A model of hippocampal neurogenesis in memory and mood disorders

Suzanna Becker (corresponding author), Department of Psychology Neuroscience & Behaviour, McMaster University
J. Martin Wojtowicz, Department of Physiology, University of Toronto, Toronto, M5S 1A8, Canada

Abstract

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, while many treatments for depression upregulate 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 play in the pathogenesis of and recovery from depression. The proposed role for 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 (see Box 1) spawned 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. Given that depression is the leading cause of disability worldwide [1]], affecting 8-12% of individuals at some point in their lives [2], a high priority for current research is to understand fully the mechanisms underlying depression, including both its pathogenesis and recovery. Hippocampal neurogenesis may be a key player in this story, but its precise role remains a mystery. Many researchers have speculated on the role of neurogenesis in normal memory functions, but none of these theories has addressed its role in mood disorders. In terms of depression, many researchers have begun to investigate the first step in the link to neurogenesis by mapping out the cellular pathways by which stress, a major suspect in the pathogenesis of

depression, may disrupt neurogenesis, but to date no-one has proposed a mechanism by which altered neurogenesis affects mood state. Moreover, the interaction between 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. We speculate that the new neurons are therefore vital to the hippocampal role in setting the context for behaviour. This requires not only the ability to encode and retrieve specific contexts (i.e. the event details that situate it in a particular place and time), but to act as a "contextual gate" over other brain regions, particularly those 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 ranging from contextual memory formation to generating appropriately contextualized responses to emotional stimuli. Treatments for depression that up-regulate neurogenesis may 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 proposed role of neurogenesis in depression, we first review the evidence. The case for hippocampal neurogenesis participating in the story of depression is built upon two lines of evidence. First, stress is widely believed to be a causal factor in the pathogenesis of major depression (see e.g. [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 include electroconvulsive therapy (ECT) [5], exercise [6,7], environmental enrichment [8] and common antidepressant drugs including selective serotonin reuptake inhibitors (SSRI's) [9]. The rather long time scale for recovery when humans are treated pharmacologically for depression (several weeks) parallels the long time course of stimulated neurogenesis induced by ECT and SSRI's in normal 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 overall efficacy of antidepressive treatments [11]. However, in several different

animal models of depression, disruption of neurogenesis blocks the behavioural efficacy of SSRI's [12], while 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. Evidence available thus far is limited by technical issues and choice of the patients. Reif et al. [14], for example, found no reduction of cell proliferation in post-mortem brains of depressed patients relative to controls, in contrast to reduced proliferation in schizophrenic patients. However, a major confounding factor in patient selection is their use of medication at the time of death. Moreover, the exclusive reliance on the proliferative marker Ki-67 is a methodological shortcoming that will have to be overcomed by other measures of neurogenesis. The Ki-67 gives a readout of the number of cells dividing in the brain during the last 24 hrs of life. This may be strongly influenced by a subject's health just prior to death and not representative of the normal rate of neurogenesis. Thus, overall, there is strong correlational evidence for a link between stress, neurogenesis and antidepressant treatments.

Is the connection causal or merely correlational?

Although the evidence linking 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 (see Box 2) did not produce the behavioural symptoms of depression observed in other animal models. Further, primary injury to the hippocampus does not cause any personality or motivational changes [15] characteristic of depressive symptomatology. Instead, converging evidence from lesion and neuroimaging studies implicates a prefrontal deficit, coupled with a dysregulation in sub-cortical stress/emotion circuits, in the core symptoms of depression (for a review see [16]). Hippocampal pathology represents collateral damage arising from a dysregulated stress system (e.g. [3,17]), contributing to some of the cognitive deficits seen in recurrent depression. Rather than placing hippocampal neurogenesis at the root of depression, we therefore propose that neurogenesis contributes to several vital functions related to contextual processing in the normal brain. These functions become compromised in depression, and when restored, can contribute to recovery from depression indirectly, as outlined below. Thus, the link between antidepressants, neurogenesis and some of the behavioural symptoms of depression can be understood if we focus on understanding the functional role of neurogenesis in the normal brain. We can do so by considering the hippocampal-

dependent behavioural functions and deficits specifically associated with a loss of neurogenesis.

What is the function of the new neurons?

Computational models have helped to shed light on what the role of neurogenesis might be in the normal brain [18,19,20,21,22] . It is significant that neurogenesis takes place only in one region of the hippocampus, namely, the dentate gyrus. Our computational model [19] imparts a unique role to this region in encoding the specific details of episodic memories (see 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 then integrate this novel experience with prior learning episodes, and perform associative retrieval. The unique feature of the new neurons that enable them to generate distinctive episodic memories without interference is their turnover. This turnover relies on two processes, the selective cell death eliminating the redundant units and the maturation process that transforms the young , plastic units into the less plastic ones. Both groups are continuously replaced by ongoing neurogenesis, hence the turnover [20,21] (see [23,24], Box 1 and Figure 3).

Experimental manipulations that reduce the number of new neurons, such as irradiation (see Box 2), have contributed further to our understanding of possible functions of neurogenesis in the normal brain. While there are many hippocampal-dependent tasks involving different aspects of associative memory, not every task known to require the hippocampus also requires the new neurons (for a review, see [25]. For example, spatial learning in the Morris water maze is disrupted by hippocampal lesions [26] but not by irradiation [27]. However, while 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 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, as illustrated in Figure 1.

In addition to this role in encoding specific details of events, the new neurons seem to be critical for linking events across time when they are part of the same context. Thus, animals lacking new hippocampal neurons show deficits on tasks that seem to require contextual memory abilities, including

trace conditioning [28], contextual fear conditioning and delayed non-match to sample (DNMS) at long delays [29], while performing normally on corresponding non-hippocampal control tasks, delay conditioning [28], cued fear conditioning and DNMS at short delays [29], respectively. While our previous model [18,19] accounts for the role of the new neurons in forming distinct event memories, the data reviewed here suggest that they also play a role in linking events across time when they 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. It is easy to envisage how spatial or multimodal stimuli can be combined at the cellular level via NMDA-receptor-mediated summation of synaptic input in dendrites. However, temporal summation beyond the range of milliseconds is not explainable by traditional biophysical mechanisms. Temporal summation of events on the order of minutes, hours or days may be required to solve the learning tasks described here. Neurogenesis is ideally suited to encode such events. It is an ongoing process beginning with proliferation of neural precursors and ending with fully functional mature neurons (see 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 2). These clusters disperse along the SGZ within several days presumably by migration and/or attrition due to cell death. Cells within the clusters differentiate into neurons characterized by expression of specific proteins, extension of axons and dendrites and synaptogenesis [30]. Importantly, the excitatory influences in the form of depolarizing GABA-ergic responses are formed long before the new neurons integrate with the dense inhibitory circuitry in the dentate gyrus, allowing new neurons to sustain much higher activity levels than mature granule cells [31].

Hypothetically, one can envisage “waves” of neurons responding to afferent stimulation and sending impulses via mossy fibers for association via CA3 collaterals. New neurons within a cluster, innervated by different perforant path inputs, will respond to different features of an event. Some will fire to the more persistent aspects of an environment such as odours, stationary objects and boundaries, which we shall refer to as the *context*. Other neurons may respond to more transient aspects such as the occurrence of a tone or a shock. The highly plastic new neurons will become tuned to

this constellation of features, and should respond consistently when re-experiencing the same context. Targets in CA3, using plastic recurrent connections, can link the transient features with the context, thus temporally linking items into a single episode. This allows cued recall of the entire event from a single item, providing the basis of episodic memory encoding and retrieval, as illustrated in Figure 3. The new neurons will then either die or mature to the point of being less plastic, so that the memory will be protected 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 [18,20,21,22] and a recently proposed model of a mechanism separating ongoing experience into temporally tagged, unique event memories [32]. More specifically, the cluster model proposed here (not to be confused with the recently proposed "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 seen in depression. People with major depression, who are presumably lacking neurogenesis, exhibit recollection memory deficits 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 lacking details [36]. A neurogenesis deficit, in the context of a negative processing bias and a negative mood state, could bias hippocampal encoding and retrieval toward a narrow, predominantly negative represenation 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 so as to set responses into the appropriate context. While the hippocampus is widely known to be critical in memory, it is also in a key position to indirectly influence responses to stress and emotion, as illustrated in Figure 4. First, the hippocampus exerts negative feedback control over the

hypothalamic-pituitary-adrenal axis, which is responsible for the body's front-line response to stress. Second, the hippocampus projects to several structures known to be 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 involving the prefrontal cortex and striatum [37,38]. Thus, the hippocampus is not only well situated to encode context by virtue of its inputs from many divergent brain regions, and its use of neurogenesis, it is also in a position to modulate contextually appropriate responses in other brain regions.

Just as the rat with a neurogenesis deficit is able to remember its fear in response to a tone but unable to relate it to the specific acquisition context, a depressed person with a dysregulated emotional system compounded by a neurogenesis deficit may fail to relate their current circumstances to any recent positive experiences, and default to a negative contextual framework. Restoration of neurogenesis in the hippocampus may improve contextual encoding of new events. The hippocampus could use this context to more appropriately constrain responses to stimuli via its gating action on prefrontal-striatal circuits. This in turn could help the prefrontal cortex to regain control over sub-cortical emotional circuits.

Conclusions

An intriguing correlation between neurogenesis and depression has led to many unanswered questions. We propose here 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 play a fundamental role in encoding specific details of episodes, linking items to context, and indirectly (via CA3 recurrent connections), linking items across time. A neurogenesis deficit is predicted to occur in stress-related psychiatric illnesses such as depression, causing deficits in contextual memory. While a pure neurgenesis deficit would not cause depression, it could exacerbate a negative information processing bias by making it difficult to encode, retrieve and react appropriately to positive contexts. Antidepressants, ECT and exercise have in common that they upregulate neurogenesis, which may in turn help to restore appropriately contextualized reactions to stimlui.

The dependence of stress-induced memory deficits on reduced neurogenesis is still under debate. This could be addressed by animal experiments where levels of stress and levels of neurogenesis are independently manipulated.

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 discontiguously in time 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 are needed to 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 seen in animals with reduced neurogenesis. Most studies of cognitive functions in depressed patients have employed standard neuropsychological test batteries. Some researchers have begun to adapt contextual conditioning paradigms from the animal literature to human studies, particularly contextual fear conditioning, but this paradigm has yet to be tested in depressed patients. The same is true of trace conditioning.

A complication in interpreting current empirical data is that there is no single method that selectively enhances or reduces neurogenesis. SSRI's, ECT and exercise each produce a wide range of other effects, while irradiation may have unwanted side effects such as elimination of dividing cells in brain regions outside of hippocampus [39]. There are also unavoidable secondary effects in afferent cortical and efferent hippocampal regions of the dentate gyrus resulting from the lesion (see 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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Box 1: Neurogenesis in the hippocampus. The process of neurogenesis, or the creation of new neurons, was long held to be complete at the time of birth. However, it is now well established in many species including mice, rats and primates that neurogenesis continues throughout the lifespan in certain regions of the brain. Stem cells generated in the sub-ventricular 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, about 8,000-10,000 new neurons are generated per day, of which at least 40% survive to maturation [41]. Maturation from neural precursors into functioning dentate granule cells takes about 4 weeks [30], hence, the new neurons cannot be simply generated and used immediately upon demand. The newborn neurons undergo a sequential developmental process, whereby they are initially highly excitable, and only later come under the tight control of the extensive inhibitory neural circuitry within the dentate gyrus. Thus, it has been shown that GABA-ergic synapses and extrasynaptic GABA receptors appear prior to the Glutamate-ergic ones but these early-developing GABA receptors are depolarizing and probably excitatory [30]. The Glutamate-ergic synapses appear when dendrites extend into the molecular layer, the source of axonal terminals in the afferent perforant pathway. The inhibitory GABA-ergic synapses appear last at 3-4 weeks following cell birth.

The constant supply of new neurons generates a standing gradient of neurons at various stages of development, a "smörgåsbord" of plastic units for the hippocampus to choose from. Some of them are still dividing, others begin to migrate and extend processes, and still others go through the stage of dendritic growth and synaptogenesis. Younger neurons are easily excitable and plastic. As a consequence they may be recruited into the hippocampal circuitry upon demand during various behaviours such as learning, exploring a new environment, running, undergoing stress etc. Experimentally it is possible to select the new cells on the basis of their lower threshold for synaptic facilitation and lesser 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 where the afferent activity can regulate the rate of neuronal production [42].

Box 2: Manipulations that suppress neurogenesis

The most reliable and practical approach to 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 employed 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 [39]). To appreciate the effects of irradiation on neurogenesis one needs to realize that they are not instantaneous. Inhibition of cell division will not affect the young neurons born prior to the treatment so an appropriate lag time between the treatment and behavioural testing must be introduced. This delay period can become an important experimental variable and critically affect the interpretation of the data [39,21]. For example, by testing the animals 4-5 weeks after the irradiation one effectively asks whether the young neurons at 4-5 weeks of age participate in the learning process. In contrast, by testing the animals after only 1 week one can assess the participation of very immature neurons and their precursors. Use of irradiation may prove useful in future experimental tests of the hypothesis advanced in this article.

Outstanding Issues

- Does chronic stress lead to the same memory deficits as seen with irradiation-induced neurogenesis deficits?

- Are new neurons required for remembering highly similar events, and for associating events that are discontiguous in time but contextually associated?

- Do people with a first episode of major depression show memory deficits characteristic of reduced neurogenesis?

- Does increased neurogenesis play a causal role in recovery from depression?

Figure 1.

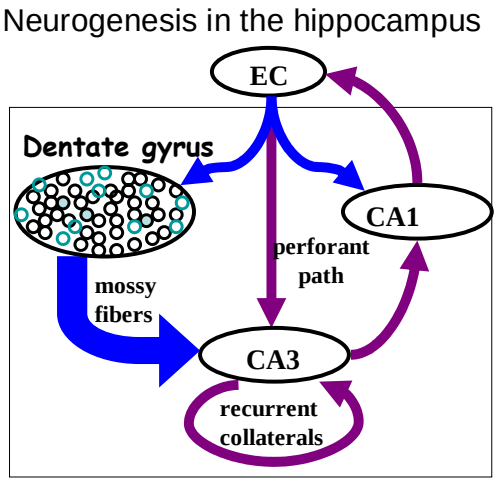

Figure 1: Neurogenesis occurs throughout the lifespan in the dentate gyrus of the hippocampus, causing continual re-wiring of the hippocampal circuit. The reason this does not compromise the integrity of older memories may be that information flows through the hippocampal circuit along two distinct pathways, one during encoding (blue arrows) and another during retrieval (violet arrows). We hypothesize that the encoding pathway via the dentate gyrus employs newly generated, highly plastic neurons to encode distinct and novel information. Our computational model predicts that this allows the animal to encode complex contextualized events with minimal interference between distinct events. EC- Entorhinal Cortex.

Figure 2. Neurogenesis and neuronal clusters

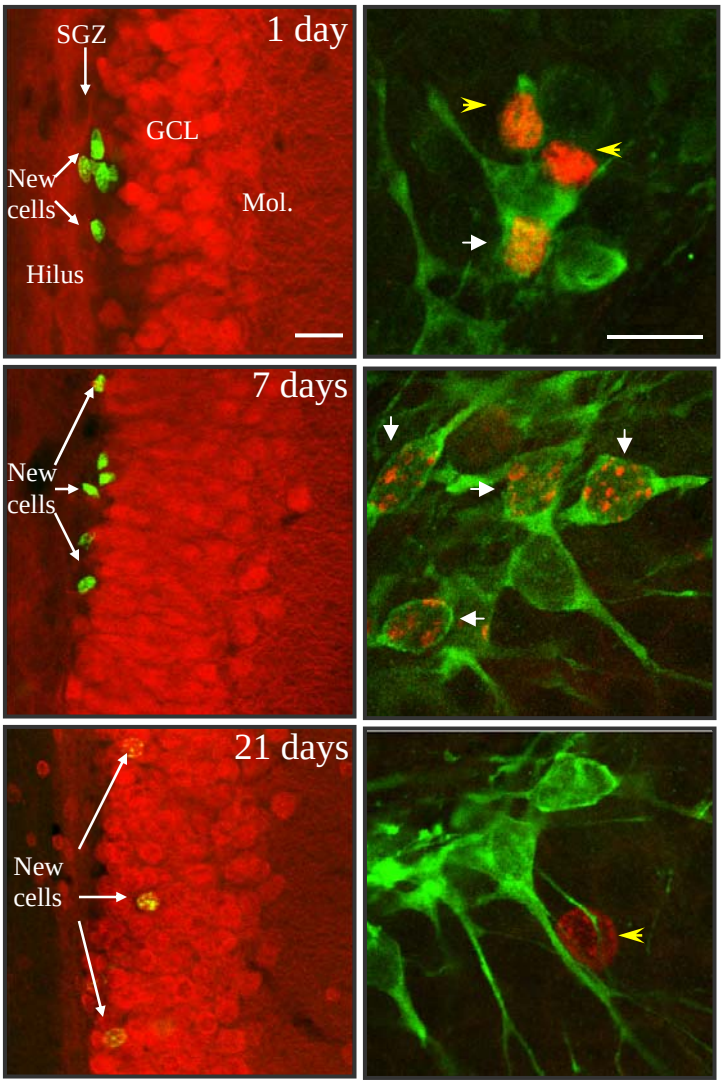

Figure 2. A study showing clusters of new cells produced in an adult rat's dentate gyrus. Left panel - illustrates new cells observed 1,7 and 21 days after birth. Progression from clusters (day 1) to more dispersed distribution along the length of the subgranular zone (day 7) and into the granule cell layer (day 21) is evident. New cells were labeled with a cell division marker (BrdU, green). The mature cells were labeled with calbindin (red). Co-labeling of BrdU and calbindin results in yellow appearance of new cells at day 21. Such co-labeling is the evidence of cell maturation.
Right panel - illustrates 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 are seen to migrate into the granule cell layer. Scale bar 20 μm. [41,43].

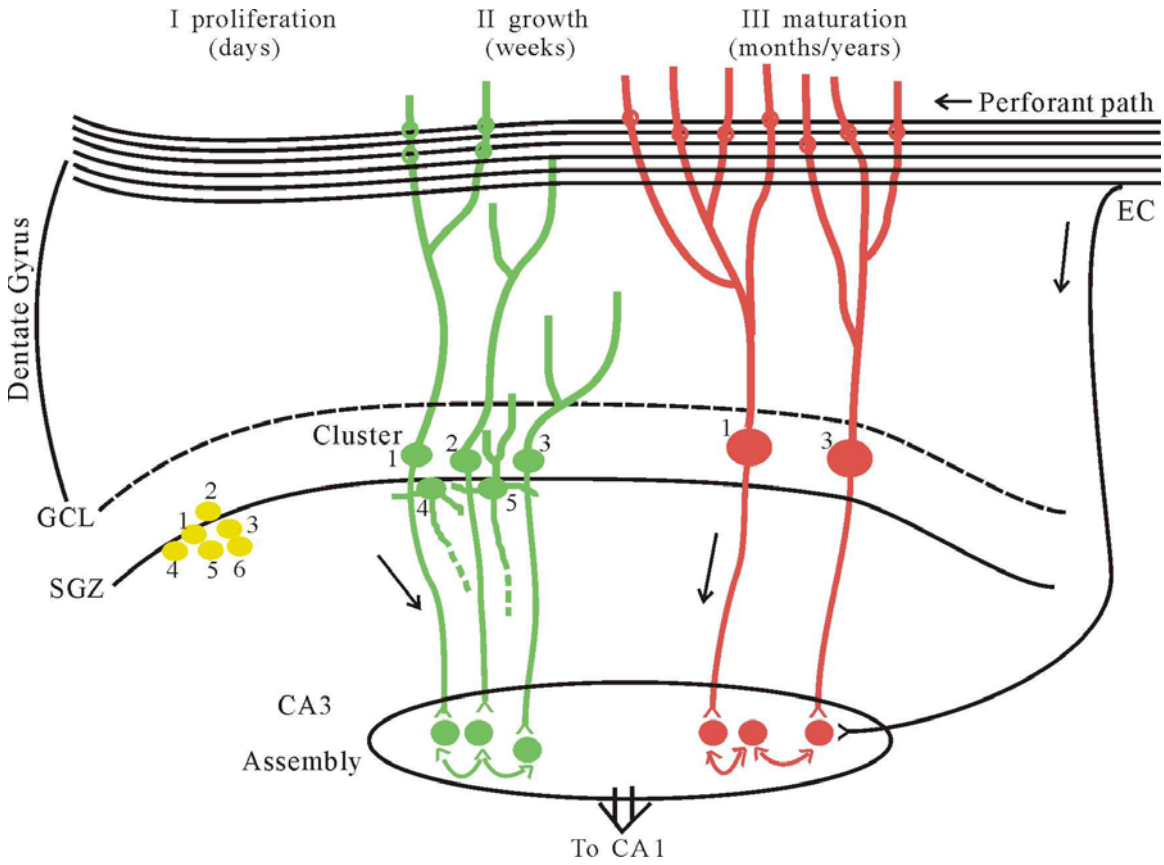

Figure 3.

1. Newly divided cells (future neurons) are often found in clusters of 2-10. This may be the result of multiple divisions of the neuronal precursors. A cluster of 6 cells is shown on the left side of the figure corresponding to the experimental data illustrated in Figure 2.

2. Each surviving neuron within a cluster may be developing at a slightly different pace with their axons rapidly extending towards CA3. Dendrites take a few weeks to grow fully in length and size. Attrition of cell numbers through apoptotic cell death begins at day 7 and continues for at least 21 days. Our model proposes that all 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 active at an earlier time would activate the same CA3 assembly as another cluster member that comes online at a later time. Assemblies of CA3 neurons could be the result of strengthened synaptic connections due to interactions of mossy fibers and CA3 axonal collaterals.

3. Learning taking several hours or days is hypothetically going to affect all members of the cluster but at different times of the learning process thus accounting for integration between trials on different days.

4. The pattern arising from such associations is likely to be transferred to CA1 via 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, by now mature granule neurons. Alternatively, retrieval could involve the direct perforant path-CA3 projection (shown in right side of the figure), with pattern completion via the CA3 recurrent collaterals.

EC- entorhinal cortex is the source of the perforant pathway

GCL- granule cell layer

SGZ- subgranular zone

Figure 4: Hippocampal role in contextual modulation of emotional behaviour.

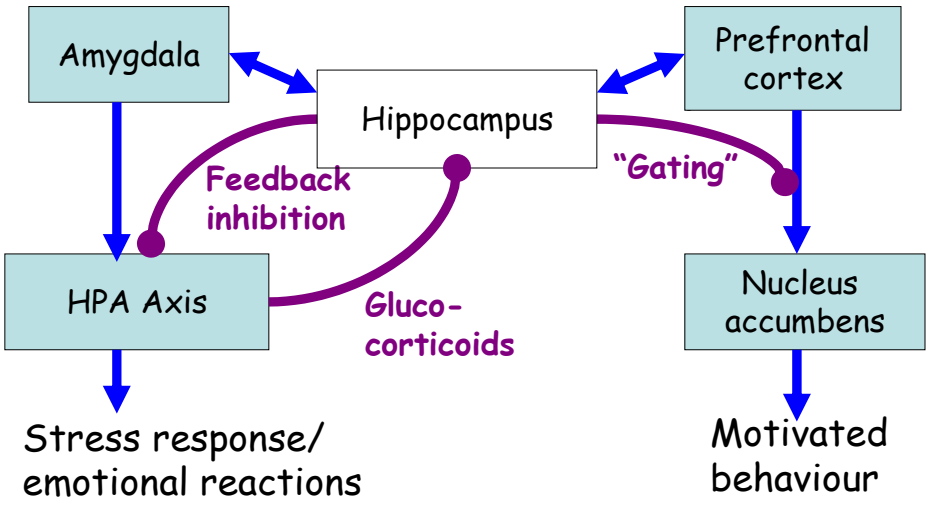

Figure 4: The hippocampus is more than just a memory structure: it modulates the flow of information in neural circuits subserving motivated behaviour and emotional reactions. Neurogenesis in the dentate gyrus is critical for maintaining distinct representations of events, e.g. in contextual fear conditioning. A deficit in neurogenesis may 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.