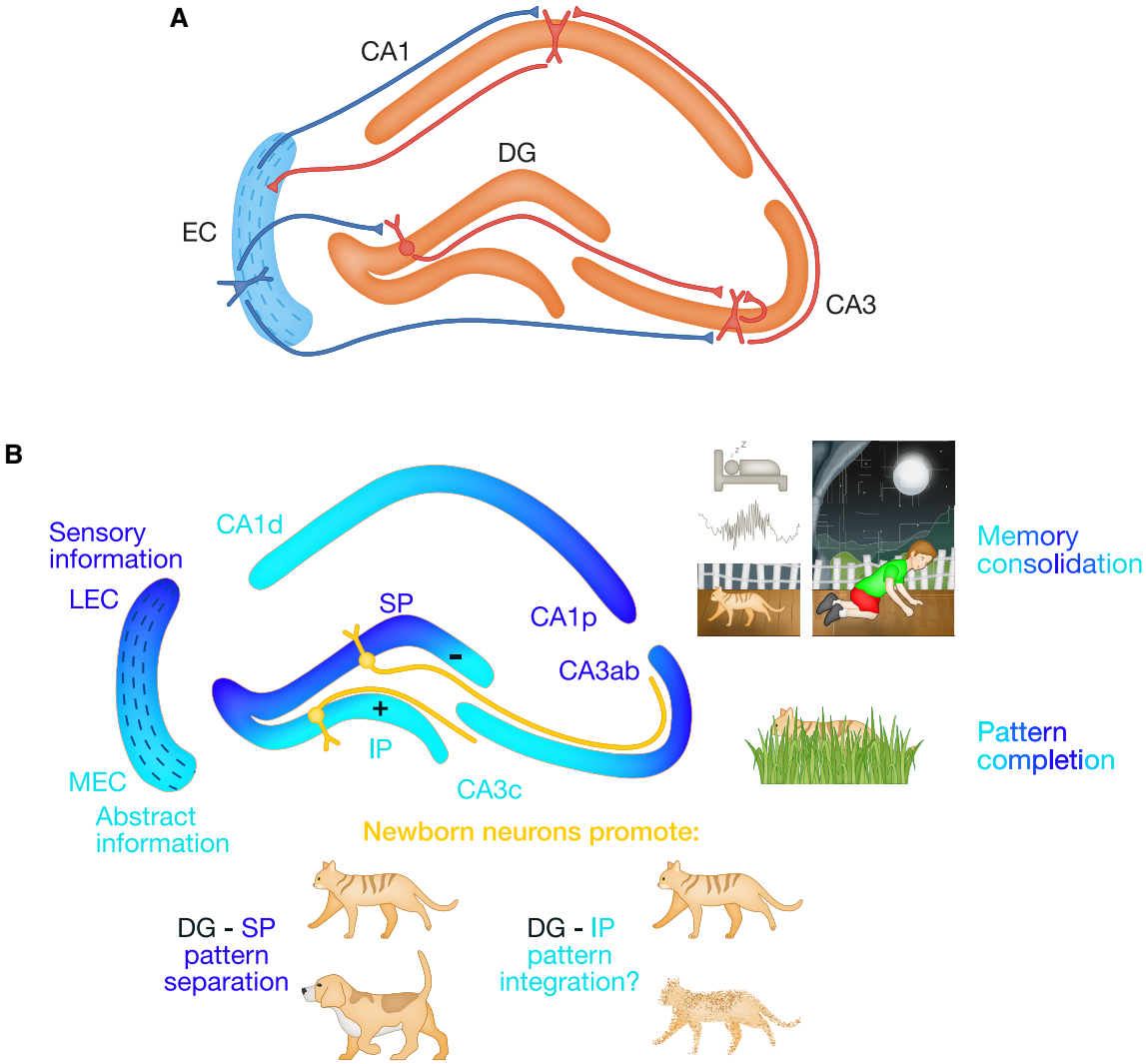

Figure 2. Differential effects of newborn neurons on parallel hippocampal processing.

(A) Simplistically, the hippocampal circuit can be thought of as a trisynaptic loop: EC - > DG - > CA3 - > CA1 - > EC. (B) Based on more recent literature, we argue that this circuit, structurally and functionally, can be thought as being comprised of two parallel streams: LEC - > SP - > CA3a - > CA1p (LSap), denoted in dark blue, and MEC - > IP - > CA3c - > CA1d (MIcd), denoted in light blue. (Please note a small degree of light blue in SP and dark blue in IP, denoting partial overlap between MEC-SP and LEC-IP). Traditionally, in memory processing, CA3 is known to participate in pattern completion, CA1 in memory consolidation (inconclusive functional distinction within CA3/CA1 during these processes is denoted with the color gradient in the text) and DG in pattern separation. But in light of differential modulation by the newborn neurons (shown in golden yellow) in the two blades of DG (inhibition (–) in SP and excitation (+) in IP), we propose that while the SP blade might perform pattern separation, the IP blade might be performing a different computation, such as pattern integration.

CA3

The axonal projections of DG granule cells to CA3 are known as mossy fibers, which primarily target pyramidal neurons and inhibitory interneurons (Amaral & Witter, 1989; Andersen *et al*, 2009). In contrast to the DG, heterogeneity at the cellular, connectivity, and functional level is well accepted in CA3 (Lee *et al*, 2020). CA3 can be subdivided into three regions along its transverse axis, namely CA3c (proximal to the DG), CA3b, and CA3a (most distal from the DG) owing to its cytoarchitecture and connectivity differences (Lorente De Nó, 1934). These include, among others, gradients in gene expression and intrinsic ephys properties, and increasing dendritic lengths along the CA3 proximo-distal axis (Ishizuka *et al*, 1995; Turner *et al*, 1995; Thompson *et al*, 2008; Sun *et al*, 2017). With regard to connectivity, mossy fibers originating in the IP blade preferentially target basal dendrites of neurons in CA3c, whereas those from the SP blade mostly project to apical dendrites of neurons in the CA3ab area (Fig 2B; Witter, 2007b).

CA1

The final stage in the trisynaptic circuit is CA1, whose pyramidal cells receive inputs primarily from CA3 through the Schaffer collaterals (Schaffer, 1892). Cellular heterogeneity has been extensively studied along the radial axis of CA1, separating its pyramidal neurons into superficial and deep layers. Neurons in these two layers

Box 1. Phylogeny and Ontogeny of an atypical neurogenic niche: the mammalian DG.

Part of the archicortex, the mammalian hippocampal formation preserves a characteristic three-layer organization ontogenetically, structurally, and functionally resembling the reptilian and avian pallium (Reiter *et al*, 2017). Several neuroanatomical studies have pointed out major variations in hippocampal volume across mammals, even among primates (Vanier *et al*, 2019), as well as differences in structure, cellular composition and connectivity of hippocampal-equivalent structures across other classes of tetrapods (Striedter, 2016). A remarkable feature that emerged from these studies is that the structural organization of the hippocampal formation seems to vary more across species than its function. For example, one key hippocampal function, spatial navigation, was found to be largely conserved across amniotes, and even lamprey fish, in spite of stark differences in anatomical structure (Colombo & Broadbent, 2000). Based on this, it was suggested that the hippocampus may represent an example of convergent evolution in function despite its origin from brain regions diverging in structure (Bingman & Gagliardo, 2006).

What appears to be a clearly distinctive feature of the mammalian hippocampus, while lacking obvious homologies in other vertebrates, is the DG (Treves *et al*, 2008; Bingman & Muzio, 2017), which has resulted in a century-old debate among neuroanatomists and neuroethologists with regard to whether or not a region structurally and functionally equivalent to the DG has evolved outside the hippocampal formation.

Ontogenetically, the mammalian DG arises from a fundamentally different developmental program and NSC behavior than other brain areas, particularly when compared with the adjacent neocortex. This might also explain why mammalian adult neurogenesis within the brain's parenchyma is restricted to hippocampal DG. Specifically, the hippocampal primordium originates during development from the medial cortical hem dorsal to the choroid plexus acting as boundary organizers source of morphogens released into the cerebrospinal fluid including Wnt, Bmp, and Shh (Rolando & Taylor, 2014; Bond *et al*, 2020). In addition, the cortical hem is also a major source of Cajal–Retzius neurons that guide the basal (pial) migration of newborn neurons by secreting the glycoprotein reelin (Meyer, 2010), which is critical for the formation of the DG. As a result, behavior of dorsal and ventral NSC of the hippocampal primordium diverge during development. While dorsal NSC progress toward a developmental program that is similar to the adjacent neocortex and giving rise to pyramidal neurons of the CA sub-regions, ventral NSC in proximity to the cortical hem/choroid plexus undergo delamination, losing apical polarity and forming a new neurogenic niche (Li *et al*, 2009). Likely resulting from exposure to high levels of morphogens and abundance of reelin-producing Cajal-Retzius neurons (Li *et al*, 2009), this new niche expands and bends resulting in a distinctive V-shaped DG, its hilus and, consequently, its two distinct blades. Likely reflecting a lack in radial glial morphology and columnar organization, neuronal migration within the DG does not reflect the stereotypical inside-out program characteristic of the neocortex and fate of newborn neurons remains distinct resulting in the formation of granule, instead of pyramidal, cells. As recently revealed by single-cell transcriptome analyses, the unique ontogeny of the DG is also accompanied by a delayed neurogenic period overlapping gliogenesis with the overwhelming majority of DG granule neurons being generated postnatally (Bond *et al*, 2020).

In conclusion, the identity and lineage of NSC in the DG, and lack of contact with the ventricular surface, make them distinct from NSC of the second adult neurogenic niche of the subventricular zone, as well as NSC of other species, making the mammalian DG, and its two distinctive IP and SP blades, a unique neurogenic niche over the course of life absent in other classes of tetrapodes.

are generated in different neurogenic waves during development and exhibit gradients in genetic, morphological and ephys properties that are well reviewed elsewhere (Soltesz & Losonczy, 2018). With regard to connectivity along the transverse axis, the CA1 neurons distal to CA3 mostly receive inputs from the CA3c sub-region, whereas the proximal part is primarily innervated by CA3ab (Fig 2B; Ishizuka *et al*, 1990). From CA1, the forward connectivity pattern becomes more elaborate, with projections to the subiculum, which constitutes the main hippocampal output to the brain, back to the EC, as well as to other cortical and subcortical areas (Andersen *et al*, 2009; Witter, 2012).

Altogether, as noted by several neuroanatomical studies, the cellular and structural organization of the EC-DG-CA3-CA1 trisynaptic circuit appears to be well designed to support the separation of information into two parallel streams, namely: (i) MEC–IP–CA3c–distal CA1 (further referred to as MIcd stream) and (ii) LEC–SP–CA3ab–proximal CA1 (LSap stream; Fig 2B). Next, we discuss whether these parallel streams of information provide a substrate for differential computations within different hippocampal sub-regions.

Function of the mammalian hippocampus

As outlined above, the hippocampus receives processed sensory, motor, and proprioceptive information from almost all cortical areas. Thus, to understand the role of the hippocampus, one would need to decode the stimuli that the hippocampal neurons respond to, which could be a combination of processed sensory responses, paired with various behavioral correlates. Using Fig 1, but now taking the perspective of the child, it is possible that a hippocampal neuron in his brain responds only if a white fence is 1 m to his left while he is walking at 5 km/h, while this same cell might not be active if he is instead walking at 4 km/h, or if the fence is 2 m away. Therefore, in Systems Neuroscience, wherein we study higher-order brain functions or decipher the contribution of a brain region toward a behavior, such issues of complex stimuli–response pairing are usually addressed by combining experiments with computational/theoretical modeling of the data representing network activity. Such an approach has been used, with considerable success, in hippocampal research in order to understand its overarching role in complex cognitive functions and the roles of its sub-regions. We take an analogous approach here by reviewing experimental findings and computational models in parallel. We firstly describe the overall functions of the hippocampus in learning and memory followed by discussing the computational processes carried out by its individual sub-regions that together are believed to underlie its roles in cognition.

Two major findings from the past decades shed light on the role of hippocampus in learning and memory. First, lesion of the hippocampus and other temporal lobe structures led to selective amnesia in patients such as H.M. (Scoville & Milner, 1957), suggesting hippocampus being fundamental for declarative memory and explicit storage and retrieval of facts (termed episodic memory if personal or semantic memory if general;Tulving, 1972). Abundant research since then confirmed hippocampus to be key in the acquisition and recall of ongoing life's experiences and personal facts (Squire, 1986, 2004; Eichenbaum, 2000), while numerous computational models

have attempted to explain how it participates in those roles (Marr & Brindley, 1971; McNaughton & Morris, 1987; Buzsáki, 1989; McClelland *et al*, 1995; Rolls, 1996; Nadel *et al*, 2000).

The earlier models and experimental evidence provided support for the role of hippocampus in memory encoding (see Glossary) and recent retrieval (see Glossary), as well as a progressive involvement of cortical structures in remote retrieval due to consolidation of information (see Glossary) as long-term memory through the passage of time. This was termed 'System Consolidation Theory' of memory formation (Scoville & Milner, 1957; Squire *et al*, 2015). A number of variations of this theory tried to accommodate the relative differences in retrieval seen in amnesic patients and animals (for instance, remote memory impairments among patients with hippocampal damage), with later studies and models suggesting a more permanent role of the hippocampus in retrieval of episodic memories, irrespective of how remote they became. Among the ones gaining major support, the 'Index Theory' elegantly portrays the hippocampus as a librarian generating indexes of the neocortical activity patterns present during a given experience, storing their location and facilitating their retrieval (Teyler & DiScenna, 1986; Teyler & Rudy, 2007). Both these theories garnered support from the discovery of 'engrams', which have been proposed as ensembles of neurons that store contextual information in episodic memories (Tonegawa *et al*, 2018), and could act as hippocampal cellular substrates indexing cortical memory representations (Tanaka & McHugh, 2018). Engram cells were first discovered in the hippocampus, although later research has also revealed their presence in other brain regions including cortical areas (Kitamura *et al*, 2017; DeNardo *et al*, 2019).

Second, concomitantly with the first computational models on hippocampal function (Marr & Brindley, 1971), came the discovery of 'place cells', i.e., neurons that selectively fire at specific locations during navigation, by O'Keefe & Dostrovsky (1971). This finding promoted the notion that the hippocampus acts as a repository for allocentric spatial maps (i.e., maps that are independent from the observer's view-point and solely represent the external world), and plays a role in the formation of spatial cognitive maps. 'Cognitive-Map Theory', as first used by Tolman (1948), was posited as brain's ability to form internal neural representations that systematically organize knowledge for future generalizations and flexible behavior (Eichenbaum, 2017a; Behrens *et al*, 2018). This theory was further elaborated in the spatial domain by O'Keefe & Nadel (1978, 1979), and expanded after the discovery of a large set of spatially-tuned cells, including place cells, head-direction cells, grid cells, border cells, boundary-vector cells and landmark-vector cells in the various sub-regions, and input/output regions of the hippocampus (Wills *et al*, 2014; Moser *et al*, 2017). These discoveries affirmed the role of hippocampus in spatial cognition and flexible navigation. Theories and computational models explaining how these various spatial tunings might arise, and how they help with navigation, have been appearing in the literature for decades (Zipser, 1985; Sharp, 1991; Burgess & O'Keefe, 1996; Burgess *et al*, 2002; Byrne *et al*, 2007).

The above two seemingly distant functions of the hippocampus, indexing memories and creating a spatial representation of the world, started getting tied together with the discovery of 'time cells' (MacDonald *et al*, 2011). The finding of time cells provided a possible mechanism for previous results showing the involvement of the hippocampus in sequence learning (Eichenbaum, 2014) and composing sequential memories (Meck *et al*, 1984; Hales *et al*, 2009; Staresina & Davachi, 2009) in both rodents and humans. With this, the Index and Cognitive Map Theories started to be viewed as two sides of the same coin by Eichenbaum & Cohen (2014), wherein they suggested that the hippocampus processes and organizes both spatial and temporal information in a relational manner for the formation of cognitive, rather than solely spatial, maps (Rubin *et al*, 2014; Eichenbaum, 2017b; Benna & Fusi, 2021). This idea implied that the hippocampus maps and organizes memories in abstract cognitive representations, i.e., it might serve as a 'librarian' indexing maps of not only physical space, but also 'cognitive space' by storing locations of episodic memories.

Extending our example from Fig 1, while the child is taking a stroll, his hippocampus is mapping the physical space around him due to various place cells being active at different locations on the path in relation to the sensory cues encountered or even to cardinal directions. Now, say at a certain location, the cat gets too close to his feet resulting in the child tripping and scraping his knee (Fig 1F). This moment will probably get stored in his brain as an episodic memory. The details of this memory, such as sights, smells or sounds, might be stored in the corresponding cortical areas, the spatial location in the hippocampus, while the emotions of experiencing pain and annoyance in some other regions of the limbic system. As the pieces of this memory are spread out in the cognitive space, the hippocampus would create and store indexes for the locations of the individual pieces to aid with later recall of the whole episode (Fig 1G). At a later time, upon encountering just one stimulus from the time of memory acquisition, say upon seeing a dog similar to the cat (Fig 2B) or passing by the location where the episode happened, these indexes and the associated pieces of the memory could get activated at once, leading to the recall of the full episode, including the emotions associated with it. In fact, hippocampal structural abnormalities and functional deficits are shown to be correlated with overgeneralization of fear and severity of post-traumatic stress disorder (PTSD; Karl *et al*, 2006; Shin *et al*, 2006; Besnard & Sahay, 2016). Thus, hippocampal representations might be available for use by multiple systems during various cognitive processes, such as spatial navigation, contextual learning and, in humans, even explicit memory recall, future planning, and imagination (Rubin *et al*, 2014).

Computations within hippocampal sub-regions

EC

As described above, the MEC and LEC initiate parallel, yet interconnected, streams relaying information to different hippocampal sub-regions (Knierim *et al*, 2014). Both streams are involved in the formation of distinct neural representations and transmission of information that, while partially separated, would ultimately be integrated toward a comprehensive hippocampal role. This idea gains support from studies finding that the MEC contains neurons that are activated specifically in response to spatial metrics, including grid cells, border cells and others (Moser *et al*, 2017), whereas LEC neurons are posited to integrate time (Tsao *et al*, 2018) and changes in local cues and objects (Knierim *et al*, 2014). Thus, spatial information (the 'where') is primarily provided by the MEC, while non-spatial information (the 'what' and 'when') is majorly provided

by the LEC (Deshmukh & Knierim, 2011; Fig 2B). Clearly, these two streams of information need to be effectively processed at each station of the hippocampal sub-regions and integrated by the whole hippocampus for emergence of meaningful cognitive behavior.

The functional dichotomy between MEC and LEC has been described using various terms, at times contrasting each other, such as where versus what (Suzuki *et al*, 1997; Sugar & Moser, 2019), spatial versus non-spatial (Knierim *et al*, 2006), place versus context, object or content (Eichenbaum, 2007; Knierim *et al*, 2014), abstract versus sensory (Whittington *et al*, 2022), and others. In line with the most recent models, here we adopt the terms abstract and sensory to describe the distinct roles of MEC and LEC, respectively, supporting the notion that cognitive space is not limited to physical space.

In other words, to completely understand the world surrounding us, one would need to combine information about space, relevance of objects, relationship between events, etc. (abstract information) with our own perception of the world including sights, sounds, smells, etc. (sensory information). In our example from Fig 1F, accurate memory acquisition of the moment of child's tripping would require combining abstract map-like information from the MEC about the specific location, and sensory specifics of the moment from LEC (Fig 2B).

DG

Traditional theories trying to decipher the function of the DG considered some form of 'competitive learning' Hebbian plasticity happening in this region that results in 'pattern separation' during the encoding of similar memories (Rolls & Kesner, 2006). Briefly, pattern separation is defined as a process aimed at reducing the overlap in representations triggered by similar inputs or, in other words, disambiguation of information. The divergent afferent connections from the EC to the DG at a 1:10 ratio and the intrinsically sparse activity of granule cells (Jung & McNaughton, 1993; Chawla *et al*, 2005) synergize to minimize the probability that similar information transmitted by the EC would be encoded by partly overlapping ensembles of DG granule cells. As a result, DG promotes emergence of distinct memory representations from experiences that might have many similar aspects in common. In the more recent years, many studies have provided experimental evidence for this theoretical framework and how this process might be taking place in the DG (Leutgeb *et al*, 2007; Yassa & Stark, 2011; Schmidt *et al*, 2012; Santoro, 2013).

Pattern separation in the DG has been proposed to occur through changes in either firing rate or population overlap (see Glossary; Johnston *et al*, 2016; Chavlis & Poirazi, 2017). In vivo ephys recordings provided evidence for the former (Leutgeb *et al*, 2007; Alme *et al*, 2010), while in-situ hybridization and immunostaining for immediate-early-genes (IEG) corroborated the latter (Chawla *et al*, 2005; Deng *et al*, 2013). Notably, IEG such as c-Fos or Arc have traditionally been used as a proxy for neuronal activation since these transcription factors are transitorily expressed immediately after neuronal depolarization and play key roles in regulating the transcriptional response to stimulation (Minatohara *et al*, 2016). These and other possible cellular responses and functions of the DG are elegantly summarized by Kesner (2018).

With regard to the LSap and MIcd streams, sensory and abstract information might undergo competitive learning in the DG, resulting in object – place (Kim *et al*, 2020) / object – context conjunctive tuning. DG might also perform 'spatial pattern separation' to process the abstract information from the MIcd stream, and 'temporal pattern separation' to process the sensory information from the LSap stream. Combined information from both the streams might also undergo 'contextual pattern separation' in the DG, such as of the environmental geometry (Leutgeb *et al*, 2007; Cai *et al*, 2016). Recent findings also report the presence of functionally segregated cells within the same DG blades (Erwin *et al*, 2020; Sun *et al*, 2020; Tuncdemir *et al*, 2022), which could propagate such functional differences downstream into different ensembles of the hippocampal circuit. Understanding the implications of such roles of the DG also becomes relevant in the context of therapy, since a reduced ability to discriminate between partially overlapping memories is at the basis of several mental conditions, including PTSD, in which a tragic memory is retrieved in generalized contexts (Maren *et al*, 2013; Besnard & Sahay, 2016).

CA3

The DG-CA3 projection is, as opposed to the EC-DG, strongly convergent (Amaral *et al*, 1990), which together with the highly recurrent (see Glossary) internal connectivity of CA3, makes this structure an optimal retrieval network (Rolls, 2013). CA3 is thus implicated in performing a process referred to as 'pattern completion', which is defined as the ability to retrieve coherent representations from fragments of information (Fig 2B; Guzowski *et al*, 2004; Neunuebel & Knierim, 2014; Guzman *et al*, 2016). In other words, this refers to the ability of recalling a complete memory of a complex event after only being exposed to a fragment of it, such as only getting a partial view of the same cat leading to the child recalling the painful memory of tripping. Unlike the DG, functional heterogeneity along the CA3 axis is well accepted and has been described elsewhere (Lee *et al*, 2020).

Studies investigating IEG expression suggested differential processing of abstract information along the CA3 (and CA1) axis, as observed in different versions of spatial and non-spatial tasks (Nakamura *et al*, 2013; Beer *et al*, 2018; Flasbeck *et al*, 2018), and hinted at a role of CA3ab – proximal CA1 in the processing of abstract information. Other experiments showed that CA3c lesions produced greater impairments in processing small spatial changes with no effects in broader task and environmental changes (Hunsaker *et al*, 2008), suggesting a preferential role of CA3c, rather than CA3ab, in processing abstract information. These seemingly contradictory results have also been linked to the possibility of the proximo-distal axis of CA3 contributing to both pattern separation and completion, which has also gotten support through ephys recordings (Lee *et al*, 2015; Lu *et al*, 2015) and IEG reactivation experiments (Marrone *et al*, 2014). In essence, while CA3c activity is consistent with pattern separation computations, CA3ab activity patterns can be attributed to pattern completion. This is in line with the lesser degree of recurrence reported in CA3c (Ishizuka *et al*, 1990) and with the higher engram reactivation rate upon contextual recall in CA3ab (Sun *et al*, 2017).

CA1

The functional segregation of the streams originating from MEC and LEC, related to abstract and sensory information, and passing through IP-CA3c and SP-CA3ab, are also transmitted to CA1 distal

(CA1d) and proximal (CA1p) segments, respectively (Fig 2B). But in addition, studies also found a big influence of direct EC inputs to CA1 bypassing the trisynaptic circuit, with LEC preferentially projecting to distal CA1 and MEC to proximal CA1 (Knierim *et al*, 2014). Several studies have also described the presence of parallel microcircuitry not only in the proximo-distal axis, but also in deep and superficial layers of CA1 pyramidal cells (Soltesz & Losonczy, 2018). All such observations might increase the complexity of computations in CA1 and diffuse the separation of abstract versus sensory streams.

Experiments examining ensemble reactivation showed a preferential reactivation of CA1p upon contextual memory retrieval (Nakazawa *et al*, 2016), in line with its preferential connection with CA3ab. Supporting this, the same study found that lesioning proximal, but not distal, CA1 impaired retrieval. Although this suggests a role of CA1p in processing of contextual information, ephys experiments contrastingly found that pyramidal cells in CA1p are more spatially tuned that those in CA1d (Henriksen *et al*, 2010), raising the possibility of CA1p being more involved in processing of abstract information. Recent ephys experiments also demonstrated a segregation of roles among cells in CA1, with c-Fos– cells representing spatial information and c-Fos + engram cells representing sensory information upon exposure to a novel environment (Tanaka *et al*, 2018; Tanaka & McHugh, 2018). Interestingly, another study found c-Fos + cells to strongly form spatial maps upon repeated navigation of a familiar environment (Pettit *et al*, 2022).

In summary, and following an effective analogy by Sugar & Moser (2019), the EC input might play a movie of ongoing experiences to the hippocampus, which in turn acts as the editor of this continuous flow of information. Through various computational processes such as pattern separation in DG, but also others such as spike-time dependent plasticity and replay (see Glossary), the hippocampus might extract and tag memorable events to be consolidated into an episodic memory. During retrieval, even if it is subjected to partial or degraded input of the encoded memory trace, CA3 might efficiently perform pattern completion and correctly instruct the memory indices in CA1 that route cortical reactivation for recall. Following this and expanding on our own analogy, we believe that the abstract and sensory components of the events played by the EC (the location of the cat and the circumstances that led to the child tripping) could be relayed separately in the two parallel hippocampal networks to finally be merged in engram indices in CA1.

Adult neurogenesis: new role(s) for new neurons in the hippocampal network

The discovery of neurogenesis in the DG of adult rat (Altman & Das, 1965) challenged the assumption that the brain was incapable of generating new neurons after development and introduced a potentially new level for structural and functional plasticity. Since its discovery over five decades ago, adult hippocampal neurogenesis has been documented in several species (Snyder, 2019), and though its presence in humans was heavily debated for many years (Eriksson *et al*, 1998; Kempermann *et al*, 2018; Moreno-Jiménez *et al*, 2021), it has now gotten validated in our species using single cell-sequencing analyses (Franjic *et al*, 2022; Wang *et al*, 2022). At the turn of the century, hippocampal studies started looking into the function of newborn neurons in learning and memory processes (Shors *et al*, 2001; Cameron & Glover, 2015). To understand how adult neurogenesis might affect information processing within hippocampal sub-regions, two dominating views proposed that newborn neurons act either as 'direct encoders' or 'activity modulators' in the DG (Ming & Song, 2011; Piatti *et al*, 2013).

Newborn neurons as direct encoders

Initial attempts to model the role of newborn neurons in memory processing considered them as electrophysiologically identical to mature granule cells and getting directly involved in the encoding of information. Under this assumption, some models proposed the need for newborn neurons to achieve memory stability and recall accuracy (Meltzer *et al*, 2005; Chambers & Conroy, 2007) by maintaining homeostatic population activity and neuronal turnover i.e., death of older neurons being compensated by newborn neurons. Such network models found that adult neurogenesis enhanced the speed and accuracy of learning new information, but accompanied by loss of recall accuracy of old information i.e., newborn neurons helped the network by forgetting prior data and driving memory clearance (Chambers *et al*, 2004; Deisseroth *et al*, 2004; Crick & Miranker, 2006). Experimental support for these models was obtained through observations of newborn neurons competing with mature granule cells for EC inputs (Adlaf *et al*, 2017), and remodeling of synapses in CA3 (see Box 2) leading to forgetting of previous memories (Akers *et al*, 2014; Epp *et al*, 2016). In parallel, other models (Wiskott *et al*, 2006) assumed a net growth of the network throughout life to circumvent potential 'catastrophic interference' caused by overlapping of new and old memories' neural representations. Such models proposed that adult neurogenesis helps generate a wider neural network, leading to sparser orthogonal representation of new memories, preventing interference from the old ones.

Subsequently, evidence mounted for newborn neurons transitorily exhibiting distinct ephys features before becoming indistinguishable from fully mature granule cells (Zhao *et al*, 2006; Aimone *et al*, 2014). Specifically, four-to-six weeks after birth, newborn neurons were shown to develop elaborate dendritic arbors coated with spines and exhibit increased synaptic plasticity and hyperexcitability compared to the mature granule neurons (Snyder *et al*, 2001; Schmidt-Hieber *et al*, 2004; Espósito *et al*, 2005; Gu *et al*, 2012). Forming functional connections with CA3 (van Praag *et al*, 2002; Zhao *et al*, 2006; Toni *et al*, 2008; Denoth-Lippuner & Jessberger, 2021), newborn neurons are recruited into the local circuitry in an activity-dependent manner, which influences their survival (Biebl *et al*, 2000; Kempermann *et al*, 2003; Tashiro *et al*, 2006; Sierra *et al*, 2010). Based on this, it has been proposed that newborn neurons provide a critical window of opportunity for structural and functional plasticity, transitorily making them efficient substrates for Hebbian potentiation and memory encoding that is subsequently lost (Deng *et al*, 2010).

Various experiments confirmed the involvement of adult neurogenesis in encoding by revealing impairments in contextual memory acquisition, expression, and extinction (Saxe *et al*, 2006; Pan *et al*, 2012; Denny *et al*, 2014; Danielson *et al*, 2016; Huckleberry *et al*, 2018) upon silencing or ablating newborn cells. The addition of highly excitable neurons in the mostly silent and highly input-specific layer of mature granule cells might bias entorhinal inputs toward the broadly tuned (Danielson *et al*, 2016) and more

Box 2. Beyond the DG: effects of newborn neurons on CA3 and CA1.

Effects of neurogenesis downstream of the DG to the CA3 and CA1 have traditionally received much less attention. On their way to CA3, mossy fibers of newborn neurons innervate canonical granule cells including CA3 pyramidal cells and inhibitory interneurons (Acsády *et al*, 1998; Zhao *et al*, 2006; Toni *et al*, 2008). Axons of newborn neurons reach CA3 as early as 2 weeks after birth (Zhao *et al*, 2006; Toni *et al*, 2008) and postsynaptic excitatory activity reaches maximal responses at 4-weeks of age (Gu *et al*, 2012), coinciding with their period of increased excitability and plasticity. During this critical period, excitatory mossy fibers from newborn neurons are less developed than their mature counterparts (Faulkner *et al*, 2008), but extend more filopodial contacts recruiting feed-forward inhibition through CA3 interneurons (Restivo *et al*, 2015) suggesting that newborn neurons innervation to CA3 has excitatory/inhibitory effect different from that of mature granule cells.

Feed-forward inhibition into CA3 by mature granule cells was proposed to control the timing of CA3 spiking (Mori *et al*, 2004; Torborg *et al*, 2010), and has been associated with memory precision (Ruediger *et al*, 2012; Guo *et al*, 2018). Newborn neurons could be enhancing feed-forward inhibition during the initial phase of their critical plastic period, during which their activity seems to be more tuned to contextual rather than spatial features (Danielson *et al*, 2016). Thus, newborn neurons can not only influence the function of the DG, but also of the CA3 in a bidirectional way. According to the 'direct encoder' view, newborn neurons could contribute information to CA3 and, additionally, regulate the activity of this region through feed-forward inhibition. According to the 'activity modulator' view, newborn neurons would dictate patterns of activity in the DG that later influence activity in CA3.

Suppressing neurogenesis decreases reactivation upon contextual memory recall (Denny *et al*, 2014) while increasing overlap between neural representations of different contexts (Niibori *et al*, 2012) in the whole CA3. Conversely, enhancing neurogenesis increased activity in CA3 during contextual discrimination (Besnard & Sahay, 2020), whereas it improved separation of memory ensembles in CA3 during spatial navigation (Berdugo-Vega *et al*, 2021), suggesting that a role of neurogenesis in population coding beyond the DG could be task-dependent. Functionally, IP/SP newborn neurons are likely to differentially contribute to the processing of abstract versus sensory information in different segments in CA3 as well. Consistently, a recent preprint reported effects on spatial remapping in CA3c upon optogenetic stimulation of immature newborn neurons (preprint: Mugnaini *et al*, 2022).

This regulatory effect of neurogenesis in CA3 could be particularly important during aging. Aged hippocampal circuits are characterized by impairments in excitation/inhibition balance (Leal & Yassa, 2015). In particular, hyperexcitability of aged CA3 circuits has been proposed to interfere with new contextual encoding leading to memory rigidity (Wilson *et al*, 2005). Interestingly, previous experiments increasing feed-forward inhibition from mature granule cells into the CA3 showed better engram separation and improved memory precision during aging (Guo *et al*, 2018). Extending the same concept to neurogenesis, a genetic manipulation increasing newborn neurons similarly enhanced feed-forward inhibition and increased the inhibitory tone of CA3 and CA1 parvalbumin interneurons (Berdugo-Vega *et al*, 2020). Given that CA1 parvalbumin cells are not directly innervated by newborn neurons, this suggests an overall attenuation of hippocampal activity upon increased neurogenesis that has also been linked to forgetting (Evans *et al*, 2022).

Importantly, enhancing neurogenesis also had consequences in the profile of sharp-wave ripples in CA1 (Berdugo-Vega *et al*, 2020), which are important patterns of activity associated with memory consolidation (Buzsáki, 2015). This correlated with rejuvenated learning and memory in navigational and contextual discrimination tasks (Berdugo-Vega *et al*, 2020) highlighting the strong influence of neurogenesis in the downstream hippocampal network.

responsive newborn neurons during learning, which would later reactivate in response to inputs present during their maturation. While IEG analysis failed to show such preferential recruitment of newborn neurons during learning (Stone *et al*, 2011; Berdugo-Vega *et al*, 2021), *in vivo* calcium imaging and ephys seemed to support their preferential activation (Danielson *et al*, 2016; McHugh *et al*, 2022). Consistently, newborn neurons that are immature at the time of learning have been shown to be active and necessary for remote memory retrieval and reconsolidation (Lods *et al*, 2021).

Under this assumption of newborn neurons going through a hyperexcitable window, computational models proposed that while the mature granule cells help with pattern separation of events that are temporally far or contextually unrelated, newborn neurons might help with better association of temporally or contextually closer events (Becker, 2005; Aimone *et al*, 2006, 2009). These studies posited that the newborn neurons act as 'pattern integrators' of closer events, temporally or contextually, with a possible switch from encoding to retrieval functions as they mature and refine their input-specificity. These models found support from both computational (Becker *et al*, 2009; Weisz & Argibay, 2009, 2012; Finnegan & Becker, 2015) and experimental studies (Tashiro *et al*, 2007; Trouche *et al*, 2009; Rangel *et al*, 2014; Lods *et al*, 2021), including the recent hypothesis that newborn neurons might expand the index of engrams in the DG to increase the library of hippocampal experiences and facilitate their retrieval (Miller & Sahay, 2019).

Newborn neurons as activity modulators

In the more recent years, newborn neurons have been proposed to modulate the activity of mature granule cells in the DG, rather than being direct encoders of information. Based on a large body of literature (Alme *et al*, 2010; Deng *et al*, 2013; Piatti *et al*, 2013; McAvoy *et al*, 2015; Drew *et al*, 2016; Johnston *et al*, 2016), the field has started considering DG as being comprised of two distinct granule cell populations, including mature (reviewed in Lopez-Rojas & Kreutz, 2016) and immature neurons that interact with each other and with the memory system by different means (Aimone, 2016).

Several experiments directly showed that inhibiting neurogenesis predominantly increased DG activity (Burghardt *et al*, 2012; Lacefield *et al*, 2012; Ikrar *et al*, 2013; Drew *et al*, 2016), while increasing neurogenesis silenced it (Ikrar *et al*, 2013; Anacker *et al*, 2018). Enhanced feedback inhibition to the DG via hilar interneurons was the first mechanism proposed for activity regulation by newborn neurons (Ming & Song, 2011; Sahay *et al*, 2011; McAvoy *et al*, 2015; Temprana *et al*, 2015), although recent ephys evidence revealed that such regulation also occurs via monosynaptic lateral inhibition of mature granule cells (Luna *et al*, 2019). This supported a role of newborn neurons in promoting pattern separation, since a reduction in DG activity would reduce the probability of overlap between cellular representations of similar memories. This has been corroborated by two studies using different genetic strategies to increase neurogenesis, followed by the assessment of ensemble overlap by

cat-FISH (McAvoy *et al*, 2016) or engram-labelling (Berdugo-Vega *et al*, 2021).

A major hypothesis emerging from these studies is that newborn neurons may promote a global inhibition of the mature granule cells (achieved by lateral inhibition and leading to their sparse activation and rate-encoding processing), or even create a net inhibitory environment in the DG and CA3 (achieved via feedback and forward inhibition, and leading to population-encoding processing, see Box 2; Drew *et al*, 2016; Christian *et al*, 2020). In either case, though various groups have reported higher number of newborn neurons in the SP than in the IP blade (Kempermann *et al*, 2003; Jinno, 2011), and how they get differentially affected by various factors, such as learning and stress (Ambrogini *et al*, 2000; Ramirez-Amaya *et al*, 2006; Tashiro *et al*, 2007; Dranovsky *et al*, 2011; Wu *et al*, 2015), the effect of newborn neurons in regulating the activity of the two blades was assumed to be the same.

Challenging this view that newborn neurons are homogeneous in function across the DG, and further extending their role in regulating the activity of mature granule cells, recent work showed that their effect is not exclusively inhibitory, but rather depends on the origin and content of the incoming cortical information (Luna *et al*, 2019; Tuncdemir *et al*, 2019). In brief, Luna *et al* (2019) found that newborn neurons monosynaptically excite mature granule cells in response to MEC inputs, while inhibit the same in response to LEC inputs. They report that newborn neurons exposed to MEC inputs release higher concentrations of glutamate, recruiting depolarizing NMDA receptors in mature granule cells, whereas newborn neurons activated by LEC inputs result in lower glutamate levels and primarily engage inhibitory-metabotropic receptors in mature granule cells. Subsequent studies using genetic manipulations to increase neurogenesis found blade-specific changes in the number of c-Fos + cells, namely an increase in the IP after contextual discrimination (Besnard & Sahay, 2020), and an increase or decrease in the IP or SP blade respectively, after navigational learning (Berdugo-Vega *et al*, 2021), which are consistent with the previously reported differential modulation by newborn neurons (Luna *et al*, 2019). The opposite effects of newborn neurons on mature granule cells, tied with the knowledge that the IP and SP blades are more exposed to inputs from MEC and LEC respectively (discussed above), could have intriguing implications in the understanding of how abstract versus sensory information is differentially processed in the parallel MIcd and LSap hippocampal streams. Several observations are consistent with and expand this novel framework.

The two faces of the DG: can blade-specific computations by newborn neurons aid different aspects of cognition?

Even without considering adult neurogenesis, early investigations using IEG expression as a means to assess the sparse coding by DG granule cells reported functional differences between the two DG blades, such as an increase in activity specifically within the SP upon behavioral exploration (Chawla *et al*, 2005; Ramirez-Amaya *et al*, 2006, 2013; Alme *et al*, 2010). Consistently, increased reactivation of SP ensembles upon exposure to the same environment (Marrone *et al*, 2011, 2012), as well as upon repetition of the same searching strategy during navigation (Satvat *et al*, 2011), was found. This suggested a role of the SP in contextual specificity that was in turn not found in the IP. Interestingly, studies on spatial learning in rats during aging found a correlation in the number of IEG+ cells in the SP and learning performance, whereas in the IP, IEG+ cells were correlated with both learning and memory performance (Marrone *et al*, 2012), suggesting a functional separation between the DG blades.

With focus on adult neurogenesis, three recent studies suggested the possibility of the two DG blades performing different roles in the processing of information (Luna *et al*, 2019; Besnard & Sahay, 2020; Berdugo-Vega *et al*, 2021). Of these, the recent work from our group (Berdugo-Vega *et al*, 2021) studied the effects of increased neurogenesis on spatial versus reversal learning during navigation in the Morris Water Maze (MWM), finding opposite effects in the number of IEG+ active granule cells in the IP-CA3c versus SP-CA3ab circuits. During spatial learning, increased neurogenesis correlated with an increase in active granule cells predominantly in the IP-CA3c circuit, which is consistent with the predominantly excitatory effect of newborn neurons which receive more projections from the MEC. Considering that mature cells are more spatially tuned than newborn neurons (Danielson *et al*, 2016), as well as experiments showing a correlation between engram size and memory strength (Leake *et al*, 2021; Lesuis *et al*, 2021), these results suggest that a greater activity of mature granule cells in the IP upon increased neurogenesis may in turn provide greater spatial representations and precision during learning, effects that were indeed observed in our work (Berdugo-Vega *et al*, 2021). Conversely, during reversal learning, increased neurogenesis was associated with a reduction in the activity in the SP-CA3ab circuit and reduced overlap of memory representations in both regions. This supports the notion that newborn neurons help in reducing memory interference during reversal learning by recruiting non-overlapping neurons in the SP-CA3ab circuit and, thus, help improve cognitive flexibility, as was also observed (Berdugo-Vega *et al*, 2021).

Although causal experiments are needed to corroborate these conclusions, these results hint at a role of newborn neurons in supporting different aspects of cognitive processes in the partially segregated compartments of DG and CA3, namely memory precision in the IP–CA3c and separation in the SP–CA3ab. In turn, this fits well with several studies suggesting a role of the SP blade in behavior-dependent processing (Chawla *et al*, 2005), CA3c in spatial discrimination (Hunsaker *et al*, 2008) and CA3ab in contextual recall (Sun *et al*, 2017). On the other hand, potential participation of a hippocampal sub-region in a pattern integration-like role comes from the results of a variation of the MWM task, where rats exhibited one-trial learning (Steele & Morris, 1999). These results were explained through a model (Foster *et al*, 2000), wherein it was suggested that after the initial learning, the animal would have to build a thorough goal-independent allocentric representation of the environment to be able to demonstrate such one-trial spatial memory. We hypothesize that to build such a representation in the hippocampus, the newborn neurons in the DG might be performing a computation to precisely integrate the elements of the allocentric space, alongside pattern separation that reduces previous days' memory interference. Altogether, this hypothesis highlights the possibility of functional heterogeneity in the DG underscoring the importance of adult neurogenesis in differentially driving hippocampal computations.

Continuing the analogy from above (Sugar & Moser, 2019) about EC playing an episodic movie while hippocampus edits it, the

parallel MIcd and Lsap streams might respectively play the abstract and sensory components of the movie, which are additionally differentially edited in the hippocampus. For instance, in an actual movie clip, an actor performing a stunt in front of a green screen and a separately filmed outdoor location would have to be superimposed for a complete scene. During editing, it might be more feasible to remove frames from the video stream of actor's performance while adding more relevant frames to the outdoor filming i.e., the two streams might have to be processed not only separately but also by different means, to produce a satisfactory end-product.

Discussion

Here, we reviewed evidence from anatomical, ephys, behavioral, and computational studies, supporting the existence of two parallel hippocampal streams for transmission and processing of information, the MIcd and LSap, in which newborn neurons play a pivotal role. In this hypothesis, two effects synergize together to modulate different aspects of hippocampal function. First, a different source and type of information is segregated in the hippocampal circuit owing to the abstract and sensory nature of information projected to and from the MEC and LEC, and propagated via the MIcd and LSap streams (Fig 2B; denoted in light blue and dark blue), respectively. Second, the type of processing that this information is subjected to would also differ, owing to the opposite effects that the newborn neurons mostly exert on mature granule cells in the IP and SP, i.e., excitatory and inhibitory (Fig 2B; denoted with + and -), respectively. The most intriguing question arising from these observations is whether blade-specific computational processes, mediated by newborn neurons, might underlie different aspects of hippocampal learning and memory.

As described above, a large body of work assumed DG to be functionally homogenous, highlighting its role in pattern separation due to its sparse activity. This role is consistent with and supported by the inhibitory effect of newborn neurons predominantly in the SP blade (Sahay *et al*, 2011; Luna *et al*, 2019; Berdugo-Vega *et al*, 2021). However, the opposite excitatory effect of newborn neurons seems incompatible with a role in pattern separation. Could the DG also perform computations other than pattern separation?

Similar line of questioning has been brought up in the past, but never with regard to the two DG blades participating in different computations. For instance, previous works have suggested that the mature neurons in the DG facilitate pattern completion while newborn neurons perform pattern separation (Nakashiba *et al*, 2012) or, alternatively, act as 'pattern integrators' (Aimone *et al*, 2006, 2009). Another mnemonic function that has been attributed to the DG is the binding (or linking) of sensory elements, such as visual cues, to abstract map-like representations (Lee & Jung, 2017; Hainmueller & Bartos, 2020). Considering that sustained neuronal excitability was identified as a possible mechanism critical for memory linking (Cai *et al*, 2016; Shen *et al*, 2022), it is conceivable that increased excitability predominantly in the IP blade due to adult neurogenesis might lead to improved 'pattern integration' during memory encoding i.e., linking of memories close in time (Fig 2B). In parallel, newborn neurons triggering mostly inhibition within the SP blade would promote pattern separation therein. More studies are needed to validate this conceptual framework of different computational processes occurring within different DG blades (Box 3), and to assess if this can be exploited to improve or rescue cognitive function during aging, injury or disease.

Box 3. Future directions.

To dissect and understand the functional differences between the two blades of the DG, below we highlight various approaches that should be considered in future studies:

- **Cellular analyses** – Immunostaining for IEG markers, such as cFos and Arc, can provide information about differential neuronal activation in the two blades under different behavioral paradigms and memory processes. Combining these approaches with specific markers for mature and newborn neurons will enable us to understand the role of these cell populations under different conditions.
- **Electrophysiology** – Due to differences in the levels of excitation and inhibition, electrical characteristics of the two DG blades are likely to differ at the cellular and regional level. These can be assessed *ex-vivo*, such as by using multi-electrode arrays, or *in-vivo*, such as by using calcium-imaging, silicon probes, or tetrodes, coupled with optogenetics for simultaneous identification of newborn neurons. These characteristics should be assessed separately for the two blades of the DG.
- **Behavior** – Separate assessment of different task modalities, such as learning versus re-learning, or context versus sequence learning, should be considered, as they might involve different memory processes. Similar considerations should be applied while interpreting behavioral performance (e.g., latency in MWM), independently from the underlying behavioral processes (e.g., the navigational strategy adopted). Differentiating between such seemingly equivalent aspects, may reveal an involvement of the two blades of DG in subtly different mnemonic functions.
- **Modeling** – Computational models of DG and hippocampal function are needed that incorporate not only the differential modulatory effect of newborn neurons on the mature granule cells (excitatory versus inhibitory), but also include the effect of 4–6 weeks of transitory hyperexcitability period.

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Author contributions

Gabriel Berdugo-Vega: Conceptualization; writing – original draft; writing – review and editing. **Shonali Dhingra:** Conceptualization; writing – original draft; writing – review and editing. **Federico Calegari:** Conceptualization; supervision; writing – original draft; writing – review and editing.

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The authors declare that they have no conflict of interest.

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