WIREs COGNITIVE SCIENCE

Article type: Advanced Review

Article title: Adult hippocampal neurogenesis and its role in cognition

Full name and affiliation; email address if corresponding author; any conflicts of interest

First author: Full name and affiliation; plus email address if corresponding author Charlotte A. Oomen*, Department of Psychology, University of Cambridge, Cambridge, UK **&** MRC and Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK, charlotte.oomen@gmail.com
Second author: Full name and affiliation; plus email address if corresponding author Pedro Bekinschtein, Instituto de Biología Celular y Neurociencias, Facultad de Medicina, UBA-CONICET, Paraguay 2155 3er piso, Buenos Aires (C1121ABG), Argentina
Third author: Full name and affiliation; plus email address if corresponding author Brianne A. Kent, Department of Psychology, University of Cambridge, Cambridge, UK **&** MRC and Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
Fourth author: Full name and affiliation; plus email address if corresponding author Lisa M. Saksida, Department of Psychology, University of Cambridge, Cambridge, UK **&** MRC and Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
Third author: Full name and affiliation; plus email address if corresponding author Timothy J. Bussey, Department of Psychology, University of Cambridge, Cambridge, UK **&** MRC and Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK

Abstract

Adult hippocampal neurogenesis (AHN) has intrigued neuroscientists for decades. Several lines of evidence show that adult-born neurons in the hippocampus are functionally integrated and contribute to cognitive function, in particular learning and memory processes. Biological properties of immature hippocampal neurons indicate that these cells are more easily excitable compared to mature neurons, and demonstrate enhanced structural plasticity. The structure in which adult-born hippocampal neurons are situated -the dentate gyrus- is thought to contribute to hippocampus function by disambiguating similar input patterns, a process referred to as pattern separation. Several ideas about AHN function have been put forward; currently there is good evidence in favour of a role for AHN in pattern separation. This function of AHN may be understood within a 'representational-hierarchical' view of brain organisation.

The discovery of neurogenesis in the brain of adult mammals[1-3], including humans[4], received considerable attention as it challenged the prevailing dogma that the brain is 'post-mitotic' and as such is endowed with limited regenerative capacity. In the mammalian brain, adult neurogenesis is restricted to two regions: 1. the DG, at the border of the granule cell layer and hilus (the subgranular zone) where adult neurogenesis gives rise to the primary granule cells (GCs), and 2. the subventricular zone of the lateral ventricles; cells born here subsequently migrate to the olfactory bulb[5-7]. Given the well-established role of the hippocampus in learning and memory[8], it was soon suggested that AHN may contribute to these functions in some way. This idea was supported by the finding that memory demand correlated with AHN in birds[9] and that in rats AHN could be stimulated by learning a spatial task[10]. In this manuscript, we will review some of the biological properties of adult-born hippocampal neurons and provide an overview of the structure in which adult-born hippocampal neurons are situated, the dentate gyrus. This is followed by an overview of studies that have addressed a putative role of AHN in learning and memory function and a discussion of the ideas on how adult-born hippocampal neurons may contribute to hippocampus function.

Properties of adult-born neurons

Before proceeding to a discussion on the exact role of AHN it is important to understand the biological properties of these neurons and especially how these properties are distinct from developmentally-born GCs. Adult-born neurons are targeted by axons originating in the entorhinal cortex (EC)[11]; recently it has also been shown that these cells initially receive most input from intra-hippocampal cells and are later innervated mostly by perirhinal- and lateral entorhinal cortex (LEC) neurons[12]. Adult-born neurons grow axons onto target cells in CA3[13, 14] and functionally, these cells integrate into the DG network[15]. By 4 weeks after birth new GCs evoke stable action potentials in CA3 neurons[16]. At the level of neurotransmission, adult-born neurons follow a similar maturation pattern as neurons born during development[17]. Newborn cells are initially electrically silent, and then γ-Aminobutyric acid (GABA) innervation switches from a depolarizing to a hyperpolarizing state, in ways analogous to developmental neurogenesis[18-20]. GABA, the major inhibitory neurotransmitter in the adult brain, plays an important role in the maturation of adult-born neurons[21, 22]. Several other factors are involved in maturation and integration of adult-born neurons, such as Disrupted in Schizophrenia-1 (DISC-1), which acts in concert with GABA[23]; N-methyl-D-aspartate (NMDA) receptor activation[24, 25] and hilar mossy cell activation[26], amongst others. AHN is under strong regulatory control of the internal and external environment, thus endowing this part of the brain with a high level of structural plasticity capacity. AHN was found to correlate positively with exercise[27], enviromental enrichment[28] and roaming behaviour[29] and was shown to be changed after exposure to (stress) hormone levels [30-34]; early life experience[35, 36]; antidepressants[37, 38] and various other factors. Many of these also affect hippocampus function and in several of these studies, a positive correlation between the level of AHN and memory performance has been found.

A unique property of immature neurons is a lower threshold for firing action potentials compared to the surrounding mature GCs. In addition, long-term potentiation (LTP) is more easily induced in these neurons[17, 39-41]. Importantly, 7-8 weeks after cell birth, adult-born neurons are physiologically indistinguishable from mature neurons in the network [15, 19, 20, 42] and based on this property it may be suggested that their unique contribution occurs in the earlier stages of maturation[16]. This increased

excitability has been at the core of theories and computational models of AHN, as will be discussed later.

In addition to the increased excitability and synaptic plasticity, recent evidence also shows that adult-born neurons are unique at the level of structural plasticity. It was found that exposure to a learning experience can alter the shape of the dendritic tree of adult-born neurons in a persistent manner; a phenomenon absent in mature cells[43]. AHN thus endows a subset of neurons with a unique experience-dependent 'structural plasticity capacity'. This capacity to change shape in response to learning was found to be retained by adult-born neurons up to 4 months after cell birth[44]. Whether or not this property contributes to a unique function of adult-born neurons within the DG remains to be shown, but in support of this, AHN ablation during a restricted 2 week time-window impaired water maze acquisition 2 and 4 months later[44]. In addition, it was shown that 5 month old adult-born neurons are preferentially activated in response to exploration[45]. These findings suggest that adult-born neurons retain certain unique characteristics for a relatively long period (and beyond the 7-8 weeks as defined by their physiological properties), favouring their involvement in funtional networks.

Properties of the dentate gyrus

As AHN occurs within the DG, a good place to start a discussion about its function is to start with discussion of the anatomy, properties and putative functions of the DG.

Anatomy

The DG is the first input region of the hippocampus from the parahippocampal region via the perforant path, which originates mainly in layer II of the LEC and medial entorhinal cortex (MEC), (for an extensive connectivity diagram, see[46]). Perforant path fibers project to the DG, which then relays information to CA3. Information from the EC is dispersed onto a relatively large number of GCs and then subsequently converges onto a lower number of neurons in its output region, the CA3. The large number of DG neurons and subsequent convergence onto CA3 may allow subtle differences in the original EC input to be amplified during encoding. From CA3, Schaffer collaterals connect to the CA1 after which information exits the hippocampus, to the EC. In addition to this classical "trisynaptic circuitry" involving DG, EC neurons also project directly onto CA3 pyramidal cells[47]. Thus, the DG can be bypassed and may function as a side-loop[48] in which information from the EC to the CA3 is duplicated. Furthermore, the DG also receives input from the CA3, through back-projections onto hilar mossy cells and interneurons[49].

Network activity

The DG has a unique pattern of activity, such that it is relatively silent while the animal is awake or during exploration[50], but shows increased activity during rest/sleep[50-52]. GCs have a strongly hyperpolarized resting membrane potential[53] and are under a high level of inhibitory control of hilar interneurons through feedforward (from EC neurons) and feedback (from GCs) inhibition[54-56]. Immediate-early gene expression studies have confirmed this so-called sparse coding of the DG and show that only 1-5% of all GCs are active at a given time during behavioural activity, compared to about 40% of CA neurons[45, 57]. Even though only a few GCs are active at any given time, powerful output of these cells via large so-called detonator synapses onto CA3 apical dendrites facilitates

further processing of this sparse code. For example, a single mossy fiber was shown to elicit an action potential in a downstream CA3 neuron[58].

Firing properties of DG GCs differ from cells in the CA regions. Cells in the CA regions can have a single 'place field' that becomes active whilst exploring a particular location in an environment[59]. A change of environment induces rearrangement of place cell activity, which is referred to as remapping. Remapping either occurs as an overall change of place cell activity (i.e. global remapping), in which individual place cell activity is uncorrelated to a different previous environment, or it occurs upon minor contextual changes in the environment, expressed as changes in firing rates of individual cells (i.e. rate remapping)[60]. In the DG, rate remapping is thought to occur upon the convergence of spatial (grid cell) information from MEC input[61] with sensory information from the LEC[62-64], allowing for location-coupled sensory representations[65-67]. Like CA cells, most GCs have place fields[50]. It should be noted however, that the GC population may be heterogeneous in terms of spatial firing properties and GCs with both single and multiple place fields have been reported[52]. This latter study emphasized the importance of relating spatial firing properties to specific DG cell types (i.e. mature- or immature GCs, or potentially mossy cells in the hilus), a methodological issue that has not yet been resolved. As a consequence, it is not known whether all cells types within the DG (including hilus) tend to fire with the same level of sparsity (or lack thereof). Whether adult-born neurons facilitate sparse firing or whether these neurons actually comprise the majority of active cells (and thus themselves fire in a less sparse manner), remains to be determined[68].

Behaviour

For several tasks that are considered hippocampus-dependent, an intact DG is required (for reviews, see[48, 69, 70]). DG function has often been studied using lesions induced by colchicine (an alkaloid that produces selective damage to DG GCs and mossy fibres while leaving other hippocampal subfields reasonably intact) or diethyldithiocarbamate (DDC), which inactivates mossy fiber transmission. Using these methods, the DG was shown to be necessary for spatial working memory and reference memory[71-74], in addition to associative memory as tested using contextual fear conditioning paradigms[75, 76]. Performance on delayed-(non)-matching-to-sample paradigms may be less dependent on the DG as deficits were found to be transient and reverted by post-lesion training[77, 78].

Pattern separation

More specifically, it has been suggested that the DG is required for pattern separation[79], which refers to the computational process by which a neural circuit decorrelates similar input into a more orthogonal output signal. As discussed in the computational literature[80, 81 82], pattern separation is thought to be necessary for the formation of unique, non- (or less-) overlapping representations and thus successful memory storage. In particular, the DG is thought to pre-process information, which facilitates pattern completion (retrieval of a complete memory from a partial cue) in the downstream CA3 attractor circuitry. This putative role in pattern separation is consistent with sparse coding in the DG and the fact that information from the EC is dispersed onto a relatively large number of GCs and then subsequently converges onto a lower number of neurons in its output region, the CA3.

Some of the most direct evidence for a role for the DG in pattern separation comes from electrophysiological experiments. Neural coding in the DG was investigated in an open field, the shape of which was gradually morphed from circular to square, thus requiring discrimination of a change in context[83]. Small contextual alterations induced substantial changes in the location- and firing rate of place fields in GCs, whereas activity of CA3 cells changes only gradually, at the level of firing rate. Discrimination of dissimilar events in the same study, as measured by placing animals in a different room, recruited different cell populations of CA3, although the same set of neurons in the DG were active (but see[84]). Global remapping may be accomplished independently of the DG through the direct connections of grid cells of EC to CA3[83]. Whether rate remapping is a candidate by which the EC-DG-CA3 network accomplishes pattern separation of spatial information remains to be determined. More recently, Neunuebel & Knierim (2014)[85] recorded single-unit activity simultaneously from CA3 and DG and provided direct quantitative evidence of a pattern completion-like process in the CA3. In this study it was shown that the CA3 produced an output pattern closer to the originally stored representation, whereas the DG activity showed degraded input patterns as would be expected to occur during pattern separation.

To specifically assess pattern separation ability at the level of behaviour, several tests have been developed. These tasks reasonably assume that the representations formed after effective pattern separation will be useful in tasks with a high demand on resolving the confusability of inputs, for example in tasks requiring discrimination of contexts, locations and episodes. Such discrimination had already been shown to depend on the hippocampus, using tasks requiring discrimination between chambers[86, 87], neighbouring food wells in a delayed matching task[88], and more recently, neighbouring locations on a touchscreen[89, 90]. To our knowledge the first study explicitly testing the involvement of the DG in pattern separation behaviourally was that of Gilbert and colleagues (2001)[79], who used a delayed-matching-to-sample paradigm in a circular arena with baited food wells. In this study location discrimination performance was assessed using pairs of similar locations (i.e. locations near to each other) and less similar locations (i.e. locations farther apart from one another). Animals with selective DG lesions were impaired at discriminating similar but not dissimilar locations, while those with CA1 lesions were not. Lee and Solivan (2010)[91] took a somewhat similar approach using a radial arm maze. Rats were required to discriminate object-place pairs. DG lesions resulted in severe and sustained impairments in disambiguating objects. The authors concluded that the DG is necessary for discriminating highly overlapping object and/or spatial information, but is less important when there was minimal overlap in either object or spatial information. McHugh and colleagues (2007)[92] showed that knockout mice that lacked the gene encoding the essential subunit of the N-methyl-D-aspartate (NMDA) receptor NR1 in dentate gyrus GCs specifically were impaired in contextual fear conditioning requiring the discrimination of similar contexts. In parallel, NR1 knockout led to impaired population coding in the CA3-CA1 fields showing DG requirement for successful downstream processing. The authors suggested that this similarity-dependent effect provides evidence that GCs in the DG play a critical role in pattern separation. Recently it was shown that BDNF in the DG is necessary for the consolidation, but not retrieval of similar (and not dissimilar) locations in a spontaneous location recognition task[93]. In this study, BDNF was found to be expressed on an 'as needed' basis, only in response to exposure to spatial locations with high similarity. These data indicated that pattern separation function may be particularly important during the encoding/consolidation phase. Finally, a pattern separation function in the DG-CA3 region has been reported in human subjects. Using functional imaging, subjects were scanned during

incidental encoding of objects that were either presented repeatedly or alternating with lure objects (i.e. a similar condition). The authors conclude that activity in the DG-CA3 region is associated with pattern separation, whereas CA1 activity is associated with pattern completion[94].

Adult neurogenesis in learning and memory

Overview

The first studies to report a direct relationship between AHN and learning and memory processes inhibited cell proliferation by administration of methylazoxymethanol acetate (MAM). These studies found impairments in trace eyeblink conditioning and trace fear conditioning[95], but not water maze acquisition and retention, and contextual fear conditioning[96]. From these findings it was concluded that AHN may be particularly involved in more challenging memory tests such as those in which the to-be-remembered associations are temporally separated by a short interval (i.e. trace conditioning). Other studies using toxins replicated some of these findings: trace eyeblink conditioning was impaired after temozolomide (TMZ) treatment[97] and, consistent with earlier findings, MAM treatment did not affect contextual fear conditioning or water maze acquisition[98, 99]. Contrary to Shors et al. (2002) however, others have found that retention of platform location in the water maze was impaired by MAM ablation[98], and that AHN may control the use of spatial strategies (using TMZ[100]). Recently, TMZ ablation was shown to affect water maze acquisition in juvenile but not in older animals[101].

Other, arguably better methods of AHN ablation have been developed, as some neurotoxins were shown to cause unwanted side-effects, especially when applied systemically[102]. Alternative methods include (focal, forebrain specific) X-ray irradiation and genetic tools. Despite this progress, studies using these methods have also yielded inconsistent findings on classical tests of learning and memory. To summarize, effects of AHN ablation on acquisition of spatial navigation tests resulted in impairments in some[103-108], but not all[105, 109-113]experiments. Of note, in some studies AHN ablation particularly impaired *retention* of spatial locations[103, 106, 108, 110, 114-116], but others found no such effect[105, 109, 111]. A retention deficit in spatial memory was recently confirmed in a study using optogenetic tools, in which the importance of the age of adult-born neurons was also highlighted[16]. The authors reported involvement of 4 week-old neurons (but not 2 or 8 week-old neurons) in retention, but not acquisition, of the water maze. Studies on contextual fear conditioning and object (or object location) memory show mixed results; both impaired[16, 106, 107, 111, 117-119] and unaffected[103, 108, 115, 120] memory performance has been found, for reviews see[121-123].

Other evidence for a role for AHN in learning and memory was found in imaging studies, where results indicate a preferential recruitment of adult-born neurons in spatial exploration[45] and learning and memory[124]. In addition, genetic AHN ablation results in compromised LTP and long-term depression (LTD) in DG-slices[125], and genetically-induced *higher* levels of AHN result in enhanced levels of LTP[126]. In vivo, AHN ablation through X-ray irradiation did not reduce the level of LTP (one day after induction) and was shown to *enhance* retention of LTP in the DG for up to 2 weeks[127]. Others found that in vivo, reduced AHN through irradiation lowered responsiveness of perforant path stimulation and increased spontaneous gamma-oscillations[128]. In sum, the presence of adult-born neurons can affect electrophysiological properties of the DG and thus potentially memory

processing, although the functional consequences of increased excitability of these neurons are not always straightforward.

Together, these data suggest that the specific involvement of AHN in classical learning and memory tests may depend on a number of factors such as the relative age of neurons, the phase of memory addressed and the type of test used. Also, it has been suggested that sex[33]- and species-specific differences exist. For example, some researchers have suggested that AHN levels and the involvement of adult born neurons in memory performance may be less in mice compared to rats[129]. Several ideas have been developed and tested regarding a more specific role of AHN in learning and memory, which may explain some of the inconsistencies that have been reported; some of these ideas are outlined below along with any empirical evidence that has been gathered in support.

A potential role in clearance or forgetting

Some of the earlier computational modelling studies emphasized that adding new neurons to a network leaves existing circuitries intact, thus avoiding 'catastrophic interference' of already formed memories[130, 131]. Others have suggested the opposite: the addition and integration of new neurons can lead to structural remodelling of existing networks and information storage may be affected by AHN *after the learned event* leading to forgetting[132]. Such a mechanism has also been proposed to underlie infantile amnesia[133]. The idea that AHN may stimulate forgetting is reminiscent of some earlier models in which neuronal turnover accelerated the removal of memories from the network[134]. Removal of information from such networks was indeed shown to occur as a result of cell turnover, and this removal was in some models paralleled by increased quality of more recent memories[135]. This has been referred to as the "memory clearance hypothesis".

Some evidence that AHN may remove existing memories and thus promote forgetting was provided using presenilin-1 knock-out (PS1 KO) mice that lack environmental enrichment-induced increased AHN[136]. In a learning-enrichment-retrieval paradigm, PS1 KO mice, in the absence of AHN, showed *enhanced* contextual memory during retrieval. The authors thus concluded that AHN results in memory clearance from the hippocampus. However, another study using a similar design found no evidence for a role of AHN in memory clearance[137]. Here the authors used wheel running to upregulate AHN between learning and the subsequent retrieval phase of a spatial Y-maze task, and found that this led to *improved* retention. This has been contradicted by a recent, extensive study by Akers et al (2014)[138]. They showed, using several animal models, that levels of AHN correlate with forgetting of previously learned information. Of interest compared to the previous study, a causal approach was taken, using AHN ablation models in a learning-exercise-retrieval similar to Van der Borght et al (2007). Akers and collegues found that, using genetically-induced AHN knockdown in mice, an increase in AHN between encoding and retrieval facilitates forgetting of the previously learned information.

Kitamura and co-workers[127] took a somewhat different approach. They tested whether AHN is required to clear memory traces from the hippocampal circuits in the context of the systems consolidation hypothesis, which suggests that the hippocampus temporarily stores memories that are later transferred to cortical regions for permanent storage[139]. To address whether AHN is involved in such transfer, they used two methods of AHN ablation (irradiation and a transgenic mouse model that overexpresses follistatin) with transient hippocampal inactivation. Firstly, AHN ablation did not affect memory, as tested by contextual fear conditioning. In addition, hippocampal

inactivation 1 day after contextual fear conditioning training impaired retrieval in both animals with ablated AHN and controls. Interestingly, hippocampal inactivation 28 days after training also impaired retrieval in animals with ablated AHN, but did not impair retrieval in controls. Thus, the authors concluded that blockade of AHN extends the period of hippocampal dependency for contextual fear memories. Further potential support for the idea that AHN contributes to memory through forgetting and/or clearance was provided by the finding that the removal of adult-born neurons changes memory formation[140]. Overall, these ideas deserve more attention in future studies.

A potential role in pattern separation

Consistent with the idea that the DG is important for pattern separation (see above), Becker (2005) developed a computational model in which a specific role for AHN in recall of highly similar representations was assessed, by simulating the effect of neuronal turnover on recall performance of unrelated items, unrelated paired associates or related, highly confusable, items[141]. Neuronal turnover positively affected recall performance only in the case of related items, suggesting a role for AHN in pattern separation specifically. Empirically, Clelland et al (2009)[142] compared two different techniques for ablating immature neurons, X-ray irradiation and lentiviral expression of dominant-negative version of the Wnt protein, accomplished through intra-DG injection. Both methods produced impairments discriminating similar, but not dissimilar locations in two very different behavioural tasks, a spatial memory task in a radial arm maze and a touchscreen-based automated spatial discrimination task in an operant chamber. Confirmatory evidence has since been provided using several different behavioural methods. For example, AHN-knockdown disrupted memory for similar contexts in a fear conditioning paradigm[143, 144].

Further support for a functional role of AHN in pattern separation came from experiments in which AHN was increased. For example, Sahay et al. (2011)[126] used a genetic manipulation to artificially increase AHN. This resulted in improved context discrimination in a fear conditioning paradigm in which animals were trained to discriminate between two similar contexts across repeated sessions. (It should be noted that this fear conditioning paradigm has not always included a critical 'dissimilar' control condition to vary the load on pattern separation so non-specific effects cannot be definitively excluded; however see references[145, 146]. Creer and colleagues (2010)[147] demonstrated that wheel running in mice increased AHN and pattern separation in a touchscreen-based behavioural task and that this treatment was ineffective in aged animals that lacked running-dependent increase in AHN, providing some evidence that it was the increase in AHN and not other, exercise-induced effects, that were responsible for the improvements.

Impaired pattern separation after AHN ablation has been shown to accompany changes in activation of CA3 neurons. Niibori and colleagues (2012)[146] showed that ablation of adult-born neurons impairs contextual discrimination of similar- but not dissimilar contexts. In addition, they addressed changes in downstream network activity by analysing Arc expression through cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) in the CA3. AHN ablation was shown to result in an increased overlap of neural activity in CA3 during exposure to similar contexts (i.e. the same neurons were activated upon exposure to both contexts), indicating population coding in response to similar, but distinct contexts. From this, it was concluded that pattern separation had been impaired by AHN ablation in the DG.

In summary, although ablation of AHN has yielded inconsistent results on standard, general spatial memory tasks, when pattern separation is explicitly manipulated, impairments have been obtained in several laboratories using a variety of methods in both mice and rats. We suggest that a plausible explanation for the differences found with standard spatial memory tests may come from uncontrolled variation in the load on pattern separation across these studies[148].

How do adult-born neurons contribute to pattern separation?

How adult-born neurons may contribute to DG function and pattern separation is not fully understood. As described earlier, adult-born neurons have unique physiological properties such as a relatively low firing threshold, which has been at the core of most ideas on the contribution of AHN to function. Based on this property, some have suggested that immature neurons are the principal coding units in the DG network, encoding information during the initial hyper-plastic period, but becoming less active as they mature, an idea formalised in the 'early retirement' hypothesis[149]. How this process facilitates pattern separation specifically remains unclear. Opposing this view, it has now been shown that neurons may be involved in function up to 4 or 5 months after birth beyond their hyper-plastic period[44, 45] and that mature GCs are, in fact, activated in response to perforant path stimulation[150]. An alternative hypothesis was proposed by Aimone et al. (2006; 2009),[151, 152] who suggested that because of their unique electrophysiological properties, immature neurons are less discriminating than mature GCs and therefore are more likely than mature GCs to be integrated into the representation of an event. In other words, newborn neurons may act as 'pattern integrators'. The effect of this is that events occurring at the same time will activate the same immature GC population, whereas events occurring days/weeks later will activate different sets of immature GCs. Thus, over time, the activation of these different immature GC populations would actually increase pattern separation over time by providing a temporal context for events[151]. To our knowledge, this idea has not yet been tested empirically, although recent electrophysiological data indicate that immature neurons may act as pattern integrators as they have a low activation threshold due to an enhanced excitation/inhibition balance compared with mature GCs[150]. However, the finding that sufficient levels of AHN are required for the consolidation of similar, but not dissimilar spatial memories encoded during a single behavioural episode, within the same temporal context[153], suggests that these cells contribute to DG function in an immediate fashion.

In order to better understand how adult-born neurons contribute to DG function and potentially pattern separation, a few things should be considered. An important question is whether immature neurons contribute in a *unique* way to DG signalling (instead of merely adding numbers without performing a specific function)? In order to claim a specific role for adult-born neurons, AHN knock-down should be compared to the removal of a similar number of mature GCs. If inactivation of adult GCs does not impair pattern separation, a unique contribution to function may be assumed. A recent publication has offered some evidence in favour of this, as inhibiting neurotransmission of the majority of *adult* GCs resulted in either enhanced or unchanged performance on tasks for pattern separation[144]. How a potential unique contribution is achieved in mechanistic terms remains the subject of speculation. Either the unique electrophysiological properties, or the (as of yet less explored) enhanced capacity for structural plasticity[44] may allow immature GCs to dictate DG network activity. Adult-born cells may do so as principal coding units or alternatively, by recruiting mechanisms that facilitate DG network activity[128] such as the activation of inhibitory circuits[154, 155]. Finally, a role for other plasticity related factors should be taken into account, such as brain-derived

neurotrophic factor (BDNF)[148]. BDNF in itself was shown to be required for the succesful consolidation of similar spatial memories, suggesting a role in pattern separation[93]. Of interest, it was recently shown that BDNF interacts with adult born neurons in the formation of such memories[153].

Pattern separation within a wider framework

Although we have focused on the role of DG neurogenesis for pattern separation, we suggest that pattern separation is not unique to the DG. The ability of neural networks to 'pattern separate', the process of producing outputs that are less correlated than their inputs, may be a ubiquitous property fundamental to neural networks in general. Indeed, for some time we have argued that unique conjunctive representations that reduce interference exist throughout ventral visual stream, continuing into the temporal lobe[156-160]. Each step, as information is processed through the stream, results in the formation of increasingly complex representations. The hippocampus is regarded as a late stage in this processing hierarchy, mediating high-level relational/spatiotemporal representations[161]. As a consequence, each brain region within this object-processing hierarchy may perform pattern separation for the level of stimulus complexity that it represents.

Within this framework, impairments in memory have been explained in terms of interference[161]. The model successfully predicts that manipulations that affect (e.g., impair) encoding, when carried out during a retention interval, can affect subsequent memory performance in the opposite direction (e.g., leading to improved memory performance)[162-164]. Viewed from this perspective, the previously described reports of AHN 'clearing' memories, or inducing 'forgetting'[132],may be more parsimoniously explained in terms of enhanced encoding of similar, interfering information during the retention interval, an explanation consistent with the proposed role for AHN in encoding/consolidation and pattern separation.

Although we have focussed in our work on the ventral visual-perirhinal-hippocampal stream, the "representational-hierarchical" principle of organisation almost certainly applies to many other systems, for example the dorsal visual stream, and cortical auditory processing stream, both of which are thought to be organized in a hierarchical manner[165-167] and so, by extension, would operate in the same way, with higher-level representations resolving ambiguity/interference from lower-level ones. Thus, rather than being restricted to the DG, a strong claim would be that pattern separation is a wide-spread, possibly ubiquitous principle of brain function[160].

Others have suggested, however, that the DG is a "domain general" pattern-separator -- while also acknowledging that pattern separation happens in many brain regions and for many cognitive processes, including perirhinal cortex-dependent object recognition, and also visual perception[168, 169]. It is known that the hippocampus processes sensory and non-spatial information through LEC input[64, 66, 170, 171] as part of a multi-level contextual representation. However the idea that inputs are, e.g., separated in perirhinal cortex into new representations of objects, and then separated *again* in the DG into new representations of objects, seems logically problematic. Perhaps the separation process in the DG and other regions is somehow qualitatively different, but this needs to be explained. Indeed, there is also clear causal (lesion) evidence against the idea that DG has the same pattern-separating function as other regions. For example, tasks designed to test the use of "pattern-separated" conjunctive object representations are reliably impaired by perirhinal cortex lesions, but are completely unaffected, or even facilitated, by hippocampus lesions (e.g,[172, 173]).

Therefore, whether there is a necessary role for immature neurons in the DG outside of spatial/contextual pattern separation (i.e. universal pattern separation) remains an open question.

Conclusion

Given the empirical results described above, there is considerable evidence that adult-born neurons in the DG can contribute to cognitive function. Several studies and methods have now shown that the human DG produces new neurons during adult life[4, 174]. The functional and clinical potential for cognitive function in humans is evident and many have suggested AHN as a potential biomarker, cause or treatment target in brain-related diseases[175-178]. Some evidence for changes in the level of AHN has been found in disorders such as schizophrenia[179] but remains a topic of debate in others (e.g., Alzheimers' disease[180-182] and depression[183-185]). Although preliminary evidence exists that AHN may correlate positively with memory performance in humans, as measured by the proliferation and differentiation of adult hippocampal stem cells[186], it remains to be determined to which extent AHN is relevant for human cognitive function.

As for the specific contribution of AHN to memory processing, recent evidence from animal models for a role for these neurons in pattern separation is strong and this may offer an explanation for the variation found in earlier studies. If the representational-hierarchical view discussed above is correct, unique conjunctive representations in the DG would be expected to contribute to tasks in the spatial/contextual domain in the same way that perirhinal cortex contributes to tasks in the object domain, for example by reducing interference[187], facilitating complex perceptual discriminations[188], and mediating configural learning[157]. Indeed, the reduction of interference by adult-born neurons has already been suggested[189]. However, complete understanding of the role of AHN in cognition will require a synthesis of this view with other findings including the role of AHN in memory clearance, transfer and forgetting.

Acknowledgements

The authors would like to acknowledge financial contribution from the following funding sources: the Innovative Medicine Initiative Joint Undertaking under grant agreement no. 115008, of which resources are composed of a European Federation of Pharmaceutical Industries and Associations in-kind contribution and financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013); The Wellcome Trust/Medical Research Council (089703/Z/09/Z) and the Biotechnology and Biological Sciences Research Council (grant BB/G019002/1).

References

1. Altman, J. Are new neurons formed in the brains of adult mammals? *Science* **135**, 1127-1128 (1962).
2. Altman, J. Autoradiographic investigation of cell proliferation in the brains of rats and cats. *Anat Rec* **145**, 573-591 (1963).
3. Cameron, H.A., Woolley, C.S., McEwen, B.S. & Gould, E. Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. *Neuroscience* **56**, 337-344 (1993).
4. Eriksson, P.S. et al. Neurogenesis in the adult human hippocampus. *Nat Med* **4**, 1313-1317 (1998).

5. Altman, J. Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. *J Comp Neurol* **137**, 433-457 (1969).
6. Kaplan, M.S. & Hinds, J.W. Neurogenesis in the adult rat: electron microscopic analysis of light radioautographs. *Science* **197**, 1092-1094 (1977).
7. Kempermann, G. Adult neurogenesis, Stem Cells and Neuronal Development in the Adult Brain. (Oxford University Press, New York; 2005).
8. Scoville, W.B. & Milner, B. Loss of recent memory after bilateral hippocampal lesions. 1957. *J Neuropsychiatry Clin Neurosci* **12**, 103-113 (2000).
9. Barnea, A. & Nottebohm, F. Seasonal recruitment of hippocampal neurons in adult free-ranging black-capped chickadees. *Proc Natl Acad Sci U S A* **91**, 11217-11221 (1994).
10. Gould, E., Beylin, A., Tanapat, P., Reeves, A. & Shors, T.J. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci* **2**, 260-265 (1999).
11. Toni, N. et al. Synapse formation on neurons born in the adult hippocampus. *Nat Neurosci* **10**, 727-734 (2007).
12. Vivar, C. et al. Monosynaptic inputs to new neurons in the dentate gyrus. *Nature communications* **3**, 1107 (2012).
13. Toni, N. et al. Neurons born in the adult dentate gyrus form functional synapses with target cells. *Nat Neurosci* **11**, 901-907 (2008).
14. Sun, G.J. et al. Seamless reconstruction of intact adult-born neurons by serial end-block imaging reveals complex axonal guidance and development in the adult hippocampus. *J Neurosci* **33**, 11400-11411 (2013).
15. van Praag, H. et al. Functional neurogenesis in the adult hippocampus. *Nature* **415**, 1030-1034 (2002).
16. Gu, Y. et al. Optical controlling reveals time-dependent roles for adult-born dentate granule cells. *Nat Neurosci* **15**, 1700-1706 (2012).
17. Esposito, M.S. et al. Neuronal differentiation in the adult hippocampus recapitulates embryonic development. *J Neurosci* **25**, 10074-10086 (2005).
18. Ben-Ari, Y. Excitatory actions of gaba during development: the nature of the nurture. *Nat Rev Neurosci* **3**, 728-739 (2002).
19. Laplagne, D.A. et al. Functional convergence of neurons generated in the developing and adult hippocampus. *PLoS Biol* **4**, e409 (2006).
20. Laplagne, D.A. et al. Similar GABAergic inputs in dentate granule cells born during embryonic and adult neurogenesis. *Eur J Neurosci* **25**, 2973-2981 (2007).
21. Ge, S. et al. GABA regulates synaptic integration of newly generated neurons in the adult brain. *Nature* **439**, 589-593 (2006).
22. Song, J. et al. Parvalbumin interneurons mediate neuronal circuitry-neurogenesis coupling in the adult hippocampus. *Nat Neurosci* **16**, 1728-1730 (2013).
23. Kim, J.Y. et al. Interplay between DISC1 and GABA signaling regulates neurogenesis in mice and risk for schizophrenia. *Cell* **148**, 1051-1064 (2012).
24. Gould, E., Cameron, H.A. & McEwen, B.S. Blockade of NMDA receptors increases cell death and birth in the developing rat dentate gyrus. *J Comp Neurol* **340**, 551-565 (1994).
25. Tashiro, A., Sandler, V.M., Toni, N., Zhao, C. & Gage, F.H. NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. *Nature* **442**, 929-933 (2006).
26. Marques-Mari, A.I. et al. Loss of input from the mossy cells blocks maturation of newly generated granule cells. *Hippocampus* **17**, 510-524 (2007).
27. van Praag, H., Kempermann, G. & Gage, F.H. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* **2**, 266-270 (1999).
28. Kempermann, G., Kuhn, H.G. & Gage, F.H. More hippocampal neurons in adult mice living in an enriched environment. *Nature* **386**, 493-495 (1997).

29. Freund, J. et al. Emergence of individuality in genetically identical mice. *Science* **340**, 756-759 (2013).
30. Cameron, H.A. & Gould, E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* **61**, 203-209 (1994).
31. Tanapat, P., Hastings, N.B., Reeves, A.J. & Gould, E. Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. *J Neurosci* **19**, 5792-5801 (1999).
32. Garza, J.C., Guo, M., Zhang, W. & Lu, X.Y. Leptin increases adult hippocampal neurogenesis in vivo and in vitro. *J Biol Chem* **283**, 18238-18247 (2008).
33. Galea, L.A. Gonadal hormone modulation of neurogenesis in the dentate gyrus of adult male and female rodents. *Brain Res Rev* **57**, 332-341 (2008).
34. Heine, V.M., Maslam, S., Zareno, J., Joels, M. & Lucassen, P.J. Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. *Eur J Neurosci* **19**, 131-144 (2004).
35. Lemaire, V., Koehl, M., Le Moal, M. & Abrous, D.N. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc Natl Acad Sci U S A* **97**, 11032-11037 (2000).
36. Mirescu, C., Peters, J.D. & Gould, E. Early life experience alters response of adult neurogenesis to stress. *Nat Neurosci* **7**, 841-846 (2004).
37. Duman, R.S., Nakagawa, S. & Malberg, J. Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology* **25**, 836-844 (2001).
38. Santarelli, L. et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301**, 805-809 (2003).
39. Schmidt-Hieber, C., Jonas, P. & Bischofberger, J. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* **429**, 184-187 (2004).
40. Ge, S., Yang, C.H., Hsu, K.S., Ming, G.L. & Song, H. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. *Neuron* **54**, 559-566 (2007).
41. Mongiat, L.A., Esposito, M.S., Lombardi, G. & Schinder, A.F. Reliable activation of immature neurons in the adult hippocampus. *PLoS One* **4**, e5320 (2009).
42. Zhao, C., Teng, E.M., Summers, R.G., Jr., Ming, G.L. & Gage, F.H. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci* **26**, 3-11 (2006).
43. Tronel, S. et al. Spatial learning sculpts the dendritic arbor of adult-born hippocampal neurons. *Proc Natl Acad Sci U S A* **107**, 7963-7968 (2010).
44. Lemaire, V. et al. Long-lasting plasticity of hippocampal adult-born neurons. *J Neurosci* **32**, 3101-3108 (2012).
45. Ramirez-Amaya, V., Marrone, D.F., Gage, F.H., Worley, P.F. & Barnes, C.A. Integration of new neurons into functional neural networks. *J Neurosci* **26**, 12237-12241 (2006).
46. van Strien, N.M., Cappaert, N.L. & Witter, M.P. The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network. *Nat Rev Neurosci* **10**, 272-282 (2009).
47. Steward, O. & Scoville, S.A. Cells of origin of entorhinal cortical afferents to the hippocampus and fascia dentata of the rat. *J Comp Neurol* **169**, 347-370 (1976).
48. Treves, A., Tashiro, A., Witter, M.P. & Moser, E.I. What is the mammalian dentate gyrus good for? *Neuroscience* **154**, 1155-1172 (2008).
49. Scharfman, H.E. The CA3 "backprojection" to the dentate gyrus. *Prog Brain Res* **163**, 627-637 (2007).
50. Jung, M.W. & McNaughton, B.L. Spatial selectivity of unit activity in the hippocampal granular layer. *Hippocampus* **3**, 165-182 (1993).

51. Skaggs, W.E., McNaughton, B.L., Wilson, M.A. & Barnes, C.A. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* **6**, 149-172 (1996).
52. Neunuebel, J.P. & Knierim, J.J. Spatial firing correlates of physiologically distinct cell types of the rat dentate gyrus. *J Neurosci* **32**, 3848-3858 (2012).
53. Lambert, J.D. & Jones, R.S. A reevaluation of excitatory amino acid-mediated synaptic transmission in rat dentate gyrus. *J Neurophysiol* **64**, 119-132 (1990).
54. Scharfman, H.E. Dentate hilar cells with dendrites in the molecular layer have lower thresholds for synaptic activation by perforant path than granule cells. *J Neurosci* **11**, 1660-1673 (1991).
55. Ewell, L.A. & Jones, M.V. Frequency-tuned distribution of inhibition in the dentate gyrus. *J Neurosci* **30**, 12597-12607 (2010).
56. Rolls, E.T. A computational theory of episodic memory formation in the hippocampus. *Behav Brain Res* **215**, 180-196 (2010).
57. Chawla, M.K. et al. Sparse, environmentally selective expression of Arc RNA in the upper blade of the rodent fascia dentata by brief spatial experience. *Hippocampus* **15**, 579-586 (2005).
58. Henze, D.A., McMahon, D.B., Harris, K.M. & Barrionuevo, G. Giant miniature EPSCs at the hippocampal mossy fiber to CA3 pyramidal cell synapse are monoquantal. *J Neurophysiol* **87**, 15-29 (2002).
59. O'Keefe, J. & Dostrovsky, J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Res* **34**, 171-175 (1971).
60. Leutgeb, S. et al. Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. *Science* **309**, 619-623 (2005).
61. Hafting, T., Fyhn, M., Molden, S., Moser, M.B. & Moser, E.I. Microstructure of a spatial map in the entorhinal cortex. *Nature* **436**, 801-806 (2005).
62. Burwell, R.D. The parahippocampal region: corticocortical connectivity. *Ann N Y Acad Sci* **911**, 25-42 (2000).
63. Burwell, R.D. & Amaral, D.G. Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. *J Comp Neurol* **398**, 179-205 (1998).
64. Carlsen, J., De Olmos, J. & Heimer, L. Tracing of two-neuron pathways in the olfactory system by the aid of transneuronal degeneration: projections to the amygdaloid body and hippocampal formation. *J Comp Neurol* **208**, 196-208 (1982).
65. Knierim, J.J. Neural representations of location outside the hippocampus. *Learn Mem* **13**, 405-415 (2006).
66. Hargreaves, E.L., Rao, G., Lee, I. & Knierim, J.J. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. *Science* **308**, 1792-1794 (2005).
67. Renno-Costa, C., Lisman, J.E. & Verschure, P.F. The mechanism of rate remapping in the dentate gyrus. *Neuron* **68**, 1051-1058 (2010).
68. Piatti, V.C., Ewell, L.A. & Leutgeb, J.K. Neurogenesis in the dentate gyrus: carrying the message or dictating the tone. *Frontiers in neuroscience* **7**, 50 (2013).
69. Xavier, G.F. & Costa, V.C. Dentate gyrus and spatial behaviour. *Prog Neuropsychopharmacol Biol Psychiatry* **33**, 762-773 (2009).
70. Kesner, R.P. An analysis of the dentate gyrus function. *Behav Brain Res* **254**, 1-7 (2013).
71. McLamb, R.L., Mundy, W.R. & Tilson, H.A. Intradentate colchicine disrupts the acquisition and performance of a working memory task in the radial arm maze. *Neurotoxicology* **9**, 521-528 (1988).
72. Walsh, T.J., Schulz, D.W., Tilson, H.A. & Schmechel, D.E. Colchicine-induced granule cell loss in rat hippocampus: selective behavioral and histological alterations. *Brain Res* **398**, 23-36 (1986).

73. McNaughton, B.L., Barnes, C.A., Meltzer, J. & Sutherland, R.J. Hippocampal granule cells are necessary for normal spatial learning but not for spatially-selective pyramidal cell discharge. *Exp Brain Res* **76**, 485-496 (1989).
74. Jeltsch, H., Bertrand, F., Lazarus, C. & Cassel, J.C. Cognitive performances and locomotor activity following dentate granule cell damage in rats: role of lesion extent and type of memory tested. *Neurobiol Learn Mem* **76**, 81-105 (2001).
75. Lee, I. & Kesner, R.P. Differential contributions of dorsal hippocampal subregions to memory acquisition and retrieval in contextual fear-conditioning. *Hippocampus* **14**, 301-310 (2004).
76. Hernandez-Rabaza, V. et al. The hippocampal dentate gyrus is essential for generating contextual memories of fear and drug-induced reward. *Neurobiol Learn Mem* **90**, 553-559 (2008).
77. Costa, V.C., Bueno, J.L. & Xavier, G.F. Dentate gyrus-selective colchicine lesion and performance in temporal and spatial tasks. *Behav Brain Res* **160**, 286-303 (2005).
78. Emerich, D.F. & Walsh, T.J. Selective working memory impairments following intradentate injection of colchicine: attenuation of the behavioral but not the neuropathological effects by gangliosides GM1 and AGF2. *Physiol Behav* **45**, 93-101 (1989).
79. Gilbert, P.E., Kesner, R.P. & Lee, I. Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. *Hippocampus* **11**, 626-636 (2001).
80. Marr, D. Simple memory: a theory for archicortex. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences* **262**, 23-81 (1971).
81. McNaughton, B.L. & Morris, R.G.M. Hippocampal synaptic enhancement and information storage within a distributed memory system. *Trends in Neuroscience* **10**, 408-415 (1987).
82. Treves, A. & Rolls, E.T. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. *Hippocampus* **2**, 189-199 (1992).
83. Leutgeb, J.K., Leutgeb, S., Moser, M.B. & Moser, E.I. Pattern separation in the dentate gyrus and CA3 of the hippocampus. *Science* **315**, 961-966 (2007).
84. Park, E., Dvorak, D. & Fenton, A.A. Ensemble place codes in hippocampus: CA1, CA3, and dentate gyrus place cells have multiple place fields in large environments. *PLoS One* **6**, e22349 (2011).
85. Neunuebel, J.P. & Knierim, J.J. CA3 Retrieves Coherent Representations from Degraded Input: Direct Evidence for CA3 Pattern Completion and Dentate Gyrus Pattern Separation. *Neuron* **81**, 416-427 (2014).
86. Frankland, P.W., Cestari, V., Filipkowski, R.K., McDonald, R.J. & Silva, A.J. The dorsal hippocampus is essential for context discrimination but not for contextual conditioning. *Behav Neurosci* **112**, 863-874 (1998).
87. Selden, N.R., Everitt, B.J., Jarrard, L.E. & Robbins, T.W. Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. *Neuroscience* **42**, 335-350 (1991).
88. Gilbert, P.E., Kesner, R.P. & DeCoteau, W.E. Memory for spatial location: role of the hippocampus in mediating spatial pattern separation. *J Neurosci* **18**, 804-810 (1998).
89. McTighe, S.M., Mar, A.C., Romberg, C., Bussey, T.J. & Saksida, L.M. A new touchscreen test of pattern separation: effect of hippocampal lesions. *Neuroreport* **20**, 881-885 (2009).
90. Talpos, J.C., McTighe, S.M., Dias, R., Saksida, L.M. & Bussey, T.J. Trial-unique, delayed nonmatching-to-location (TUNL): a novel, highly hippocampus-dependent automated touchscreen test of location memory and pattern separation. *Neurobiol Learn Mem* **94**, 341-352 (2010).
91. Lee, I. & Solivan, F. Dentate gyrus is necessary for disambiguating similar object-place representations. *Learn Mem* **17**, 252-258 (2010).
92. McHugh, T.J. et al. Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science* **317**, 94-99 (2007).

93. Bekinschtein, P. et al. BDNF in the Dentate Gyrus Is Required for Consolidation of ''Pattern-Separated'' Memories. *Cell Reports* **5**, 1-10 (2013).
94. Bakker, A., Kirwan, C.B., Miller, M. & Stark, C.E. Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science* **319**, 1640-1642 (2008).
95. Shors, T.J. et al. Neurogenesis in the adult is involved in the formation of trace memories. *Nature* **410**, 372-376 (2001).
96. Shors, T.J., Townsend, D.A., Zhao, M., Kozorovitskiy, Y. & Gould, E. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus* **12**, 578-584 (2002).
97. Nokia, M.S., Anderson, M.L. & Shors, T.J. Chemotherapy disrupts learning, neurogenesis and theta activity in the adult brain. *Eur J Neurosci* **36**, 3521-3530 (2012).
98. Goodman, T. et al. Young hippocampal neurons are critical for recent and remote spatial memory in adult mice. *Neuroscience* **171**, 769-778 (2010).
99. Ko, H.G. et al. Effect of ablated hippocampal neurogenesis on the formation and extinction of contextual fear memory. *Molecular brain* **2**, 1 (2009).
100. Garthe, A., Behr, J. & Kempermann, G. Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. *PLoS One* **4**, e5464 (2009).
101. Martinez-Canabal, A., Akers, K.G., Josselyn, S.A. & Frankland, P.W. Age-dependent effects of hippocampal neurogenesis suppression on spatial learning. *Hippocampus* **23**, 66-74 (2013).
102. Dupret, D. et al. Methylazoxymethanol acetate does not fully block cell genesis in the young and aged dentate gyrus. *Eur J Neurosci* **22**, 778-783 (2005).
103. Dupret, D. et al. Spatial relational memory requires hippocampal adult neurogenesis. *PLoS One* **3**, e1959 (2008).
104. Fan, Y., Liu, Z., Weinstein, P.R., Fike, J.R. & Liu, J. Environmental enrichment enhances neurogenesis and improves functional outcome after cranial irradiation. *Eur J Neurosci* **25**, 38-46 (2007).
105. Raber, J. et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiation research* **162**, 39-47 (2004).
106. Imayoshi, I. et al. Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. *Nat Neurosci* **11**, 1153-1161 (2008).
107. Farioli-Vecchioli, S. et al. The timing of differentiation of adult hippocampal neurons is crucial for spatial memory. *PLoS Biol* **6**, e246 (2008).
108. Zhang, C.L., Zou, Y., He, W., Gage, F.H. & Evans, R.M. A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature* **451**, 1004-1007 (2008).
109. Meshi, D. et al. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. *Nat Neurosci* **9**, 729-731 (2006).
110. Snyder, J.S., Hong, N.S., McDonald, R.J. & Wojtowicz, J.M. A role for adult neurogenesis in spatial long-term memory. *Neuroscience* **130**, 843-852 (2005).
111. Saxe, M.D. et al. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc Natl Acad Sci U S A* **103**, 17501-17506 (2006).
112. Iwata, Y. et al. Irradiation in adulthood as a new model of schizophrenia. *PLoS One* **3**, e2283 (2008).
113. Wojtowicz, J.M., Askew, M.L. & Winocur, G. The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. *Eur J Neurosci* **27**, 1494-1502 (2008).
114. Jessberger, S. et al. Dentate gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in adult rats. *Learn Mem* **16**, 147-154 (2009).
115. Deng, W., Saxe, M.D., Gallina, I.S. & Gage, F.H. Adult-born hippocampal dentate granule cells undergoing maturation modulate learning and memory in the brain. *J Neurosci* **29**, 13532-13542 (2009).

116. Rola, R. et al. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp Neurol* **188**, 316-330 (2004).
117. Winocur, G., Wojtowicz, J.M., Sekeres, M., Snyder, J.S. & Wang, S. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. *Hippocampus* **16**, 296-304 (2006).
118. Hernandez-Rabaza, V. et al. Inhibition of adult hippocampal neurogenesis disrupts contextual learning but spares spatial working memory, long-term conditional rule retention and spatial reversal. *Neuroscience* **159**, 59-68 (2009).
119. Warner-Schmidt, J.L., Madsen, T.M. & Duman, R.S. Electroconvulsive seizure restores neurogenesis and hippocampus-dependent fear memory after disruption by irradiation. *Eur J Neurosci* **27**, 1485-1493 (2008).
120. Jaholkowski, P. et al. New hippocampal neurons are not obligatory for memory formation; cyclin D2 knockout mice with no adult brain neurogenesis show learning. *Learn Mem* **16**, 439-451 (2009).
121. Deng, W., Aimone, J.B. & Gage, F.H. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci* **11**, 339-350 (2010).
122. Koehl, M. & Abrous, D.N. A new chapter in the field of memory: adult hippocampal neurogenesis. *Eur J Neurosci* **33**, 1101-1114 (2011).
123. Marin-Burgin, A. & Schinder, A.F. Requirement of adult-born neurons for hippocampus-dependent learning. *Behav Brain Res* **227**, 391-399 (2012).
124. Kee, N., Teixeira, C.M., Wang, A.H. & Frankland, P.W. Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nat Neurosci* **10**, 355-362 (2007).
125. Massa, F. et al. Conditional reduction of adult neurogenesis impairs bidirectional hippocampal synaptic plasticity. *Proc Natl Acad Sci U S A* **108**, 6644-6649 (2011).
126. Sahay, A. et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* **472**, 466-470 (2011).
127. Kitamura, T. et al. Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. *Cell* **139**, 814-827 (2009).
128. Lacefield, C.O., Itskov, V., Reardon, T., Hen, R. & Gordon, J.A. Effects of adult-generated granule cells on coordinated network activity in the dentate gyrus. *Hippocampus* **22**, 106-116 (2012).
129. Snyder, J.S. et al. Adult-born hippocampal neurons are more numerous, faster maturing, and more involved in behavior in rats than in mice. *J Neurosci* **29**, 14484-14495 (2009).
130. Nottebohm, F. Neuronal replacement in adult brain. *Brain Res Bull* **57**, 737-749 (2002).
131. Wiskott, L., Rasch, M.J. & Kempermann, G. A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. *Hippocampus* **16**, 329-343 (2006).
132. Frankland, P.W., Kohler, S. & Josselyn, S.A. Hippocampal neurogenesis and forgetting. *Trends Neurosci* **36**, 497-503 (2013).
133. Josselyn, S.A. & Frankland, P.W. Infantile amnesia: a neurogenic hypothesis. *Learn Mem* **19**, 423-433 (2012).
134. Chambers, R.A., Potenza, M.N., Hoffman, R.E. & Miranker, W. Simulated apoptosis/neurogenesis regulates learning and memory capabilities of adaptive neural networks. *Neuropsychopharmacology* **29**, 747-758 (2004).
135. Deisseroth, K. et al. Excitation-neurogenesis coupling in adult neural stem/progenitor cells. *Neuron* **42**, 535-552 (2004).
136. Feng, R. et al. Deficient neurogenesis in forebrain-specific presenilin-1 knockout mice is associated with reduced clearance of hippocampal memory traces. *Neuron* **32**, 911-926 (2001).

137. Van der Borght, K., Havekes, R., Bos, T., Eggen, B.J. & Van der Zee, E.A. Exercise improves memory acquisition and retrieval in the Y-maze task: relationship with hippocampal neurogenesis. *Behav Neurosci* **121**, 324-334 (2007).
138. Akers, K.G. et al. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. *Science* **344**, 598-602 (2014).
139. Squire, L.R. Mechanisms of memory. *Science* **232**, 1612-1619 (1986).
140. Dupret, D. et al. Spatial learning depends on both the addition and removal of new hippocampal neurons. *PLoS Biol* **5**, e214 (2007).
141. Becker, S. A computational principle for hippocampal learning and neurogenesis. *Hippocampus* **15**, 722-738 (2005).
142. Clelland, C.D. et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* **325**, 210-213 (2009).
143. Tronel, S. et al. Adult-born neurons are necessary for extended contextual discrimination. *Hippocampus* **22**, 292-298 (2012).
144. Nakashiba, T. et al. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* **149**, 188-201 (2012).
145. Kheirbek, M.A., Tannenholz, L. & Hen, R. NR2B-dependent plasticity of adult-born granule cells is necessary for context discrimination. *J Neurosci* **32**, 8696-8702 (2012).
146. Niibori, Y. et al. Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. *Nature communications* **3**, 1253 (2012).
147. Creer, D.J., Romberg, C., Saksida, L.M., van Praag, H. & Bussey, T.J. Running enhances spatial pattern separation in mice. *Proc Natl Acad Sci U S A* **107**, 2367-2372 (2010).
148. Bekinschtein, P., Oomen, C.A., Saksida, L.M. & Bussey, T.J. Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable? *Seminars in cell & developmental biology* **22**, 536-542 (2011).
149. Alme, C.B. et al. Hippocampal granule cells opt for early retirement. *Hippocampus* **20**, 1109-1123 (2010).
150. Marin-Burgin, A., Mongiat, L.A., Pardi, M.B. & Schinder, A.F. Unique processing during a period of high excitation/inhibition balance in adult-born neurons. *Science* **335**, 1238-1242 (2012).
151. Aimone, J.B., Wiles, J. & Gage, F.H. Potential role for adult neurogenesis in the encoding of time in new memories. *Nat Neurosci* **9**, 723-727 (2006).
152. Aimone, J.B., Wiles, J. & Gage, F.H. Computational influence of adult neurogenesis on memory encoding. *Neuron* **61**, 187-202 (2009).
153. Bekinschtein, P. et al. Brain-derived neurotrophic factor interacts with adult-born immature cells in the dentate gyrus during consolidation of overlapping memories. *Hippocampus* (2014).
154. Sahay, A., Wilson, D.A. & Hen, R. Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. *Neuron* **70**, 582-588 (2011).
155. Burghardt, N.S., Park, E.H., Hen, R. & Fenton, A.A. Adult-born hippocampal neurons promote cognitive flexibility in mice. *Hippocampus* **22**, 1795-1808 (2012).
156. Barense, M.D. et al. Functional specialization in the human medial temporal lobe. *J Neurosci* **25**, 10239-10246 (2005).
157. Bussey, T.J. & Saksida, L.M. The organization of visual object representations: a connectionist model of effects of lesions in perirhinal cortex. *Eur J Neurosci* **15**, 355-364 (2002).
158. Bussey, T.J. & Saksida, L.M. Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus* **17**, 898-908 (2007).

159. Cowell, R.A., Bussey, T.J. & Saksida, L.M. Components of recognition memory: dissociable cognitive processes or just differences in representational complexity? *Hippocampus* **20**, 1245-1262 (2010).
160. Nadel, L. & Peterson, M.A. The hippocampus: part of an interactive posterior representational system spanning perceptual and memorial systems. *Journal of experimental psychology. General* **142**, 1242-1254 (2013).
161. Cowell, R.A., Bussey, T.J. & Saksida, L.M. Why does brain damage impair memory? A connectionist model of object recognition memory in perirhinal cortex. *J Neurosci* **26**, 12186-12197 (2006).
162. McTighe, S.M., Cowell, R.A., Winters, B.D., Bussey, T.J. & Saksida, L.M. Paradoxical false memory for objects after brain damage. *Science* **330**, 1408-1410 (2010).
163. Winters, B.D., Bartko, S.J., Saksida, L.M. & Bussey, T.J. Scopolamine infused into perirhinal cortex improves object recognition memory by blocking the acquisition of interfering object information. *Learn Mem* **14**, 590-596 (2007).
164. Winters, B.D., Saksida, L.M. & Bussey, T.J. Paradoxical facilitation of object recognition memory after infusion of scopolamine into perirhinal cortex: implications for cholinergic system function. *J Neurosci* **26**, 9520-9529 (2006).
165. Goodale, M.A. Transforming vision into action. *Vision research* **51**, 1567-1587 (2011).
166. Rauschecker, J.P. & Scott, S.K. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. *Nat Neurosci* **12**, 718-724 (2009).
167. Ungerleider, L. & Mishkin, M. in Analysis of Behavior. (eds. D. Ingle, M. Goodale & R. Mansfield) 549-586. (MIT Press, Cambridge, MA; 1983).
168. Yassa, M.A. & Stark, C.E. Pattern separation in the hippocampus. *Trends Neurosci* **34**, 515-525 (2011).
169. Azab, M., Stark, S.M. & Stark, C.E. Contributions of human hippocampal subfields to spatial and temporal pattern separation. *Hippocampus* **24**, 293-302 (2014).
170. Wood, E.R., Dudchenko, P.A. & Eichenbaum, H. The global record of memory in hippocampal neuronal activity. *Nature* **397**, 613-616 (1999).
171. Wood, E.R., Dudchenko, P.A., Robitsek, R.J. & Eichenbaum, H. Hippocampal neurons encode information about different types of memory episodes occurring in the same location. *Neuron* **27**, 623-633 (2000).
172. Saksida, L.M., Bussey, T.J., Buckmaster, C.A. & Murray, E.A. No effect of hippocampal lesions on perirhinal cortex-dependent feature-ambiguous visual discriminations. *Hippocampus* **16**, 421-430 (2006).
173. Saksida, L.M., Bussey, T.J., Buckmaster, C.A. & Murray, E.A. Impairment and facilitation of transverse patterning after lesions of the perirhinal cortex and hippocampus, respectively. *Cereb Cortex* **17**, 108-115 (2007).
174. Spalding, K.L., Bhardwaj, R.D., Buchholz, B.A., Druid, H. & Frisen, J. Retrospective birth dating of cells in humans. *Cell* **122**, 133-143 (2005).
175. Dranovsky, A. & Hen, R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biol Psychiatry* **59**, 1136-1143 (2006).
176. Duman, R.S. Depression: a case of neuronal life and death? *Biol Psychiatry* **56**, 140-145 (2004).
177. Jacobs, B.L., Praag, H. & Gage, F.H. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry* **5**, 262-269 (2000).
178. Voss, M.W., Vivar, C., Kramer, A.F. & van Praag, H. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci* **17**, 525-544 (2013).
179. Reif, A. et al. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. *Mol Psychiatry* **11**, 514-522 (2006).

180. Boekhoorn, K., Joels, M. & Lucassen, P.J. Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the presenile Alzheimer hippocampus. *Neurobiol Dis* **24**, 1-14 (2006).
181. Jin, K. et al. Increased hippocampal neurogenesis in Alzheimer's disease. *Proc Natl Acad Sci U S A* **101**, 343-347 (2004).
182. Marlatt, M.W. & Lucassen, P.J. Neurogenesis and Alzheimer's disease: Biology and pathophysiology in mice and men. *Current Alzheimer research* **7**, 113-125 (2010).
183. Sahay, A. & Hen, R. Adult hippocampal neurogenesis in depression. *Nat Neurosci* **10**, 1110-1115 (2007).
184. Czeh, B. & Lucassen, P.J. What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? *Eur Arch Psychiatry Clin Neurosci* **257**, 250-260 (2007).
185. Eisch, A.J. et al. Adult neurogenesis, mental health, and mental illness: hope or hype? *J Neurosci* **28**, 11785-11791 (2008).
186. Coras, R. et al. Low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction in humans. *Brain : a journal of neurology* **133**, 3359-3372 (2010).
187. Bartko, S.J., Cowell, R.A., Winters, B.D., Bussey, T.J. & Saksida, L.M. Heightened susceptibility to interference in an animal model of amnesia: impairment in encoding, storage, retrieval--or all three? *Neuropsychologia* **48**, 2987-2997 (2010).
188. Bussey, T.J., Saksida, L.M. & Murray, E.A. Impairments in visual discrimination after perirhinal cortex lesions: testing 'declarative' vs. 'perceptual-mnemonic' views of perirhinal cortex function. *Eur J Neurosci* **17**, 649-660 (2003).
189. Luu, P. et al. The role of adult hippocampal neurogenesis in reducing interference. *Behav Neurosci* **126**, 381-391 (2012).

Related Articles

WIREsCogSci_article-list.doc

Article ID	Article title
e.g., COGSCI-003	e.g., Psychological and neural principles of long-term memory