Published in final edited form as:
Curr Opin Neurobiol. 2015 February ; 0: 51–58. doi:10.1016/j.conb.2014.08.012.

THE CURRENT STATE OF THE NEUROGENIC THEORY OF DEPRESSION AND ANXIETY

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Abstract

Newborn neurons are continuously added to the adult hippocampus. Early studies found that adult neurogenesis is impaired in models of depression and anxiety and accelerated by antidepressant treatment. This led to the theory that depression results from impaired adult neurogenesis and restoration of adult neurogenesis leads to recovery. Follow up studies yielded a complex body of often inconsistent results, and the veracity of this theory is uncertain. We propose five criteria for acceptance of this theory, we review the recent evidence for each criterion, and we draw the following conclusions: Diverse animal models of depression and anxiety have impaired neurogenesis. Neurogenesis is consistently boosted by antidepressants in animal models only when animals are stressed. Ablation of neurogenesis in animal models impairs cognitive functions relevant to depression, but only a minority of studies find that ablation causes depression or anxiety. Recent human neuroimaging and postmortem studies are consistent with the neurogenic theory, but they are indirect. Finally, a novel drug developed based on the neurogenic theory is promising in animal models.

Introduction

Within each adult human hippocampal dentate gyrus, approximately 700 newborn granule cells are added daily [1]. First formally proposed in 2000, the neurogenic theory of depression posits that impaired adult hippocampal neurogenesis (AHN) triggers depression and restoration of AHN leads to recovery [2]. This speculative theory initially rested several correlations between depression and AHN: depressed patients on average have smaller hippocampi (reviewed in [3]), elevation of glucocorticoids can trigger depression and impair AHN [4], and serotonergic agents used to treat depression can boost AHN [5]. Major

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depression is more often than not accompanied by an anxiety disorder [6], and the neurogenic theory has been extended to anxiety disorders because stress and glucocorticoid dysregulation also induce anxiety, and serotonergic agents are also effective for anxiety disorders [7].

The neurogenic theory is mechanistically plausible, as adult born neurons are added to the ventral dentate gyrus, a key regulator of mood and anxiety [8]. Furthermore, adult born hippocampal neurons are required for efficient pattern separation and cognitive flexibility in rodents – cognitive functions that can be impaired in patients with depression and anxiety disorders [7,9]. Finally, as detailed throughout this review, AHN is required for some effects of antidepressants in animal models [10].

While speculative, this theory is exciting because the pathophysiology of depression and anxiety is poorly understood and the theory may lead to neurogenesis targeted treatments. New treatments are sorely needed as depression is the second leading cause of disability worldwide by some measures [11], depression persists in approximately 70% of patients after first-line treatment, and at least 30% of patients remain depressed even after exhaustively proceeding through four rounds of distinct treatments [12].

Mood and anxiety disorders are highly heterogeneous and any one theory of their pathophysiology or treatment will not capture their complexity. However, the neurogenic theory may help to subcategorize these disorders and guide treatment.

In this review, we propose five criteria for the acceptance of the neurogenic theory of depression and anxiety (Table 1). We organize evidence for each criterion by species. Each of these criteria should be met in human studies before fully accepting the theory. We take stock of the current evidence for each criterion, with a focus on recent studies, and we propose future studies. We contend that addressing the fifth criterion – namely, that boosting neurogenesis is sufficient to alleviate depression or anxiety – is essential as the viability of neurogenesis based treatments rests on this.

Evidence that AHN is altered in depression and anxiety

If impaired AHN triggers depression or anxiety, then AHN should be impaired in animal models and depressed and anxious patients.

Rodent models

Independent groups found that AHN is impaired in some rodent models of depression and anxiety. Many chronic stressors cause depression and anxiety-like behaviors in rodents and result in impaired AHN. These include repeat restraint stress [13], chronic unpredictable mild stress [14], social defeat stress [15], social isolation [16], and corticosterone administration [4]. Thus, AHN is impaired in multiple rodent chronic stress models of depression and anxiety.

A recent study challenged this. Hanson et al. subjected rats to a battery of severe chronic stress paradigms and found no change in neurogenesis [17]. The authors called into question whether chronic stress impairs neurogenesis. While their paradigms were highly stressful,

the authors did not determine if their stressors in fact induced depression and anxiety-like behaviors. Thus, it is unclear if their interventions are models of depression or anxiety. It raises the interesting possibility that chronic stress impairs AHN only in cases that animals also begin to show depression and anxiety-like behaviors.

AHN is also impaired in other rodent models of depression and anxiety. For instance, rodent models of hypothyroidism, a cause of depression in humans, show both depression-like behaviors and reduced AHN [18]. In a model of childhood neglect, a risk factor for mood and anxiety disorders, young rats separated from their mothers have both increased anxiety in adulthood [19] and decreased AHN [20].

Non-human primate

Social stress in non-human primates induces depressive and anxiety-like behaviors [21]. AHN is impaired in multiple models of social stress including intruder stress in marmosets [22], social isolation in bonnet monkeys [21], and in socially subordinate baboons [23].

Human

Measurement of AHN in humans is currently limited to postmortem brains. To measure AHN directly, one must birthdate neurons, for instance using radiocarbon birthdating [24]. No published studies have directly measured AHN in postmortem brains of depressed or anxious patients. As a surrogate of AHN, three independent groups counted the total number of dentate gyrus neural progenitor cells. The first group found no difference between brains from control and depressed subjects [25], the second found a non-significant trend towards a decrease in progenitor cells in depressed patients [26], and the third group, using a different progenitor cell marker, found a significant decrease in progenitor cells in depressed patients [27]. Thus, human postmortem studies of progenitor cell numbers are inconsistent. This may be due to the limited power of these small studies.

However, both postmortem and high-resolution MRI volumetric studies consistently show smaller dentate gyrus size in patients with depression or anxiety disorders [28–30]. While many forms of structural plasticity likely contribute to smaller dentate gyrus size, postmortem studies show a decrease in dentate gyrus granule cell numbers [28]. This may reflect impairment in AHN after the progenitor phase – for instance, in the differentiation or survival of adult born neurons. Alternatively, it may reflect a developmental defect or the degeneration of neurons born during early development. Consistent with a depression-related structural plasticity in adulthood, rather than a developmental defect, a recent longitudinal MRI study of major depression found that patients in the midst of a major depressive episode had smaller hippocampi than patients with remitted major depression [31]. The extent to which this is due to changes in AHN or other forms of structural plasticity remains to be determined.

Another indirect approach to assess impaired AHN in clinical populations is to determine if the cognitive dysfunction induced by ablation of AHN in rodent models is also present in patients. Pattern separation, the ability to distinguish between similar but distinct stimuli, is impaired after ablation of AHN in rodents, and this leads to over-generalization across stimuli [32]. In humans, over-generalization is a hallmark of many anxiety disorders and this

may reflect impaired AHN [7]. More recent human studies found a correlation between depression scores and poor pattern separation [33,34]. This result was replicated and extended in subsequent human studies showing that high depression scores correlate with poor pattern separation among neutral stimuli, and with enhanced pattern separation among emotionally negative stimuli [9]. This enhanced attunement to emotionally negative stimuli correlated with decreased activity in the dentate gyrus and increased activity in the amygdala [35]. While speculative, this may represent a shift from AHN dependent hippocampal processing to amygdala driven processing of negative stimuli in depressed subjects.

Conclusions and future directions

AHN is impaired in diverse models of depression and anxiety rodents and after social stress in primates. In humans, current postmortem studies are inconclusive. Smaller dentate gyrus in depression and anxiety disorders on MRI is suggestive of impaired AHN but it is non-specific and may be due to other forms of structural plasticity. Similarly, the correlation between depression scores and abnormal pattern separation in humans suggests a defect in AHN but is indirect.

Whether AHN is impaired in depression or anxiety will remain an open question until AHN is measured directly in clinical samples. Non-invasive measurements of AHN in humans, for instance using SPECT or MRI, would be ideal for making this link. Such techniques are in development but are not yet validated [36–38]. Alternatively, rates of AHN could be measured directly in postmortem brains from patients with depression and anxiety– a technique applied successfully in non-clinical samples [1].

Evidence that impaired AHN is sufficient to induce depression or anxiety

Impaired AHN is just one of many structural hippocampal changes that correlate with depression and anxiety. It is unclear if impaired AHN can cause depression and anxiety, or if it is a barometer of general dentate gyrus dysfunction.

Rodent

As thoroughly reviewed elsewhere [39], many studies have tested if ablating AHN in mice increases depression or anxiety-like behaviors. Most studies show no effect on baseline depression or anxiety-like behaviors after ablating AHN. However, one study found heightened baseline anxiety behavior after AHN ablation [40]. A second study found no effect on baseline behaviors, consistent with many other studies, but found that after an acute moderate stressor, mice with ablated AHN had significantly increased depression and anxiety-like behavior compared to mice with intact AHN [41]. Consistent with prior results [42], mice with ablated AHN also had an increased corticosterone spike after acute stress. Hence, adult born neurons may dampen both the behavioral and hormonal responses to acute stressors.

While it is debatable if impaired AHN can induce depression or anxiety in rodents, it is well established that ablation of AHN in rodents impairs cognition. This is directly relevant to human depression and anxiety, as impaired cognition can count towards a diagnosis of many of the classified affective and anxiety disorders in the DSM-5 [43]. Notably, ablation of

AHN is sufficient to impair pattern separation and cognitive flexibility – cognitive functions relevant to depression and anxiety [32,44].

Non-human primate

To our knowledge, there are no studies directly testing in non-human primates if ablation of AHN leads to increased depression and anxiety-like behaviors.

Human

In humans, many cancer therapies impair the survival of dividing cells indiscriminately and likely ablate AHN [45]. Following cancer treatment, patients often have impairment in hippocampus dependent memory, and depression and anxiety is common among patients undergoing treatment for cancer [45,46]. These effects following cancer treatments may be due to impaired AHN, but there are clearly too many confounding factors to draw a causal link.

Conclusions and future directions

Ablation of AHN in rodents is sufficient to impair cognitive functions that are relevant to depression and anxiety. Furthermore, ablation of AHN in rodents may be sufficient to potentiate depression and anxiety-like behaviors after an acute stressor. Follow up studies are needed to determine if this is specific to adult born neurons or if ablation of similar numbers of mature dentate neurons also potentiates the stress response. Optogenetic and pharmacogenetic approaches can be used to determine when the activity of adult born neurons is required to buffer stress. In primates, irradiation could be used to directly test whether ablating AHN leads to depression and anxiety-like behaviors.

Such direct tests are impossible in humans. However, using cancer treatment trials that compare standard treatments that indiscriminately kill dividing cells to newer more targeted treatments, researchers could determine if there are higher rates of depression and anxiety in patients receiving treatments that ablate AHN.

Evidence that treatments of depression and anxiety alter AHN

If AHN is important for the effects of antidepressants, then antidepressant treatment should alter AHN.

Rodents

In 2000, three of the most effective treatments of affective disorders in humans – electroconvulsive shock [47,48], fluoxetine (the prototypic SSRI) [5], and lithium [49] – were shown to boost AHN. Agents used to augment first-line antidepressants, including antipsychotics [50] and thyroid hormone [51], were subsequently shown to increase AHN. Newer antidepressants, such as subanesthetic doses of ketamine, also boost AHN [52].

Thus, initial studies found that diverse medications that decrease depression and anxiety also boost AHN. However, this was challenged when multiple groups failed to find an increase in AHN after fluoxetine treatment [53–55]. Interestingly, all of the studies showing no AHN

increase were in rats or mice that were not subject to a chronic stressor, and were therefore not models of depression or anxiety *per se*. Follow up studies have found that the ability of fluoxetine to boost AHN is sensitive to stress, corticosterone levels, rodent strain, and method of drug administration [56–59]. A complete account of these subtleties is out of the scope of this review. However, it appears that antidepressants most consistently boost AHN in stressed rodents that display increased depression and anxiety-like behaviors and likely have elevated stress hormone signaling [59]. Consistent with this, glucocorticoid signaling promotes antidepressant induced AHN (though the mechanism of this effect is unclear) [60].

Non-human primates

In non-human primates repeated electroconvulsive shocks increase AHN [61]. The results of fluoxetine is mixed, but in line with rodent results. One study found increased AHN when fluoxetine was given to bonnet monkeys subjected to repeat social isolation [21]. A more recent study in baboons found no evidence of increased AHN after fluoxetine treatment [23]. A potential cause of this discrepancy is that the fluoxetine treated group in this recent study was not subject to a chronic stressor. Thus, similar to rodents, consistent fluoxetine induced increases in AHN may require chronic stress.

Humans

Current studies of postmortem human brains measure AHN indirectly and find inconsistent effects of antidepressants. The first study found no effect of antidepressants on neuronal progenitor cell numbers [25]. However, medication adherence was not confirmed in this study. A second study that included confirmation of medication adherence, found a significant increase in neuronal progenitor cells and dividing cells in the dentate gyrus [26]. These increases were restricted to the anterior dentate gyrus – the region most clearly linked to mood and anxiety. A third study that focused on elderly patients showed no effect of antidepressants on AHN [27].

In contrast to the inconsistent results from counts of progenitor cells and dividing cells, postmortem studies consistently show an increase in total dentate granule cell number and dentate gyrus size in medicated depressed patients as compared to non-medicated patients [28,62]. This may be a better integrated measure of AHN than counts of progenitor cells.

Human MRI studies show larger hippocampi in medicated patients with affective and anxiety disorders as compared to non-medicated patients. Longitudinal studies allow for assessment of hippocampal growth in individual patients after treatment and can differentiate development changes from adult plasticity. Longitudinal studies of SSRI treatment of PTSD, SSRI treatment of major depression, and ECT treatment of major depression all found hippocampal growth in response to treatment [31,63,64]. In bipolar disorder, a metanalysis found that lithium treatment correlates with significantly larger hippocampi [65].

Treatment associated hippocampal growth likely reflects multiple forms of structural plasticity. Increases in dentate gyrus size would be most suggestive of increased AHN. A recent study using high resolution MRI to measure hippocampal subfields found that non-

medicated depressed patients had a selectively smaller dentate gyri compared to depressed patients taking antidepressants [29]. This result is purely correlational, but it is consistent with the hypothesis that antidepressants increase the size of the dentate gyrus – the locus of AHN.

Conclusions and future directions

SSRIs and electroconvulsive shock increase AHN in stressed rodents and primates. Human studies suggest that antidepressants increase AHN, but they are largely indirect and inconclusive. An *in vivo* marker of AHN in humans would revolutionize these studies. In the meantime, AHN could be measured directly in postmortem brains of patients on antidepressants using radiocarbon birthdating.

Importantly, increased AHN is one of many structural changes induced by antidepressants [66]. Boosted AHN may be one of many general indicators of overall dentate gyrus health, or it may be a key ingredient in antidepressant efficacy.

Evidence that AHN is required for antidepressant efficacy

If AHN is essential for antidepressant efficacy, then antidepressants should lose their effects after AHN ablation.

Rodent

In a provocative study in 2003, Santerelli et al. found that ablating AHN renders fluoxetine ineffective in mice [10]. This established a causal link between AHN and antidepressant efficacy. However, in follow up studies this group and others showed that AHN is not required for fluoxetine efficacy in different mouse strains [53,54,67]. These follow up studies clearly show that fluoxetine can have some antidepressant and anxiolytic effects in the absence of AHN. However, none of these follow up studies used a model of depression or anxiety – they assessed the requirement of AHN for antidepressant effects in non-stressed mice. In a subsequent study using stressed mice, some, but not all, of the behavioral effects of fluoxetine was AHN dependent [59]. More recent studies confirmed that AHN is required for some of fluoxetine's behavioral effects in stressed mice, and extended this by showing that AHN is also required for fluoxetine's ability to normalize HPA axis activity in stressed mice [68].

Non-human primate

Perera et al. found that ablation of AHN via irradiation blocks fluoxetine's ability to prevent stress induced anhedonia [21].

Human

No human studies have tested the requirement of AHN for antidepressant efficacy.

Conclusions and future directions

AHN is required in stressed mice for some, but not all, of fluoxetine's behavioral effects. AHN is required in primates for fluoxetine's ability to prevent stress induced anhedonia.

The distinct circuitry of stress-induced behavioral despair, anhedonia, and anxiety has recently been described in mice, and these studies could provide a starting point for understanding the circuitlevel role of AHN in the antidepressant response [69,70].

In humans, many non-depressed cancer patients develop depression following treatment, and SSRIs prevent depression in only a subset of such patients [46]. Future studies could determine if patients receiving treatments that ablate AHN are more likely to develop SSRI-resistant depression than patients receiving more targeted cancer treatments that spare AHN. This would suggest that SSRIs are less potent in humans with impaired AHN.

Evidence that increased AHN is sufficient to treat depression or anxiety

There are no published studies showing that selectively boosting AHN is sufficient to treat depression or anxiety. This is an essential gap in the field and it is unclear if developing AHN directed therapies will be effective. Genetic tools are now available in rodents to test if selectively boosting AHN can reverse stress induced depression and anxiety-like behaviors. Studies addressing this are underway in our laboratory, and we have preliminary evidence that boosting AHN in chronically stressed mice prevents depression and anxiety-like behaviors (A Hill et al., Abstract 504.07. Society for Neuroscience. San Diego, CA. November 2013). In contrast to the cognitive effects of boosting AHN, we see no effect of boosting AHN on baseline depression or anxiety-like behaviors in non-stressed mice [71].

An *in vivo* rodent screen for compounds that boost AHN identified the exciting P7C3 compound [72]. This compound has antidepressant-like effects in rodents, and these effects are blocked by ablation of AHN [73]. This is consistent with the hypothesis that P7C3 exerts antidepressant effects by boosting AHN, but it requires replication and a full exploration of potential non-AHN effects of P7C3. At the very least, work on P7C3 shows that studies guided by the neurogenic theory can indentify novel compounds that are effective in preclinical models.

If AHN directed therapies enter clinical trials, we propose that patients should be stratified based on the likelihood that they have impaired AHN. This should be done across current diagnostic categories, and it may lead to biologically-defined categories that guide treatment. An *in vivo* marker of AHN would make this possible. In its absence, deficits that correlate with decreased AHN in animal models could be used as proxies. Based on the current animal literature, patients with a combination of small dentate gyri, altered pattern separation, and failed dexamethosone suppression tests are most likely to have impaired AHN. Treatment responses could be compared between patients with likely impaired AHN and patients with likely normal AHN. It is an open question which group would be most responsive to AHN directed therapies. Boosting AHN may have a robust effect in patients with impaired AHN. Alternatively, such patients may be unable to mount a neurogenic response and may be most resistant to neurogenesis directed treatments.

Acknowledgements

We are grateful to Christoph Anacker, Alexis Hill, and Jae-eun Kang Miller for helpful comments on this manuscript. B.R.M. is supported by the Leon Levy Foundation and the National Institute for Mental Health (R25: MH086466-03). R.H. is supported by the National Institute for Mental Health (R37 MH068542 (MERIT)), the

National Institute on Aging (R01 AG043688), the National Institute of Neurological Disorders and Stroke (R01NS081203-01A1), NYSTEM (C029157), and the Hope for Depression Research Foundation (RGA 11-024). R.H. is a consultant for Roche and Lundbeck.

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Highlights

- Diverse animal models of depression and anxiety have impaired neurogenesis.
- Neurogenesis is consistently boosted by antidepressants in animal models when animals are stressed.
- Ablation of neurogenesis in animal models impairs cognitive functions relevant to depression, but only a minority of studies find that ablation causes depression or anxiety.
- Recent human neuroimaging and postmortem studies are consistent with the neurogenic theory, but they are indirect.
- A novel drug developed based on the neurogenic theory is promising in animal models.

Table 1

Five criteria for accepting the neurogenic theory of depression and anxiety

Criteria	Evidence
1. AHN is altered in depression or anxiety.	Rodent • Diverse rodent models of depression and anxiety impair AHN. Non-human primate • Social stress impairs AHN. Human • No direct measurements of AHN in depression or anxiety. • Postmortem studies show inconsistent effects on progenitor cells. • Postmortem studies show decreased dentate gyrus size and granule cell number. • MRI studies show decreased dentate gyrus size.
2. Impaired AHN is sufficient to induce depression or anxiety.	Rodent • Ablation of AHN does not increase baseline depression or anxiety-like behaviors in most studies, but it may potentiate these behaviors after acute stress. • Ablation of AHN impairs pattern separation and cognitive flexibility: cognitive functions relevant to depression and anxiety. Non-human primate • Not studied. Human • No direct studies. • Cancer treatments that ablate AHN increase depression and anxiety.
3. Treatments of depression or anxiety alter AHN.	Rodents • Electroconvulsive shock and diverse antidepressants boost AHN in stressed animals. Non-human primate • Electroconvulsive shock and fluoxetine boost AHN in stressed animals. Human • No direct measurements of AHN after antidepressant treatment. • Postmortem studies show inconsistent effects of antidepressants on progenitor cells. • Postmortem studies show increased dentate gyrus size and granule cell number in patients on antidepressants. • MRI studies show increased dentate gyrus size with antidepressant treatment. • Longitudinal MRI studies show hippocampal growth in response to electroconvulsive and antidepressant treatment.
4. AHN is required for antidepressant efficacy.	Rodent • AHN is required for some of fluoxetine’s behavioral effects in stressed mice. Non-human primate • AHN is required for fluoxetine’s ability to prevent stress induced anhedonia.

Criteria	Evidence
	Human • Not studied.
5. Increased AHN is sufficient to treat depression or anxiety.	Rodent • Preliminary studies show that boosting AHN prevents stress induced depression and anxiety-like behaviors. • Boosting AHN is sufficient to improve pattern separation: a cognitive function relevant to depression and anxiety. • P7C3, a novel drug discovered in a screen for pro-AHN compounds, is promising in preclinical studies. Non-human primate • Not studied. Human • Not studied.