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# Depression and Hippocampal Neurogenesis: A Road to Remission?

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## Abstract

Adult-generated hippocampal neurons are required for mood control and antidepressant efficacy, raising hopes that someday we can harness the power of new neurons to treat mood disorders such as depression. However, conflicting findings from preclinical research – involving stress, depression, and neurogenesis – highlight the complexity of considering neurogenesis as a "road to remission" from depression. To reconcile differences in the literature, we introduce the "neurogenic interactome", a platform from which to consider the diverse and dynamic factors regulating neurogenesis. We propose consideration of the varying perspectives – system, region, and local regulation of neurogenesis – offered by the interactome and exchange of ideas between the fields of learning/memory and mood disorder research to clarify the role of neurogenesis in the etiology and treatment of depression.

Major depressive disorder is a leading cause of disability worldwide (1). There is great need for improved understanding of both the pathophysiology of depression and the neuromechanisms of antidepressant therapeutics. One relatively novel and but prevalent area of research focuses on "the neurogenic hypothesis of depression". As one index of its relevance, PubMed citations related to this hypothesis (search terms "neurogenesis" and "depression") increased 14-fold from when it was first introduced (1999–2001, 21 citations) to 2011 (2009–2011, 309 citations). How did this hypothesis gain traction so quickly? And more importantly, after a decade of research, does the neurogenesis hypothesis of depression still hold promise for paving a "road to remission" from depression?

In it's simplest form, the neurogenic hypothesis of depression states that new neurons in the adult brain are needed for proper mood control and for antidepressant efficacy (2). Once a controversial phenomenon, the generation of new neurons in discrete regions of the adult brain of most mammals – including humans – has been repeatedly confirmed using modern techniques (3). One of these "neurogenic niches", the subgranular zone of the dentate gyrus (Fig. 1A–C), lies within the hippocampus. As the hippocampus is a brain region involved in memory and mood control, the discovery of adult neurogenesis launched two parallel investigations into its functional roles in memory and mood control (2, 3). The neurogenic hypothesis of depression quickly became popular due to a wealth of correlative studies. Humans with depression had decreased hippocampal volume (4, 5); decreased neurogenesis could lead to a smaller hippocampus. In laboratory animals, antidepressants enhanced hippocampal neurogenesis, and did so with a "lag time" similar to that of the delay between antidepressant administration and clinical efficacy in humans (6), reflecting the time of neuronal maturation in the adult hippocampus (3). In non-human primates, stress – a predisposing factor to depression in humans – decreased neurogenesis, and neurogenesis levels were normalized by antidepressants (7). These and many other studies gave the

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neurogenic hypothesis of depression its initial robust trajectory (2): adult-generated hippocampal neurons are needed for proper mood control (Fig. 1D) and for antidepressant efficacy (Fig. 1E). Eventually, such studies paved the way for causative research showing ablation of hippocampal neurogenesis in mice indeed impairs antidepressant efficacy (8).

The neurogenic hypothesis of depression jump-started the field in regards to publications and ideas, but conflicting results have raised red flags about its validity. In laboratory animals, ablation of neurogenesis does not always cause depressive-like symptoms (9), stress does not always decrease neurogenesis (10), and some effects of antidepressants are neurogenesis-independent (11). Clinically, people with mood disorders have hippocampal dysfunction and altered stress response, but these might be predisposing rather than causative factors in depression (1, 4). Also, while neurogenesis clearly persists in the adult human hippocampus (12, 13), the levels are so low relative to laboratory animals that questions have been raised about whether alterations in neurogenesis could result in a functional change (either positive or negative) in affect or memory.

Do these findings spell the end of the road for the neurogenic hypothesis of depression? From our perspective, they do not. We propose that differences in the literature can be accounted for by considering the diverse and dynamic factors regulating neurogenesis, using a model we refer to as “neurogenic interactome” (Fig. 1F). The neurogenic interactome consists of key endocrine and neurochemical signaling cascades and reciprocal connections among brain regions that control adult neurogenesis, and their major downstream influences on behavior. Below we briefly show how evaluation of three elements in our model – interplay of different brain structures, the diverse functions of the hippocampus, and the heterogeneous components of the neurogenic niche – reconcile apparent discrepancies in the neurogenic hypothesis of depression, and lay a roadmap for future research.

First, the neurogenic interactome highlights the importance of input connections to hippocampus in regulation of adult neurogenesis. Anatomical connections among the hippocampus, dentate gyrus, and brain regions important for stress and fear/emotional memory (4) help to explain the involvement of adult-generated neurons in stress and depression (Fig. 1B,F). The hypothalamic-pituitary-adrenal (HPA) axis and stress hormones have long been known to influence adult neurogenesis (2). Recently, it was shown that adult neurogenesis reciprocally regulates the HPA axis, buffering the stress response (14). This ability of new neurons to “put the brakes” on the stress response appears significant in times of moderate to extreme or unpredictable stress (14–16), but not as important under normal conditions or mild or predictable stress (9), and may be imposed by direct regulation of the hypothalamus. While this connection is yet to be experimentally tested, it is known that inactivation of the amygdala, a limbic system involved in emotional memory, suppresses hippocampal neurogenesis (17). Thus, stimulation of the amygdala under specific conditions (such as predictable mild stress (18)) may directly upregulate adult neurogenesis.

Consideration of the involvement of stress and the connections in the neurogenic interactome may also help to explain the apparent impression from the literature that certain behavioral tests are neurogenesis-dependent while others are not, and why many effects of antidepressants are neurogenesis-independent (2, 11). Different behavioral tests for depression and anxiety induce different levels of stress and/or fear, and thus activate different subsystems of the neurogenic interactome (Fig. 1F). This secondarily can modulate the behavioral output of these subsystems (1), and also influence adult neurogenesis and neurogenesis-dependent behavior (Fig. 1F). Finally, while it is clear that unpredictable stress and stimulation of the stress axis decrease neurogenesis and can lead to depression (2), these connections explain why it is not inevitable that “stress decreases neurogenesis” (9, 14–16, 18). Rather, coping with stressful events requires neurogenesis, and predictable stress may

be beneficial for both neurogenesis and mood control (16, 18). The learned ability to inhibit fear and to cope with stress serves as a "behavioral antidepressant", which correlates with upregulated neurogenesis (16, 19). These preclinical findings map well with studies in human as well as non-human primates (12, 15, 16). Interestingly, there are similarities between endogenous stress coping strategies and the neuromechanism of antidepressants (20, 21). This suggests that antidepressants may exploit the same neural substrates as behavioral modifications. Mechanistically, the unique contribution of adult-generated neurons to hippocampal function during psychosocial stress or when the "road gets rough" is in part due to the unique physiological characteristics and anatomical connections of these neurons (3).

Second, the neurogenic interactome underscores that the control of hippocampal neurogenesis over mood and memory maybe be more interrelated than previously appreciated. Adult-generated hippocampal neurons provide a type of neuronal plasticity – pattern separation – that allows acquisition and separation of closely-spaced memories (22, 23). This is in contrast with embryonic-generated hippocampal neurons that are necessary for pattern completion and recall of memories (23). There is a clear connection between adult neurogenesis, pattern separation, and learning/memory; for example, diminished neurogenesis decreases pattern separation and learning/memory, while enhanced neurogenesis improves them (2, 22, 23). However, it is unclear how adult neurogenesis controls pattern separation and concurrently influences mood, and vice versa (Fig. 1F). Pattern separation may not only be important for learning/memory but also for recognizing dangerous and stressful signals, such as cue recognition during conflict or stress, thus triggering or aggravating anhedonic or depressive behavior (24). Interestingly, mice with stress-induced social avoidance have increased adult neurogenesis (10), suggesting they may have a better ability to discern or remember harmful signals. Prevention of this increased neurogenesis diminishes social avoidance (10), which can be interpreted as inability to cope with a stressor. Pattern separation deserves evaluation not only for its involvement in spatial learning and memory, but also in the development or persistence of mood disorders, as recognizing stressors or danger shares similar substrates with learning and memory (Fig. 1F). As strong and unpredictable stress decreases adult neurogenesis, the cognitive functions dependent on pattern separation will be impaired, only worsening the ability to recognize and cope with further incoming stressful events and situation, thus creating a vicious cycle.

Third, while not depicted in this interactome schematic (Fig. 1F), the heterogenous components of the neurogenic niche play key roles in determining the ultimate influence of adult neurogenesis on behavior and response to antidepressants. Adult-generated neurons are critical for dentate gyrus-related behavioral output and the neurobehavioral effects of antidepressants (2, 3). Despite their small number, they have a disproportionate influence on hippocampal circuitry and behavior (3), underscoring that the dentate gyrus is "not a democracy". However, other components of the niche – such as vasculature, astrocytes, and microglia (3) – regulate neurogenesis and respond to antidepressants, even in the human hippocampus (12). Aside from niche components, stem and progenitor cells should also be considered for their contribution to neurogenic control and mood regulation. They do not make or receive traditional neuronal synapses or connections, and have previously been considered passive participants in the neurogenic niche. However, we now know that stem and progenitor cells provide structural, biochemical, and metabolic signals to the niche that can regulate neurogenesis (3). Thus, we have to investigate how each individual component of the niche is influenced by potential antidepressants, and consider components of the niche themselves as specific targets for novel antidepressant therapeutics.

The neurogenic hypothesis of mood disorders remains promising for conceptualizing depression mechanisms, which may lead to novel avenues for treatments. However, more

work needs to be done. The typically parallel lines of research on memory and mood should be merged to evaluate, for example, whether enhanced pattern separation enhances stress coping and levels of neurogenesis in laboratory animals (19, 23). Other preclinical experiments are needed to fine-tune the neurogenic interactome, assessing whether stimulation of the amygdala enhances neurogenesis, and whether other brain regions involved in depression – like the nucleus accumbens – are also influenced by levels of neurogenesis. Clinically, we need more information on the level and regulation of human neurogenesis, particularly in the brains of depressed humans (12). Interestingly, neurogenesis decreases with age in humans and animals (13, 25), while depression prevalence increases with age. More research is warranted to examine to what extent the age-induced increase in depression is due to life experience, age-induced increase in medical burden, or possibly age-induced decrease in neurogenesis (4, 5, 12, 25). Also, while *in vivo* imaging of correlates of human neurogenesis is feasible (25, 26), greater technical advances are needed before we can conclude what aspects of neurogenesis structure and function are shared between humans and laboratory animals. While standard assessment of human neurogenesis *in* vivo is many years away, a destination on the road to remission for people with mood disorders may eventually be customized diagnostic evaluation that takes into account their individual levels of adult neurogenesis.

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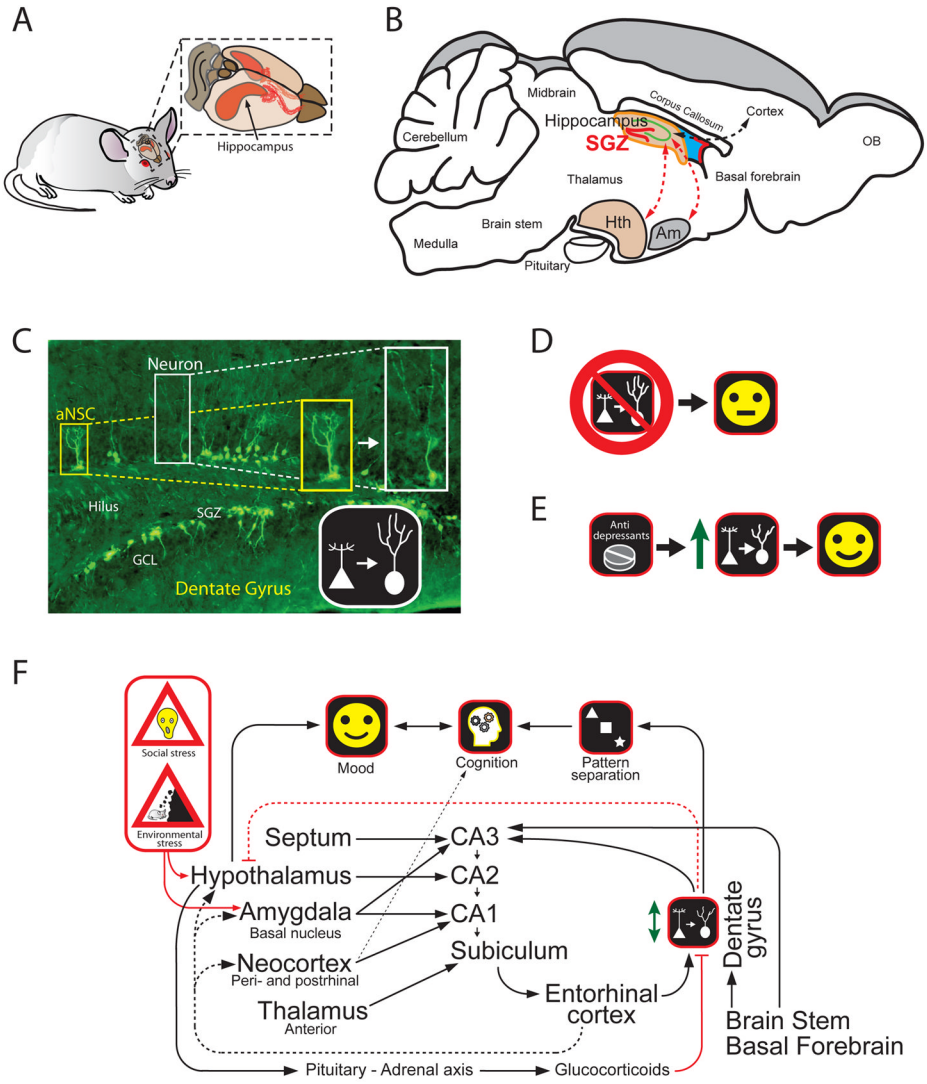


**Figure 1. Adult hippocampal neurogenesis in depression**

(**A**) Neurogenic niches in the mouse brain (inset, red) generate neurons throughout life. (**B**) The hippocampus interacts with other major brain regions (e.g. Hypothalamus, Hypo; Amygdala, Amyg; dotted lines) to contribute to brain functions like memory and mood. The hippocampal dentate gyrus hosts one neurogenic niche, the subgranular zone (SGZ; red). (**C**) Photomicrograph of the SGZ in a transgenic mouse depicts the process of neurogenesis, beginning with an adult neural stem cell (aNSC; yellow frame) and ending with a dentate gyrus neuron (white frame) that fully integrates into the granule cell layer (GCL). Neurogenesis is a process, not a timepoint (2), a message emphasized in the “road sign” that condenses the journey from NSC to GCL neuron. (**D, E**) The two branches of the neurogenic hypothesis of depression. The first branch proposes ablation of adult neurogenesis does not greatly influence mood under normal, non-stressful conditions (**E**). The second branch proposes antidepressants may confer their effects on improving mood via upregulating adult neurogenesis. (**F**) The “neurogenic interactome”. Both direct and indirect anatomical connections (solid and dashed black lines, respectively) influence adult neurogenesis in a dynamic manner (doubleheaded green line). Alterations in neurogenesis reciprocally influence the connecting regions (dashed black line). For example, intact neurogenesis inhibits the hypothalamus (dashed red line) and the “stress axis”, including the

HPA axis, thus contributing to mood control. In contrast, during stress, the HPA axis and limbic system are activated (solid red lines). This influences both levels of neurogenesis and the reliance of key brain functions – like cognition and mood – on adult-generated hippocampal neurons. Thus, the stress experience (length, duration, type) influences the importance of adult-generated neurons in buffering the stress response. Moreover, involvement of adult-generated neurons in pattern separation and thus cognition can protect against depression by improving recognition and coping with stressors. The two major functions of adult-generated hippocampal neurons – mood/stress control and learning/cognition – help explain the involvement of adult neurogenesis in etiology of depression-like phenotype, and in designing novel antidepressants.