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A model of hippocampal neurogenesis in memory and mood disorders

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The mounting evidence for neurogenesis in the adult hippocampus has fundamentally challenged the traditional view of brain development. The intense search for clues as to the functional significance of the new neurons has uncovered a surprising connection between neurogenesis and depression. In animal models of depression, neurogenesis is reduced, whereas many treatments for depression promote neurogenesis. We speculate on why the hippocampus, traditionally viewed as a memory structure, might be involved in mood disorders, and what specific role the new neurons might have in the pathogenesis of and recovery from depression. The proposed role of neurogenesis in contextual-memory formation predicts a specific pattern of cognitive deficits in depression and has important implications for treatment of this highly prevalent and debilitating disorder.

Introduction

The discovery of neurogenesis in the hippocampal region of the adult brain (Box 1) has led to an explosion of research in neuroscience over the past decade. One of the most intriguing patterns to emerge from this research is the correlation between neurogenesis and depression. Depression is the leading cause of disability worldwide [1], affecting 8–12% of individuals at some point in their lives [2]; therefore, a priority for research is to understand fully the mechanisms that underlie depression, including both its pathogenesis and recovery. Hippocampal neurogenesis might have a key role, but its precise function remains a mystery. Some researchers have speculated on the role of neurogenesis in normal memory functions but they have not addressed its role in mood disorders. Many researchers have begun to investigate the link between depression and neurogenesis by mapping out the cellular pathways by which stress, potentially a major contributor to the pathogenesis of depression, might disrupt neurogenesis, but no-one has proposed a mechanism by which altered neurogenesis affects mood state. Moreover, the interaction among the hippocampus, stress and mood is poorly understood. We propose a novel perspective on the functional role of new neurons in the hippocampus that explains their linkage to depression. We argue that the new neurons are ideally suited for generating highly distinct memories of otherwise similar events. Moreover, functional clusters of new neurons serve to link events across time. Therefore, we speculate that the new neurons are vital to the role of the hippocampus in setting the context for behaviour. This requires not only the ability to encode and retrieve specific contexts (i.e. details of the event that situate it in a particular place and time) but also the ability to act as a 'contextual gate' to other brain regions, particularly those regions that are involved in the regulation of emotional responses and motivated behaviour. A reduction in neurogenesis is hypothesized to result in a broad array of deficits in functions, including contextual-memory formation and the generation of appropriately contextualized responses to emotional stimuli. Treatments for depression that upregulate neurogenesis might exert their effects, at least in part, by restoring contextual-memory and control functions of the hippocampus.

The link between neurogenesis and depression

Before we elaborate on our proposal for the role of neurogenesis in depression, we will review the evidence. The case for a link between hippocampal neurogenesis and depression is built on two lines of evidence. First, stress is widely believed to be a causal factor in the pathogenesis of major depression (e.g. Ref. [3]) in combination with other predisposing factors, and stress also causes a reduction in hippocampal neurogenesis [4]. Second, many factors that are beneficial in treating the behavioural symptoms of depression have been shown to enhance neurogenesis in laboratory animals; these factors include electroconvulsive therapy (ECT) [5], exercise [6,7], environmental enrichment [8] and common antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs) [9]. The long timescale for recovery when humans are treated pharmacologically for depression (several weeks) parallels the long timescale of stimulated neurogenesis that is induced by ECT and SSRIs in non-depressed animals [5,9]. Moreover, the effects of SSRIs on neurogenesis are selective for the hippocampus, leaving the ongoing stem-cell proliferation in the subventricular zone unchanged [10]. It is possible that alternative mechanisms, not dependent on neurogenesis, contribute to the efficacy of antidepressive treatments [11]. However, in several animal models of depression, disruption of neurogenesis blocks the behavioural efficacy of SSRIs [12], whereas the behavioural efficacy of running is correlated with enhanced neurogenesis [13]. As with much of the research on the functional role of hippocampal neurogenesis, the link with depression requires confirmation in human subjects. Currently, evidence is limited by

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Box 1. Neurogenesis in the hippocampus

The process of neurogenesis (the creation of new neurons) was long thought to be complete by birth. However, it is now well established in many animals, including mice, rats and primates, that neurogenesis continues throughout the lifespan in certain regions of the brain. Stem cells generated in the subventricular zone migrate to their target destinations (the olfactory bulb and the dentate gyrus of the hippocampus) where they undergo cell division, specialization and maturation into functioning neurons and glia [40]. In the rat dentate gyrus, ~8000–10 000 new neurons are generated per day, of which at least 40% survive and progress to maturation [41]. Maturation from neural precursors into functioning dentate granule cells takes about four weeks [30], so the new neurons cannot be generated and used immediately upon demand. The newborn neurons undergo a sequential developmental process: initially, they are highly excitable, but later they are tightly controlled by the extensive inhibitory neural circuitry within the dentate gyrus. Thus, it has been shown that GABAergic synapses and extrasynaptic GABA receptors develop before the glutamatergic synapses and glutamate receptors, but these early-developing GABA receptors are depolarizing and probably excitatory [30]. The glutamatergic synapses develop when dendrites extend into the molecular layer, the source of axonal terminals in the afferent perforant pathway. The inhibitory GABAergic synapses develop last, at 3–4 weeks after cell birth.

The constant supply of new neurons generates a standing gradient of neurons at various stages of development, a 'smörgåsbord' of plastic units available to the hippocampus. Some are still dividing, some are migrating and extending processes, and others are undergoing dendritic growth and synaptogenesis. Younger neurons are easily excitable and plastic, so they can be recruited into the hippocampal circuitry upon demand, for example, during learning, exploring a new environment and running or when under stress. Experimentally, new cells can be selected on the basis of their lower threshold for synaptic facilitation and weaker inhibition by GABA [27,31]. In addition to this traditional 'permissive' form of plasticity, the new neurons represent a radically new form of 'instructive' neuronal adaptation, whereby the afferent activity can regulate the rate of neuronal production [42].

Box 2. Manipulations that suppress neurogenesis

The most reliable and practical approach for reducing the number of new neurons has been to use high-energy radiation to prevent stem-cell proliferation in the neurogenic regions of the brain. By using levels of radiation comparable to those used clinically in human cancer treatments, this method takes advantage of the well-established sensitivity of the mitotically dividing cells to irradiation, while leaving mature neurons intact. Antimitotic drugs can be used to obtain similar effects (reviewed in Ref. [39]). To appreciate the effects of irradiation on neurogenesis, one must realize that they are not instantaneous. Inhibition of cell division will not affect the neurons born before the treatment, so an appropriate lag time between treatment and behavioural testing must be introduced. This delay can be an important experimental variable and crucially can affect the interpretation of the data [21,39]. For example, by testing the animals 4–5 weeks after irradiation, it can be determined whether neurons at 4–5 weeks of age participate in the learning process. By contrast, by testing the animals after only one week, the participation of immature neurons and their precursors can be assessed. Use of irradiation should prove useful in future experimental tests of the hypothesis outlined in this article.

technical issues and choice of patients. For example, Reif *et al.* [14] found no reduction of cell proliferation in post-mortem brains of depressed patients relative to that in controls, in contrast to reduced proliferation in the brains of schizophrenic patients. However, a major confounding factor in patient selection is their use of medication up to the time of death. Moreover, the exclusive reliance on the proliferative marker K_i-67 has methodological shortcomings that must be overcome through the use of other measures of neurogenesis. K_i-67 gives a reading of the number of cells that divide in the brain during the last 24 h of life. This can be strongly influenced by a subject's health just before death and, therefore, not representative of the normal rate of neurogenesis. Thus, there is strong correlational evidence for a link between stress, neurogenesis and antidepressant treatments.

Is the connection causal or merely correlational?

Although the evidence that links hippocampal neurogenesis to depression is compelling, a causal link has by no means been established. On the contrary, Santarelli *et al.* [12] reported that a near-complete elimination of neurogenesis with irradiation (Box 2) did not produce the behavioural symptoms of depression that have been observed in other animal models. Furthermore, primary injury to the hippocampus does not cause any personality or motivational changes [15] that are characteristic of depressive symptomatology. Instead, converging evidence from lesion and neuroimaging studies implicates a prefrontal deficit, coupled with a dysregulation in subcortical stress and emotion circuits, in the core symptoms of depression (for a review, see Ref. [16]). Hippocampal pathology represents collateral damage that arises from a dysregulated stress system [3,17] and that contributes to some cognitive deficits in recurrent depression. Therefore, rather than placing hippocampal neurogenesis at the root of depression, we propose that neurogenesis contributes to several vital functions that are related to contextual processing in the normal brain. These functions become compromised in depression and, when restored, can contribute indirectly to recovery from depression, as outlined later in this article. Thus, the link between antidepressants, neurogenesis and some behavioural symptoms of depression can be understood by focusing on the functional role of neurogenesis in the normal brain. We can do this by considering the hippocampus-dependent behavioural functions and the deficits that are specifically associated with a loss of neurogenesis.

What is the function of the new neurons?

Computational models have helped to shed light on the role of neurogenesis in the normal brain [18–22]. Significantly, neurogenesis takes place in only one region of the hippocampus – the dentate gyrus. Our computational model [19] imparts a unique role to this region in encoding the specific details of episodic memories (Figure 1). Moreover, the constant neural turnover in the dentate region ensures that each new event is encoded uniquely, without interfering with previously or subsequently stored memories [18,19]. The associational pathways in the CA3 and CA1 regions of the hippocampus can integrate this novel experience into prior learning episodes and perform associative retrieval. The unique feature of the new neurons that enables them to generate distinctive episodic memories without interference is their turnover. This turnover relies on two processes: selective cell death, which eliminates redundant units, and maturation, which transforms young, plastic units into less plastic ones. Both groups are

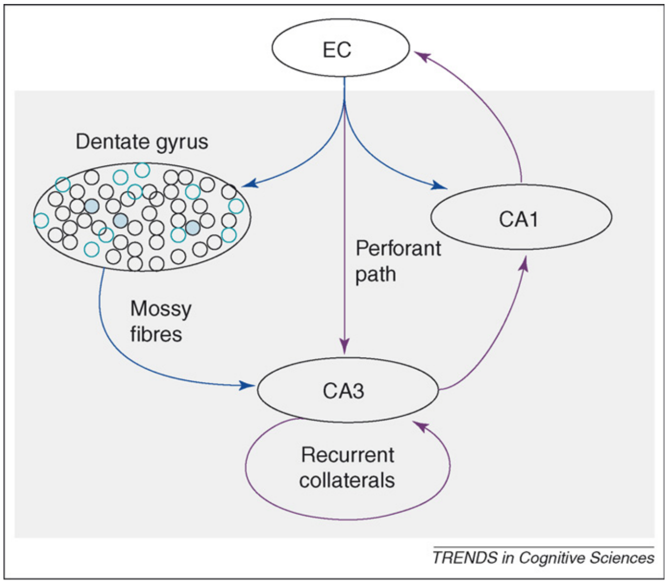

Figure 1. Proposed model of neurogenesis in the hippocampus. Neurogenesis occurs throughout the lifespan in the dentate gyrus of the hippocampus and causes continual rewiring of the hippocampal circuit. This does not compromise the integrity of older memories perhaps because the information flows through the hippocampal circuit along two distinct pathways – one during encoding (blue arrows), through the dentate gyrus to CA3 and CA1, and another during retrieval (purple arrows), bypassing the dentate gyrus. We hypothesize that the encoding pathway through the dentate gyrus uses newly generated, highly plastic neurons to encode distinct and novel information. Our computational model predicts that this enables the animal to encode complex contextualized events with minimal interference between distinct events. Abbreviation: EC, entorhinal cortex.

continuously replaced by neurogenesis; hence the turnover [20,21,23,24] (Box 1; Figure 2).

Experimental manipulations that reduce the number of new neurons, such as irradiation (Box 2), have contributed further to our understanding of possible functions of neurogenesis in the normal brain. Although many hippocampus-dependent tasks involve different aspects of associative memory, not every task that requires the hippocampus also requires the new neurons (for a review, see Ref. [25]). For example, spatial learning by rats in the Morris water maze is disrupted by hippocampal lesions [26] but not by irradiation [27]. However, although irradiated animals learn the water maze at a normal rate, their long-term memory retention of the hidden-platform location is greatly impaired relative to that in controls when they are re-tested four or more weeks later [27]. This finding is consistent with predictions of our computational model [18,19] that the new neurons are important for forming highly distinctive memories for individual episodes, thereby protecting them against retroactive interference (Figure 1).

In addition to this role in encoding specific details of events, the new neurons seem to be crucial for linking events across time when these events are part of the same context. Thus, animals that lack new hippocampal neurons show deficits on tasks that seem to require contextual-memory abilities, including trace conditioning [28], contextual fear conditioning [29] and delayed non-match to sample (DNMS) with long delays [29]. However, they perform normally on corresponding non-hippocampal control tasks: delay conditioning [28], cued fear conditioning [29] and DNMS with short delays [29]. Whereas our previous model [18,19] accounts for the role of the new neurons in forming distinct event memories, the data reviewed here suggest that these neurons also have a role in linking events across time when the events are part of a common context.

A novel proposal for the role of neurogenesis in temporal context: the functional cluster hypothesis

Understanding the role of the new neurons in temporal coding requires a more elaborate model. Traditionally, the hippocampus is thought to be responsible for associating multiple stimuli into a single episodic memory. Synaptic integration of multiple inputs carrying sensory information can occur via spatial summation of individual synaptic potentials in dendrites of granule neurons. Such synaptic responses are usually mediated by two principal types of glutamate receptors, AMPA and NMDA. AMPA is responsible for short-term interactions and NMDA for long-lasting changes in excitability, such as during learning. However, temporal summation beyond the range of milliseconds cannot be explained using traditional biophysical mechanisms. Temporal summation of events on the order of minutes, hours or days might be required to solve the learning tasks described here. Neurogenesis is ideally suited to encode such events; it is an ongoing process that begins with proliferation of neural precursors and ends with fully functional mature neurons (Box 1). One striking feature of proliferation is that it occurs in clusters. The dividing precursors are often seen in groups of 2–10 cells, tightly packed in the subgranular zone (SGZ) of the dentate gyrus (Figure 3). These clusters disperse along the SGZ within several days, presumably by migration and/or attrition due to cell death. Differentiation of cells within the clusters into neurons is characterized by the expression of specific proteins, extension of axons and dendrites, and synaptogenesis [30]. Importantly, the excitatory influences, in the form of depolarizing GABA-mediated responses, are formed long before the new neurons integrate with the dense inhibitory circuitry in the dentate gyrus, which enables new neurons to sustain much higher activity levels than mature granule cells [31].

Hypothetically, one can envisage ‘waves’ of neurons that respond to afferent stimulation and send impulses from neurons belonging to a cluster, via mossy fibres, to CA3 for association of their common inputs by CA3 axon collaterals. New neurons within a cluster, innervated by different perforant path inputs, will respond to different features of an event. Some will fire in response to persistent aspects of the environment, such as odours, stationary objects and boundaries, which we shall refer to as the context. Other neurons might respond to more transient aspects, such as a tone or a shock. The highly plastic new neurons will become tuned to this constellation of features and should respond consistently when they experience the same context again. Using plastic recurrent connections, targets in CA3 can link the transient features with the context, thus temporally linking items into a single episode. This enables cued recall of the entire event from a single item, which provides the basis of episodic-memory encoding and retrieval (Figure 2). The new neurons will then either die or mature and become less plastic,

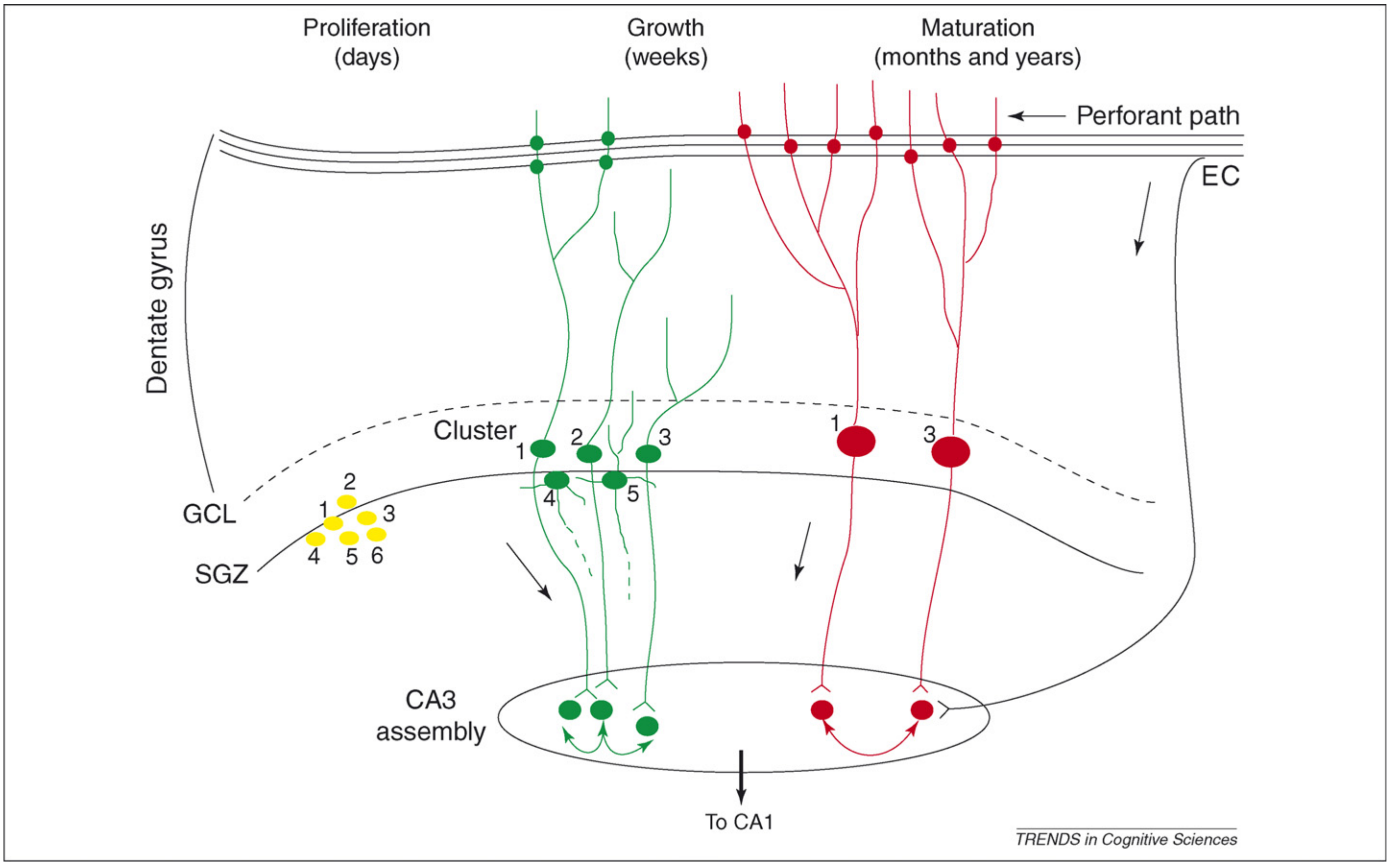

Figure 2. Proposed model of neuronal clusters that serve as a substrate for hippocampal learning. Newly divided cells (future neurons) are often found in clusters of 2–10 in adult rats. This might be because of multiple divisions of the neuronal precursors. A cluster of six cells, on the left side of the figure, corresponds to the experimental data illustrated in Figure 3. This cluster is hypothetically reduced to five immature cells and, ultimately, to two mature neurons during growth, learning and maturation. The surviving neurons within a cluster might develop at different speeds and, during development, their axons extend rapidly towards CA3. Dendrites take a few weeks to grow fully. Attrition of cell numbers through apoptotic cell death begins 7 d after cell birth and continues until at least 21 d after cell birth. Our model proposes that cells within a cluster share common target-cell assemblies in CA3. These assemblies (interconnected groups of CA3 neurons) could be formed by the recurrent collaterals of CA3 neurons, so that one member of a cluster that is active early on would activate the same CA3 assembly as another cluster member that comes online later. Assemblies of CA3 neurons could be the result of strengthened synaptic connections due to interactions of mossy fibres and CA3 axonal collaterals. Learning, which takes several hours or days, will hypothetically affect all members of the cluster but at different stages of the learning process. This accounts for integration between trials on different days. The pattern that arises from such associations is likely to be transferred to CA1 through the Shaffer collateral system and perhaps to the cortex for permanent storage. However, the pattern could be at least partly preserved and perhaps retrieved by the surviving members of the cluster, which are now mature granule neurons. Alternatively, retrieval could involve the direct perforant path–CA3 projection (on the right side of the figure) and pattern completion might occur through the CA3 recurrent collaterals. Abbreviations: EC, entorhinal cortex (the source of the perforant pathway); GCL, granule cell layer; SGZ, subgranular zone.

which will protect the memory from interference by later learning. Subsequent events could be encoded by other ‘waves’ of generations of new neurons.

This ‘functional cluster’ hypothesis shares with previous models the assumption of ‘superior plasticity’ of the new neurons [18,20–22] and is consistent with a recently proposed model of a mechanism that separates ongoing experience into temporally tagged, unique event memories [32]. More specifically, the cluster model proposed here (not to be confused with the ‘clustered plasticity model’ of Govindarajan *et al.* [33], which is a single-neuron model) assigns a unique role to the clusters of cells born at approximately the same time and their impact on the encoding of event memories in CA3.

How does a neurogenesis deficit relate to symptoms of depression?

Our proposed role for neurogenesis in forming highly specific, contextualized event memories can explain some of the learning and memory deficits in depression. People who have major depression, and presumably lack neurogenesis, exhibit recollection-memory deficits that are characteristic of hippocampal damage, accompanied by a reduction in hippocampal volume that correlates with total illness duration [34,35]. Moreover, their recall of episodic memories, particularly for positive events, is overly general and lacks detail [36]. A neurogenesis deficit, in the context of a negative processing bias and a negative mood state, could bias hippocampal encoding and retrieval towards a narrow, predominantly negative representation of context.

How could restoration of neurogenesis affect mood state?

The role we propose for neurogenesis in encoding context can be reconciled with its putative role in recovery from depression if we consider the broader function of the hippocampus in gating other brain regions and enabling responses to be set into the appropriate context. Although the hippocampus is known to be crucial in memory, it is also in a key position to indirectly influence responses to stress and emotion (Figure 4). First, the hippocampus exerts negative-feedback

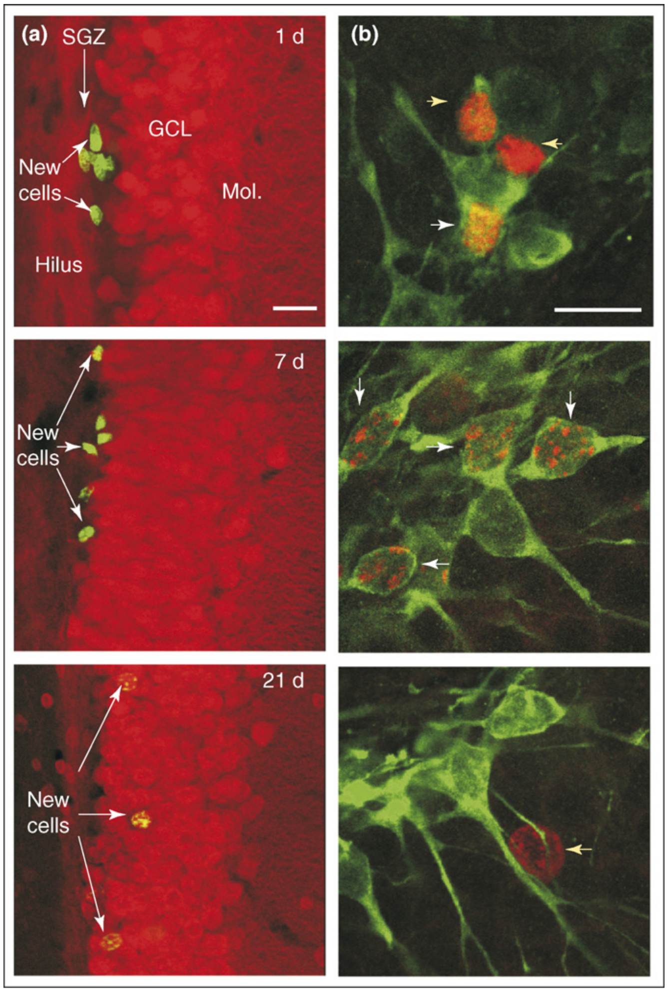

Figure 3. Clusters of new cells that were produced in the dentate gyrus of an adult rat. **(a)** New cells that were observed 1, 7 and 21 d after birth. Progression from clusters (day 1) to a dispersed distribution along the length of the subgranular zone (SGZ; day 7) and into the granule cell layer (GCL; day 21) is evident. New cells were labeled with the cell-division marker bromodeoxyuridine (BrdU, green). The mature cells were labeled with calbindin (red). Co-labeling of BrdU and calbindin results in the yellow appearance of new cells at day 21. Such co-labeling is the evidence of cell maturation. **(b)** The sequence of neuronal differentiation using BrdU (red) and doublecortin (green), an immature neuronal marker. At day 1, most cells express only BrdU (yellow arrowheads). At day 7, most cells are co-labeled with BrdU and doublecortin (white arrows), indicating neuronal differentiation. At day 21, the doublecortin label is gone and the BrdU-labeled cells migrate into the granule cell layer. Scale bar, 20 μm. Figure modified, with permission, from H.Y. McDonald, MSc thesis, University of Toronto, 2004.

control over the hypothalamic–pituitary–adrenal axis, which is responsible for the body's frontline response to stress. Second, the hippocampus projects to several structures that are important for motivation and emotion, including the amygdala, nucleus accumbens and medial prefrontal cortex. Third, electrophysiological evidence suggests that the hippocampus can gate the flow of information through motivational circuits that involve the prefrontal cortex and striatum [37,38]. Thus, not only is the hippocampus well situated to encode context through its inputs from divergent brain regions and its use of neurogenesis, but it is also in a position to modulate contextually appropriate responses in other brain regions.

A rat that has a neurogenesis deficit can remember its fear in response to a tone but cannot relate it to the specific acquisition context [29]; similarly, a depressed person who

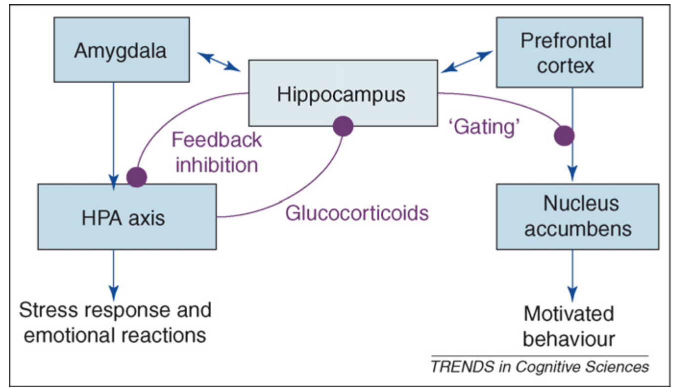

Figure 4. The role of the hippocampus in contextual gating. The hippocampus is more than just a memory structure. It receives input from most brain regions, including emotional information from the amygdala and prefrontal cortex. It gates the flow of information from the prefrontal cortex to the nucleus accumbens, a pathway that is important for motivated behaviour. Additionally, the hippocampus responds to elevated glucocorticoid output from the hypothalamic–pituitary–adrenal (HPA) stress system by exerting negative feedback control over the HPA axis. Neurogenesis in the dentate gyrus is crucial for maintaining distinct representations of events (e.g. in contextual fear conditioning). A deficit in neurogenesis might explain, at least in part, the dysregulation of context-appropriate emotional responding in stress-related psychiatric illnesses, such as post-traumatic stress disorder and depression. Information-transmitting pathways are shown in blue; modulatory connections are shown in purple.

has a dysregulated emotional system that is compounded by a neurogenesis deficit might fail to relate their current circumstances to recent positive experiences and instead default to a negative contextual framework. Restoration of neurogenesis in the hippocampus could improve contextual encoding of new events. The hippocampus might use this context to constrain responses more appropriately to stimuli by its gating action on prefrontal–striatal circuits. In turn, this could enable the prefrontal cortex to regain control over subcortical emotional circuits.

Concluding remarks

The intriguing correlation between neurogenesis and depression has led to many unanswered questions (Box 3). Here, we have proposed a framework for viewing the function of neurogenesis in the normal brain that explains its link to depression. According to our functional cluster hypothesis, the new neurons are predicted to have a fundamental role in encoding specific details of episodes, linking items to context and indirectly (via recurrent connections in CA3) linking items across time. A neurogenesis deficit is predicted to occur in stress-related psychiatric illnesses such as depression, causing deficits in contextual memory. Although a pure neurogenesis deficit would not cause depression, it could

Box 3. Questions for future research

- Does chronic stress lead to the same memory deficits as irradiation-induced inhibition of neurogenesis?
- Are new neurons required for remembering highly similar events, and are they required for associating events that are discontiguous in time but contextually associated?
- Do people who have a first episode of major depression show memory deficits that are characteristic of reduced neurogenesis?
- Does increased neurogenesis have a causal role in recovery from depression?

exacerbate a negative-information-processing bias by making it difficult to encode, retrieve and react appropriately to positive contexts. Antidepressants, ECT and exercise all upregulate neurogenesis, which might help to restore appropriately contextualized reactions to stimuli.

The dependence of stress-induced memory deficits on reduced neurogenesis is still a matter of debate. This could be addressed by independently manipulating levels of stress and levels of neurogenesis in animal experiments.

In addition, our model makes several predictions regarding the importance of neurogenesis for normal learning and memory. The cluster hypothesis predicts that new neurons should be important for binding together elements that occur at different times but are part of the same context. Additionally, animal studies could test the prediction of our computational model that reduced neurogenesis should increase interference between memories of highly similar, sequentially learned events.

Further studies in human patients could determine whether individuals in a first episode of depression, before signs of hippocampal pathology emerge, would show the same pattern of selective contextual-memory deficits as have been seen in animals that have reduced neurogenesis. Most studies of cognitive functions in patients who have depression have used standard neuropsychological test batteries. Some researchers have begun to adapt contextual conditioning paradigms from the animal literature for human studies, particularly contextual fear conditioning. However, this paradigm and the trace-conditioning paradigm have yet to be tested in patients who have depression.

A complication in interpreting current empirical data is that there is no single method that selectively enhances or reduces neurogenesis. SSRIs, ECT and exercise each produce a wide range of other effects, whereas irradiation might have unwanted side effects, such as elimination of dividing cells in brain regions outside of the hippocampus [39]. There are also unavoidable secondary effects in afferent cortical and efferent hippocampal regions of the dentate gyrus that result from the lesion (Box 2). Finally, further tests are needed to prove or disprove the necessity of restoring ongoing neurogenesis in treatments of depression.

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