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Adult hippocampal neurogenesis in depression

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The development of new treatments for depression is predicated upon identification of neural substrates and mechanisms that underlie its etiology and pathophysiology. The heterogeneity of depression indicates that its origin may lie in dysfunction of multiple brain regions. Here we evaluate adult hippocampal neurogenesis as a candidate mechanism for the etiology of depression and as a substrate for antidepressant action. Current evidence indicates that adult hippocampal neurogenesis may not be a major contributor to the development of depression, but may be required for some of the behavioral effects of antidepressants. We next revisit the functional differentiation of the hippocampus along the septo-temporal axis within the context of adult hippocampal neurogenesis and suggest that neurogenesis in the ventral dentate gyrus may be preferentially involved in regulation of emotion. Finally, we speculate on how increased adult hippocampal neurogenesis may modulate dentate gyrus function to confer the behavioral effects of antidepressants.

Hippocampus and depression

Elucidating the neurobiological basis of depression is one of the foremost challenges for today's society. Severe forms of depression affect 2–5% of the US population, and mood disorders impact 7% of the world's population and rank among the top ten causes of disability[1]. The heterogeneity of depression implies that multiple neural substrates and mechanisms contribute to its etiology[2–4]. The development of new treatments is likely to emerge from the identification of etiological mechanisms or of pivotal components of the pathophysiology of depression. This is best exemplified in development of the circuit-specific application of deep brain stimulation to ameliorate treatment-refractory depression[5]. The success of this endeavor relied on the identification of subgenual cingulate (Cg25) as a key neural substrate of the pathophysiology of depression[6–8].

The hippocampus is one of several limbic structures that have been extensively studied in individuals with depression. Magnetic resonance imaging studies have consistently shown a reduction in hippocampal volume, and two meta-analyses have compellingly demonstrated a reduction in hippocampal volume in people with recurrent depression relative to age- and sex-matched controls[9,10]. Moreover, the frequency of depressive episodes and how long the depression remains untreated correlate with the magnitude of reduction in hippocampal volume[11]. Although functional magnetic resonance imaging studies suggesting hippocampal dysfunction in depressed patients are lacking, one study assessed hippocampal function using a virtual-reality spatial memory navigation task and found that depressed subjects performed significantly worse than controls[12]. Altered hippocampal function, in turn, may influence the activity of neural circuitry in the prefrontal cortex, amygdala and nucleus accumbens, structures that receive inputs from the hippocampus and are associated with emotionality[13–17]. Moreover, optimal function of the hippocampal formation is critical for modulation of the hypothalamic-pituitary axis and regulation of the stress response, dysregulation of which is observed in almost half of all depressed patients[18,19]. The neural substrates that underlie the response to antidepressants also include the hippocampus. Positron emission tomography imaging of depressed patients treated with selective serotonin reuptake inhibitors indicates the involvement of corticolimbic circuits[6]. Structures that show changes in metabolic activity include the subgenual cingulate, hippocampus and prefrontal cortex[20,21].

Adult hippocampal neurogenesis and antidepressant action

One of the primary catalysts for focusing on adult hippocampal neurogenesis in depression is the observation that most antidepressants and environmental interventions that confer antidepressant-like behavioral effects stimulate adult hippocampal neurogenesis[22–26]. The time course of maturation of newly generated neurons in the dentate gyrus, which is generally consistent with the delayed onset of therapeutic action of antidepressants[27,28], and the unique physiological properties of adult-born dentate granule neurons qualifies adult hippocampal neurogenesis as a potential mechanism or substrate underlying antidepressant action[27,29–32]. The most compelling evidence linking adult hippocampal neurogenesis with antidepressants comes from our laboratory, in a study demonstrating that neurogenesis is necessary for the effects of imipramine, a tricyclic antidepressant, and fluoxetine, a selective serotonin reuptake inhibitor, in two mouse behavioral screens for antidepressant activity[33]. Two independent studies confirmed these initial findings. In rats, the synthetic cannabinoid HU210 has antidepressant-like behavioral effects that depend on neurogenesis[34]. The behavioral effects of fluoxetine in rats as assessed in the forced-swim test also requires neurogenesis[35]. Taken together, these studies show a requirement for adult hippocampal neurogenesis in mediating the behavioral effects of antidepressants for three different drugs in several tests for antidepressant-like activity.

Given the pleiotropic effects of antidepressants on neural circuitry[36,37], dentate gyrus neurogenesis is one of several mechanisms in the adult brain that antidepressants may harness to exert their behavioral

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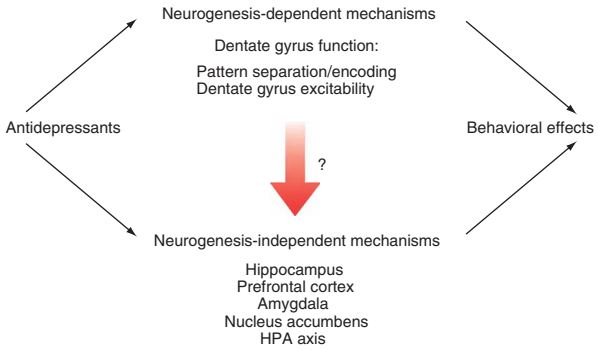

Figure 1 Antidepressants exert their behavioral effects through neurogenesis-dependent and neurogenesis-independent pathways. Increased neurogenesis after chronic antidepressant treatment may influence fundamental properties of the dentate gyrus such as pattern separation as well as dentate gyrus excitability. Antidepressants may also modulate the activity of brain regions downstream of the dentate gyrus such as the prefrontal cortex, nucleus accumbens, amygdala and hypothalamus directly or indirectly through enhancing dentate gyrus function by increasing neurogenesis. HPA, hypothalamic-pituitary-adrenal.

effects. Moreover, studies from our laboratory indicate that the dependence of behavioral effects of antidepressants on neurogenesis may be shaped by several factors, including the genetic make-up of the organism and the nature of the antidepressant (mechanism and site of action)[38]. In a highly anxious strain of mice, BALB/c, anxiolytic and antidepressant-like behavioral effects of chronic fluoxetine treatment are not blocked by ablation of neurogenesis[39]. Furthermore, drug treatment in this strain does not stimulate neural stem cell proliferation in the dentate gyrus. Beneficial effects of environmental enrichment and exercise on learning and on anxiety-like behavior can occur independently of increased adult hippocampal neurogenesis[40]. The anxiolytic and antidepressant-like effects of a melanin-concentrating hormone receptor antagonist do not require neurogenesis[41]. Thus, antidepressants are likely to exert their behavioral effects through neurogenesis-dependent and neurogenesis-independent pathways[37] (**Fig. 1**). A neurogenesis dependence of antidepressants is likely to be influenced by network activity. There is growing evidence documenting the effects of neuronal activity on the proliferation of neural stem cells and the maturation and integration of adult-born dentate gyrus neurons[42–46]. The plasticity and excitability of adult-born neurons are sensitive to the properties of the hippocampal network. Pilocarpine-induced seizures cause accelerated maturation of new neurons[47], whereas status epilepticus induced by stimulation of the ventral hippocampus causes reduced excitatory synaptic input and increased inhibitory drive in new neurons[48]. Thus, the effects of network activity on the physiological properties of new neurons are diverse, and homeostatic mechanisms ensure that the integration of new neurons in the adult dentate gyrus occurs in tune with the network's needs. Similarly, we propose that the neurogenesis dependence of antidepressants is intimately related to the properties of the hippocampal network, which in turn is shaped by genetic and environmental factors.

Identifying components of biological contexts that are conducive to a neurogenic dependence warrants further investigation. Is increasing the number of new neurons in the dentate gyrus sufficient to confer some of the behavioral effects of antidepressants? The development of noninvasive inducible genetic strategies that specifically target new neurons in the dentate gyrus will allow researchers to test this hypothesis and facilitate dissection of the interplay between adult hippocampal neurogenesis and network activity. Newly generated neurons receive excitatory inputs and show a lower threshold for LTP induction as early as 18 days after birth[27,29] but show enhanced long term potentiation at 4–6 weeks after birth[30]; this begs resolution of the age at which adult-born neurons are substrates for the behavioral effects of antidepressants.

Adult hippocampal neurogenesis and etiology of depression

The possibility that adult-born neurons are required for some of the behavioral effects of antidepressants and the well documented deleterious effects of stress on adult hippocampal neurogenesis has fueled investigation into whether impaired adult neurogenesis is an etiological factor for depression[49,50]. At the structural level, it is highly unlikely that changes in adult hippocampal neurogenesis account for the reduction in hippocampal volume in patients with depression. Stereological analysis of hippocampal volume in irradiated mice did not show a significant reduction[33]. Pathohistological studies of postmortem tissue indicate that changes in neuropil and glial cell number may be responsible for reductions in hippocampal volume[51], as do studies documenting the effects of stress on hippocampal white matter. Preclinical studies show that volumetric changes result from reduced dendritic complexity and not from ablation of hippocampal neurogenesis[33,52]. More evidence undermining a role for neurogenesis in the etiology of depression comes from studies showing that ablation of neurogenesis does not elicit a depression-like or anxiety-like phenotype[33,35]. Blocking hippocampal neurogenesis does not influence anxiety-related behavior as assessed in conflict-based tests, such as the open field, light-dark choice test, and elevated plus-maze[53], or in anxiety tests that are also used to screen for antidepressant activity, such as novelty-suppressed feeding[33,40]. Furthermore, mice lacking adult hippocampal neurogenesis do not show increased susceptibility to the effects of chronic stress as assessed by grooming response[33] or depressed-like behavior in the forced-swim test[35,39]. One apparent shortcoming of these studies is that they rely on wild-type animals and assess the effects of ablating neurogenesis independent of changes in network properties. It could be that reductions in neurogenesis when combined with a genetic predisposition or an environmental insult result in pathophysiology in adulthood. Alternatively, it may be more pertinent to ask whether altered dentate gyrus development—that is, neurogenesis during the early postnatal period when the dentate gyrus develops, rather than adult hippocampal neurogenesis—is causally related to the depression-like behaviors in animal models.

Adult hippocampal neurogenesis and cognition

Deficits in adult hippocampal neurogenesis may underlie the cognitive deficits seen in depression. Work from our laboratory and others' using animal models in which adult hippocampal neurogenesis is ablated or blocked has shown that new neurons are required for some forms of hippocampus-dependent learning. Reducing or blocking hippocampal neurogenesis in rats or mice affects hippocampus-dependent forms of fear conditioning[53–55], long-term spatial memory[56] and working memory[55,57]. In addition, several models have been proposed for how neurogenesis influences the structure and function of the dentate gyrus[58–63]. Much remains to be done to understand how blocking adult hippocampal neurogenesis relates to the deficits observed in these different behavioral paradigms. Current data imply roles for adult-born neurons in encoding and storing memory. Noninvasive genetic approaches that confer reversible manipulation of adult-born neurons are needed to replicate these findings and resolve the inconsistencies that are due to limitations of existing methodologies used to arrest neurogenesis[53–55,64]. The flexibility of inducible genetic approaches will also allow researchers to assess the contribution of new neurons to

different stages of learning such as acquisition, consolidation and retrieval.

The study of adult hippocampal neurogenesis in depressed patients is still in its infancy and has relied primarily on histological examination of postmortem tissue. The only study to date did not detect a difference in proliferation of stem cells in the hippocampus of depressed patients[65]. Although notable, the study is limited in power and confounded by the effects of medication (12 of 15 patients were on medication at time of death) that may mask small differences in proliferation. More importantly, given the built-in homeostatic mechanisms that act at each stage of progression from stem cell to mature neuron, it is very difficult to extrapolate from analysis of one stage alone[66] (A.S. and R.H., unpublished results). A more informative parameter is whether the number of newly generated young neurons is altered in patients with depression and after antidepressant treatment. Just as important as inspection of adult hippocampal neurogenesis is assessment of the integrity of the dentate gyrus in depressed patients. Histological analysis of the dentate gyrus of depressed patients shows a significant increase in packing density of dentate granule cells and a trend toward a reduction in soma size[67]. More studies with greater power and inclusion of postmortem tissue of unmedicated depressed patients are needed to follow up on these findings.

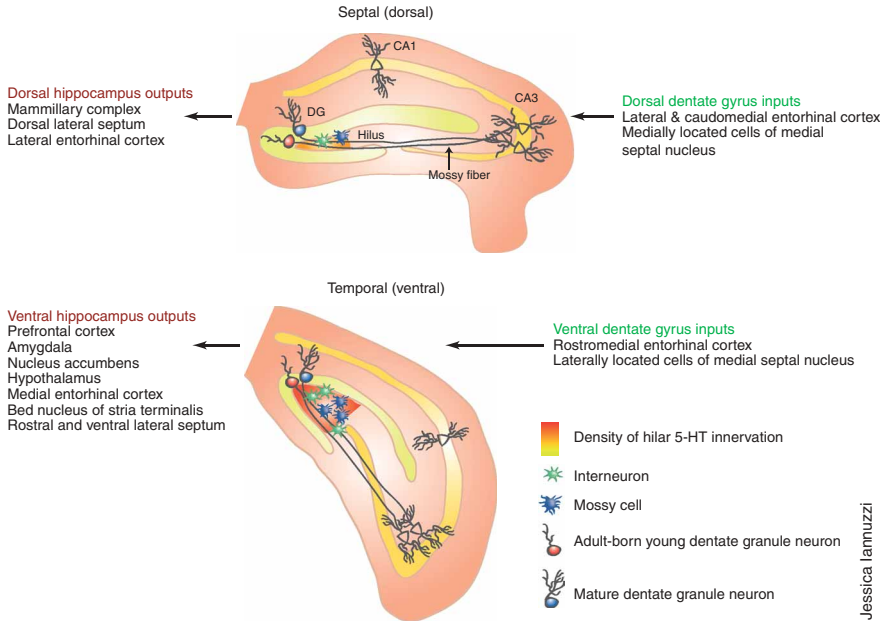

Figure 2 Distinct roles for dorsal and ventral hippocampal neurogenesis in regulation of emotion. The schematic illustrates the differences in afferent and efferent connectivity of the hippocampus along the longitudinal (septo-temporal) axis. Also shown here is the asymmetry in numbers of mossy cells and hilar interneurons and enriched innervation of the ventral hilus by serotonergic projections (see text for references). By virtue of this asymmetry in hippocampal connectivity, neurogenesis in the ventral dentate gyrus may have a distinct role in regulation of emotion from that of neurogenesis in the dorsal dentate gyrus.

In conclusion and caveats notwithstanding, the evidence to date indicates that hippocampal neurogenesis may be involved in the treatment of depression but not in its etiology. This could mean that adult hippocampal neurogenesis is a process that lies downstream of the locus or mechanisms involved in the development of depression. How adult hippocampal neurogenesis contributes to the regulation of emotion is an open question. One approach to studying this problem is to ask whether new neurons may serve distinct roles along the septo-temporal axis along which functional differentiation of the hippocampus is observed. We revisit this concept in the context of adult hippocampal neurogenesis in the next section.

Adult hippocampal neurogenesis along the longitudinal axis

The changing afferent and efferent connectivity of the hippocampus along the longitudinal axis found in early anatomical studies in rodents and primates first implied discrete functions for the dorsal (septal pole) and the ventral (temporal pole) hippocampus in learning and emotionality, respectively (see ref. 13 for a review). In rodents, the septal half of the dentate gyrus receives projections arising in the lateral and caudomedial portion of the entorhinal cortex, whereas the temporal pole of the dentate gyrus receives inputs from the most rostromedial region of the entorhinal cortex[68–70]. Functionally, this topographic pattern of innervation translates into highly processed visuo-spatial sensory information entering the dorsal dentate gyrus, unlike olfactory inputs, which appear to distribute evenly along the septo-temporal axis[70–72]. Mirroring the segregation of dentate gyrus afferents along the septo-temporal axis is the pattern of hippocampal outputs to the rest of the brain. The ventral hippocampus, unlike the dorsal hippocampus, sends projections to the prefrontal cortex[73,74]. In addition, there are strong connections of the ventral hippocampus to the amygdala, shell of nucleus accumbens, bed nucleus of stria terminalis, and structures associated with the hypothalamic-pituitary-adrenal axis[70,75–78] (**Fig. 2**).

Differences in the constituent cell types and intrinsic connectivity of the hippocampus along the septo-temporal axis distinguish the dorsal and ventral hippocampus even further. Notably, select classes of interneurons and the mossy cells, which give rise to the commissural-associational system, are more enriched in the ventral hilus[79–81]. The function of hilar mossy cells and interneurons is, in turn, modulated by dopaminergic, noradrenergic and serotonergic inputs, which also show a ventral hippocampal bias in their innervation. The innervation density of serotonergic projections, for example, varies markedly, from the very dense serotonergic plexuses in the ventral hippocampus to the weak innervation seen in the dorsal part[82–84] (**Fig. 2**).

Lesion studies in animals substantiate the dissociation between the dorsal and ventral hippocampus in learning and emotion[13]. Lesions of the dorsal hippocampus affect spatial learning and memory[85,86], whereas those of the ventral hippocampus affect anxiety and have no effect on spatial learning[87–89]. Electrophysiological evidence indicates that the ventral hippocampus may modulate dopaminergic transmission in the prefrontal cortex and nucleus accumbens[14,17,90]. In addition, the dorsal and ventral hippocampus show distinct patterns of gene expression, indicating a molecular heterogeneity along the septo-temporal axis as well[91].

Given the differences in hippocampal circuitry and functions along the septo-temporal axis, it is reasonable to suspect that neurogenesis in the dorsal and ventral dentate gyrus may contribute differentially to learning and regulation of emotion. Indeed, two recent studies indicate that antidepressants may exert their behavioral effects by increasing neurogenesis in the ventral dentate gyrus. One study showed that chronic treatment with agomelatine, an antidepressant that is a

melatonin agonist and a 5-HT_{2C} serotonin receptor antagonist, increases neurogenesis only in the ventral dentate gyrus[92]. A second study reported differential effects of chronic mild stress on dorsal and ventral dentate gyrus proliferation[93]. Specifically, exposure to chronic mild stress resulted in decreased cell proliferation in the ventral, but not dorsal, hippocampus. Furthermore, the authors showed a correlation between a behavioral response to escitalopram following chronic mild stress and increased proliferation in the ventral DG. It is possible that the asymmetry in serotonergic innervation, mossy cells and hilar interneurons may contribute to these differential effects of antidepressants on dentate gyrus neurogenesis. Although correlative, these observations warrant a direct assessment of the contribution of ventral hippocampal neurogenesis to the antidepressant response.

Concluding remarks

Based on current evidence, the neurogenic hypothesis for depression[94] warrants revision in that adult hippocampal neurogenesis is more likely a substrate for the behavioral effects of antidepressants than a pivotal contributor to the etiology of depression. That said, there is much ground to traverse before adult hippocampal neurogenesis qualifies as a bona fide target for therapeutic intervention.

First, we need to understand how increasing the number of young dentate granule neurons or modifying their properties confers antidepressant-like behavioral responses. As stated earlier, the increase in number of young dentate granule cells seen after chronic antidepressant treatment is likely to be accompanied by changes in network activity. Using gain-of-function approaches that selectively enhance distinct components of adult hippocampal neurogenesis, we can study the relationship between network activity and dentate gyrus neurogenesis and their contributions to the behavioral effects of antidepressants. One potential mechanism by which the antidepressant-dependent increase in newly generated neurons may modulate dentate gyrus function is by enhancing the decorrelation of entorhinal cortical inputs to form discrete representations in memory (pattern separation) (**Fig. 1**)[95–99]. A first step toward answering this question is to understand how adult hippocampal neurogenesis influences pattern separation in the dentate gyrus, whether through replacement of older neurons, net addition of young and more plastic units, or insertion of new neurons with specific biochemical and physiological properties related to the animal's experience. Recordings from the dentate gyrus in awake behaving animals in which neurogenesis is selectively and bidirectionally modulated, combined with visualizing dentate gyrus activity with immediate-early genes, will shed light on how neurogenesis contributes to basic processes that underlie pattern separation, such as sparse activation of dentate granule cells and decorrelation of firing rate distribution of individual dentate granule cells. It is also plausible that newly generated neurons, in addition to serving as substrates for encoding, may facilitate encoding by modulating the properties of mature dentate granule cells such as excitability (**Fig. 1**). Such a non–cell-autonomous requirement for new neurons is supported by the finding that the global increase in activity in the dentate gyrus observed after antidepressant treatment depends on neurogenesis[35]. Our understanding of the precise contribution of ventral hippocampal neurogenesis to the behavioral effects of antidepressants will benefit from a circuit-based approach that integrates the role of monoaminergic hilar afferents and hilar targets of newly generated granule cells such as mossy cells and interneurons (**Fig. 2**). Another outstanding issue is the nature of changes in circuitry downstream of the dentate gyrus. Specifically, when adult hippocampal neurogenesis is enhanced, what are the consequences for neural activity in structures that receive efferents arising in the dorsal and ventral hippocampus? Experiments addressing this issue will inform us on how enhancement of dentate gyrus function after antidepressant treatment translates into changes in the other hippocampal subfields as well as in downstream structures associated with depression, such as the prefrontal cortex, nucleus accumbens, amygdala and hypothalamus.

As much as preclinical models are indispensable instruments for establishing causality, the translation of findings from animal models to humans requires validation in depressed individuals of core concepts gleaned from animal studies. In primates, although the evidence is preliminary, some antidepressant-like treatments can stimulate adult hippocampal neurogenesis[23]. We still do not know whether dentate gyrus function is altered in human patients with depression and after antidepressant treatment. The development of imaging techniques to visualize or follow adult hippocampal neurogenesis is crucial to this endeavor[100]. It also remains to be seen whether depressed patients show deficits in dentate gyrus functions, such as pattern separation.

In conclusion, the study of adult hippocampal neurogenesis in depression has benefited tremendously from the scrutiny and attention it has received. Ultimately, parallel studies in animal models and humans will determine the value of adult hippocampal neurogenesis as a target for the treatment of depression.

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COMPETING INTERESTS STATEMENT

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/natureneuroscience/.

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