Published in final edited form as:

Neuropharmacology. 2012 January ; 62(1): 21–34. doi:10.1016/j.neuropharm.2011.09.003.

The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building?

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Abstract

Hypotheses are scaffoldings erected in front of a building and then dismantled when the building is finished. They are indispensable for the workman; but you mustn't mistake the scaffolding for the building. Johann Wolfgang von Goethe. The neurogenesis hypothesis of affective disorders – in its simplest form – postulates that the generation of neurons in the postnatal hippocampal dentate gyrus is involved in the etiology and treatment efficacy of major depressive disorder (MDD). The hypothesis was established in the 1990s but was built on a broad foundation of earlier research on the hippocampus, serotonin and MDD. It has gone through several growth phases fueled by discoveries both correlative and causative in nature. Recently, the hypothesis has also been broadened to also include potential relevance for anxiety disorders, like post traumatic stress disorder (PTSD). As any hypothesis should be, it has been tested and challenged, sometimes vigorously. Here we review the current standing of the neurogenesis hypothesis of affective and anxiety disorders, noting in particular how a central postulate – that decreased neurogenesis results in depression or anxiety – has, in general, been rejected. We also review the controversies on whether treatments for these disorders, like antidepressants, rely on intact neurogenesis for their efficacy, and the existence of neurogenesis-dependent and -independent effects of antidepressants. In addition, we review the implications that the hypothesis has for the response to stress, PTSD, and the neurobiology of resilience, and highlight our own work showing that adult-generated neurons are functionally important for the behavioral response to social stress. We conclude by emphasizing how advancements in transgenic mouse technology, rodent behavioral analyses, and our understanding of the neurogenesis process will allow us to refine our conclusions and perform ever more specific experiments. Such scrutiny is critical, since if we “mistake the scaffolding for the building” we could overlook opportunities for translational impact in the clinic.

Keywords

Hippocampus; dentate gyrus; adult neurogenesis; depression; anxiety; post-traumatic stress disorder

1. Introduction

1.1. The problem and it's existing scaffolding

Affective and anxiety disorders, like major depressive disorder (MDD), are devastating and staggering in their personal, societal, financial costs. The existing treatments benefit a great

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number of people, but there is an unacceptable percentage of diagnosed patients with mood disorders who never receive pharmacological relief, who relapse, or who commit suicide (Tanti and Belzung, 2010; Taylor et al., 2011). Clinical and preclinical research with animal models of these disorders are beginning to unravel their neurobiological underpinnings, and current progress indicates promising paths for treatment and perhaps even prevention (Krishnan and Nestler, 2008).

Affective and anxiety disorders are distinct diagnostic categories, but they share key similarities. Like all psychiatric disorders, they have complex etiologies, with a range of genetic, epigenetic, neuroanatomical, and experiential causes or triggers under consideration (Covington et al., 2010; Cryan and Slattery, 2010; Karten et al., 2005; Pittenger and Duman, 2008). Diagnosis of these disorders is made based on descriptive, not etiologically-based, symptoms that often overlap and are still widely debated (American Psychiatric Association, 2000). The essential central nervous system diagnostic symptoms include depressed mood and anhedonia for affective disorders and anxiety for anxiety disorders. The high frequency of comorbidity and similarities between other associated symptoms (such as cognitive function, changes in appetite) suggest also that depression and anxiety may have a shared etiology. This is also supported by many treatments being indicated for both depression and anxiety. The symptoms of these disorders also indicate the involvement of limbic circuitry, including the hippocampus (Dere et al., 2010; Nemeroff et al., 2006; Perera et al., 2008; Seminowicz et al., 2004; Sheline et al., 2002). In addition, the gastrointestinal, cardiovascular, endocrine, and immune systems are also notably affected (e.g. O'Mahony et al., 2011; Savignac et al., 2011; Tsigos and Chrousos, 2002). Such complex, multifaceted disorders likely require equally complex, multifaceted hypotheses about their cause and the best avenues for treatment and even prevention. Some of the most prominent hypotheses about the neural and physiological underpinnings of affective and anxiety disorders involve dysregulation of neurotransmitters (especially monoamines and serotonin) or neuropeptides; of the endocrine system (especially corticosteroid signaling); or of inflammatory responses (especially cytokines) (e.g. Brown et al., 2004; Luscher et al., 2011; Schwarzer, 2009).

As an extension of Goethe's quote offered in the abstract, these many diverse hypotheses form the "scaffolding" from which researchers have been trying to gain enough perspective to target treatment and even prevention of mood-related disorders. However, as with other psychiatric disorders (e.g. Fernando and Robbins, 2011; Frankland et al., 2008; Gottesman and Gould, 2003), depression-related disorders may actually be a range of similar disorders that result from many different factors and thus require a range of preclinical and clinical research tactics (Cryan and Slattery, 2007; Touma, 2011). In addition, depression-related disorders may actually represent one major behavioral phenotype that results from different etiologies and thus require a range of research hypotheses. Thus, a solitary hypothesis may be insufficient to explain all cases of the mood-related disorders. Fortunately, with the rapid rate of research and technical advances in neuroscience, even more scaffolding – in the form of new, complementary but distinct hypotheses – is being erected to help guide the treatment and prevention of these disorders.

1.2. New scaffolding support from new neurons?

The focus of this review is one of the newer hypothesis of affective and anxiety disorders: the neurogenesis hypothesis. In its simplest form, the neurogenesis hypothesis states that the generation of neurons in the postnatal brain is important for understanding and treating depression. More recently, the hypothesis has been broadened to also include potential relevance for anxiety disorders, like post traumatic stress disorder (PTSD), and thus may hold hope for helping understand diverse response to stress and the neurobiology of resilience. As discussed in detail in section 3, the neurogenesis hypothesis has two main postulates: decreased neurogenesis results in depression or anxiety; and effective

pharmacological or environmental treatment for affective or anxiety disorders requires intact neurogenesis.

As the neurogenesis hypothesis and its accompanying postulates have received extensive discussion in recent years (Abrous et al., 2005; David et al., 2010; Kempermann et al., 2008; Lucassen et al., 2006; Malberg and Schechter, 2005; McEwen et al., 2002; Perera et al., 2008; Sahay et al., 2007; Samuels and Hen, 2011; Schmidt and Duman, 2007; Warner-Schmidt and Duman, 2006), this present review was prompted not by a need to provide a comprehensive review of existing literature but rather by several other factors. First, as summarized in section 2.1, the neurogenesis hypothesis has gone through several growth phases fueled by correlative research findings (e.g. antidepressants increase and stress decreases neurogenesis) and very recent causative research findings (e.g. role of adult-generated hippocampal neurons in key aspects of the stress response and in cognition). We feel these growth phases and their corresponding results deserve discussion and wider dissemination than they have already received. Second, there have been notable advancements made recently in transgenic mouse technology, rodent behavioral analyses, and our understanding of the neurogenesis process (e.g. Aasebo et al., 2011; Aimone and Gage, 2011; Dhaliwal and Lagace, 2011; Imayoshi et al., 2011; Kempermann, 2011b; Marin-Burgin and Schinder, 2011; Sierra et al., 2011). We feel it is important to look at past publications relevant to the neurogenesis hypothesis and their respective conclusions with the fresh eye allowed by these recent advances. Finally, the surge of work on the neurogenesis hypothesis indicates it is an optimal time to encourage discussion on how the neurogenesis hypothesis can interdigitate with pre-existing “scaffolding” – the hypotheses that have long driven our research into and understanding of affective and anxiety disorders.

Here we combine historical and recent literature review on the neurogenesis hypothesis to briefly review the fundamental information that non-neurogenesis researchers should know about neurogenesis in general (section 2.1), and the origin and current status of this hypothesis and its main postulates in particular (sections 2.2, 3.1 and 3.2). We also discuss the relevance of this hypothesis for our understanding of the neurobiology of resilience (section 3.3). Finally, in section 4 we propose a restructuring of the neurogenesis hypothesis and suggest how it may interdigitate well with the many disparate hypotheses of affective and anxiety disorders.

2. The neurogenesis hypothesis of depression: an overview

2.1. Keystones of adult neurogenesis

To understand the neurogenesis hypothesis of affective and anxiety disorders, it is necessary to understand the fundamentals, or keystones, of adult neurogenesis. There are several detailed reviews on this subject for the reader that requires more depth or more specific knowledge (e.g. Abrous et al., 2005; Balu and Lucki, 2009; Christie and Cameron, 2006; Curtis et al., 2011; Gould, 2007; Kaneko and Sawamoto, 2009; Kempermann, 2011a; Koehl and Abrous, 2011; Li et al., 2009; Ming and Song, 2011; Suh et al., 2009; Toni and Sultan, 2011), but the essential information needed is provided in this section and in Figure 1.

Briefly, neurogenesis occurs throughout life in several regions of the brain. The region that has received the most attention for its involvement in the neurogenesis hypothesis of affective and anxiety disorders is the hippocampal dentate gyrus (DG; Fig. 1A–C). The DG is host to the subgranular zone (SGZ), the main neurogenic region of the hippocampus. The SGZ contains a range of cell types that represent different stages of cell and neuron maturity. The maturation of cell lineage in the SGZ is thought to be relatively linear. Many studies have demonstrated that the Type-1 putative neural stem cells (also called radial glial cells, Type B, or quiescent neural progenitors) give rise to rapidly dividing progenitors,

which in turn divide and give rise to immature neurons, which, if they survive, become mature DG granule cells (e.g. Encinas et al., 2006; Kempermann et al., 2004; Seri et al., 2001). Evidence strongly suggests that adult-generated hippocampal neurons incorporate into hippocampal circuitry via projections in the mossy fiber pathway, and contribute to hippocampal functions relevant to mood and memory. Neurogenesis is an extremely dynamic process, as the number of cells in each “stage” of neurogenesis can change with pharmacological, environmental, and physiological stimuli. As described in the next section, it is the responsiveness of adult neurogenesis to stimuli that first drew the attention of depression and anxiety researchers and led to the development of the neurogenesis hypothesis of affective and anxiety disorders.

2.2. Keystones of the neurogenesis hypothesis of affective and anxiety disorders

The neurogenesis hypothesis of depression was stated formally in the last decade, but it has deep roots. There is almost a century of work on the hippocampus, stress, monoamines, MDD (Conrad, 2008; Hirschfeld, 2000; Lopez-Munoz and Alamo, 2009; McEwen, 2000; Sapolsky, 2000; Sheline, 2000), and almost fifty years of work on postnatal neurogenesis in the mammalian brain (Altman, 1962). These research lines began to intersect in the 1990’s when it was discovered that stress and stress hormones robustly decrease the generation of hippocampal neurons and increased cell death (Gould et al., 1992; Gould et al., 1991) and depletion of serotonin inhibited adult neurogenesis (Brezun and Daszuta, 1999). Soon after came a seminal paper showing that chronic but not acute antidepressant treatment increased SGZ proliferation and neurogenesis (Malberg et al., 2000). Importantly, this finding generalized to different classes of antidepressants pharmacotherapeutics (such as tricyclic and selective serotonin reuptake inhibitors), as well as electroconvulsive shock therapy (ECS) and environment interventions that are anti-depressant, like running (Madsen et al., 2000; Malberg et al., 2000; Manev et al., 2001; Santarelli et al., 2003; van Praag et al., 1999b). Spurred by these and other research papers, it was around this time that review publications began to address the potential importance of neurogenesis to our understanding of hippocampal plasticity and psychiatric disorders, MDD in particular (Blows, 2000; Brown et al., 1999; Duman et al., 1999; Eisch, 2002; Jacobs et al., 2000; Perera and Lisanby, 2000). While Jacobs et al., 2000 nicely articulated key aspects of the neurogenesis hypothesis of depression – proposing that the “waxing and waning of neurogenesis [are important causal factors in depression]” – it is only when examining many of these contemporary reviews together that the entire neurogenesis hypothesis of depression and its current postulates emerge.

The field of adult neurogenesis also had many breakthroughs around this time. For example, mammalian hippocampal neurogenesis was demonstrated in humans (Eriksson et al., 1998). Also, the newly formed neurons were proven to incorporate into existing circuitry and expressed indices of functional neurons (Eckenhoff and Rakic, 1988; Hastings and Gould, 1999; Markakis and Gage, 1999; Rozental et al., 1995; Stanfield and Trice, 1988; van Praag et al., 2002). There was also reasonable evidence that adult-generated neurons were functionally important in the mammalian olfactory system and in the avian brain (Alvarez-Buylla and Kirn, 1997; Bottjer and Arnold, 1997). However, in the early 2000’s, the functional relevance of adult-generated hippocampal neurons was not clear. There were many correlative studies suggesting its importance in learning and memory (e.g. Derrick et al., 2000; Dobrossy et al., 2003; Gould et al., 1999; Kempermann et al., 1997; van Praag et al., 1999a), and a few studies using constitutive knockout mice (Feng et al., 2001), but no study had inducibly and specifically decreased neurogenesis to explore its functional relevance.

Inducible ablation of adult neurogenesis was first done in studies using cranial irradiation or antimetabolites agents (Madsen et al., 2003; Mizumatsu et al., 2003; Monje et al., 2002; Parent

et al., 1999; Peissner et al., 1999; Raber et al., 2004; Shors et al., 2002; Snyder et al., 2001; Uberti et al., 2001). As a whole, these studies showed the functional importance of adult hippocampal neurogenesis in learning and memory and in seizure induction. Most relevant for this review, in 2003, a publication in *Science* appeared whose title formulated one of the main postulates of the neurogenesis hypothesis of depression: Requirement of adult-hippocampal neurogenesis for the efficacy of antidepressants (Santarelli et al., 2003). Using irradiation-induced ablation of adult-generated hippocampal neurons, Hen and colleagues found that irradiated mice no longer responded behaviorally to antidepressants like fluoxetine. These data suggested that adult neurogenesis might be related to the pathophysiology of depression, and that enhanced hippocampal neurogenesis is required for the beneficial effects of the antidepressant treatment. There was a strong “anxiety” component to the behavioral testing in Santarelli et al., thus raising questions about whether in fact antidepressant treatments themselves (vs. antianxiety treatments) required neurogenesis. However, MDD and anxiety are comorbid in humans, so taken together with subsequent work these data suggested that the neurogenesis hypothesis may apply to both affective and anxiety disorders (e.g. David et al., 2010; Tanti and Belzung, 2010).

The neurogenesis hypothesis was highly attractive for many reasons. It offered a novel perspective on etiology of MDD, but one that fit with the existing “scaffolding”: the concept of MDD as a limbic disorder marked by hippocampus maladaptations. The hypothesis also helped to explain the delay of several weeks between the initiation of antidepressant treatment and onset of their effects (Laverne and Jay, 2010), since the maturation of the hippocampal progenitors into mature DG granule neurons and their incorporation into circuitry also takes about 3–4 weeks (Encinas et al., 2006; Kee et al., 2007; Kempermann et al., 2004). The tractability of the hypothesis, along with the rapid rate of discovery about neural stem cells, stages of neurogenesis, and novel ways to track, label and manipulate adult-generated neurons (e.g. Dhaliwal and Lagace, 2011; Imayoshi et al., 2008) led to a massive surge in publications in this area (e.g. “depression” and “neurogenesis” resulted in 8 items for the year 2000, and 79 already July, 2011). But is the hypothesis still valid? The next section addresses its component parts and their current status.

3. Postulates of the neurogenesis hypothesis of affective and anxiety disorders

While the neurogenesis hypothesis of depression remains attractive, how does it and its two main postulates hold up after almost a decade of intense research? Here we will review these two postulates: 1) Decreased adult neurogenesis results in depressive or anxious phenotypes (Fig. 1D–F, Table 1); 2) Effective treatments for these disorders require intact hippocampal neurogenesis (Fig. 2, Table 2). We will also explore how the current state of the hypothesis informs our current understanding of the response to stress, PTSD, and the related concept of the neurobiology of resilience.

3.1. Does decreased adult hippocampal neurogenesis result in depressive or anxious phenotypes?

Since the early studies on the neurogenesis hypothesis, such as Malberg et al., 2000 and Santarelli et al., 2003, there have been many correlative and causal studies that explore whether decreased hippocampal neurogenesis results in depression or anxiety. As shown in Table 1, there are currently 21 publications that have examined the depression and anxiety-related behavioral consequences of decreasing neurogenesis in laboratory animals (Airan et al., 2007; Bessa et al., 2009; David et al., 2009; Fuss et al., 2010a; Holick et al., 2008; Jayatissa et al., 2009; Lagace et al., 2010; Meshi et al., 2006; Noonan et al., 2010; Onksen et al., 2011; Revest et al., 2009; Santarelli et al., 2003; Saxe et al., 2006; Schloesser et al.,

2010; Shors et al., 2002; Singer et al., 2009; Snyder et al., 2011; Surget et al., 2008; Surget et al., 2011; Wang et al., 2008; Zhu et al., 2010). For ease of categorization, Table 1 groups these studies by behavioral test – novelty suppressed feeding (NSF), forced swim test (FST), tail suspension test (TST), etc. In addition, the studies are discussed below in two distinct sections based on whether the effect of decreasing neurogenesis was tested in non-stressed rodents (section 3.1.1) or in one of several animal models of depression (section 3.1.2).

3.1.1. Effect of decreasing neurogenesis on depression- and anxiety-like behaviors in non-stressed animals—So does decreasing adult hippocampal neurogenesis in “naïve” laboratory animals result in a depressive or anxious phenotype (Fig. 1D–F)? One of the most striking observations from this summary of 19 publications (yellow rows, Table 1) is that there is no effect of ablating neurogenesis in 32 of the 42 mood-related tests (76% of studies) completed in naïve or non-stressed rodents. This lack of effect is particularly clear from the large number of studies using tests of NSF and FST, which across many (but not all) studies show no effect of neurogenesis disruption on these behavioral tests. This argues strongly against the postulate that in solely decreasing neurogenesis – and not invoking any aspect of stress or utilizing an animal model of depression – induces a depressive-like phenotype.

Because of the challenge posed by separating depression- from anxiety-like behaviors (Crawley, 1999; Cryan and Holmes, 2005; Kalueff et al., 2010), it remains unclear from the current literature what effect disruption of neurogenesis has specifically on anxiety-related behaviors. Consider the comparison of nestin-Bax and ATR mice in Table 1, both mouse models in which neurogenesis can be inducibly decreased (nestin-Bax by overexpressing Bax specifically in nestin-expressing cells, and ATR by either inducibly knocking out this cell cycle checkpoint gene throughout the body or removing it solely from differentiated cells in the hippocampus) and to about a similar extent. Non-stressed nestin-Bax mice display increased anxiety in three separate anxiety-related behavioral tests (elevated plus maze, light-dark, and predator avoidance (Revest et al., 2009)). In contrast, non-stressed ATR mice that display reduced anxiety in three anxiety-related tests: marble burying, novelty-induced hypophagia, and zero maze (Onksen et al., 2011). It is likely these differences are in part reliant on technical aspects – e.g. the cell specificity of the gene overexpression (Bax in nestin-expressing cells) or deletion (ATR from whole body or from all differentiated cells in the hippocampus), the resulting selectivity of disruption of neurogenesis, the timing of the decrease in neurogenesis relative to the behavioral testing, and to changes that are not directly related to changes in neurogenesis (e.g. ATR mice fail to show antidepressant-induced increase in spine density in a non-neurogenic part of the hippocampus). However, the fact that disruption of neurogenesis via two different inducible transgenic mouse models results in alterations in anxiety-like behaviors contrasts with the fact that disruption of neurogenesis via more global approaches ablation (e.g. irradiation and MAM) does not alter anxietylike behaviors. Thus, this encourages the application of more specific genetic models (e.g. inducible and cell-specific manipulations which directly target adult neurogenesis) to more closely assess the possibility that neurogenesis is a regulator of anxiety-like behaviors. This also encourages development of approaches to specifically enhance adult neurogenesis, a concept we will return to in section 3.2.1. Future work should also consider the possibility that depression and anxiety-relevant behaviors may be differently associated with hippocampal neurogenesis (e.g. Uchida et al., 2011).

3.1.2. Effect of decreasing neurogenesis on depression- and anxiety-like behaviors in animal models of depression—Section 3.1.1 addressed whether decreasing neurogenesis in “naïve” laboratory animals results in a depressive- or anxiety-phenotype. However, it is possible that the importance of neurogenesis is only revealed when the animal is in a depressive-like state (Kempermann, 2008). To address this

possibility, many groups have inducibly ablated neurogenesis in animal models of depression – animals that have received injections of corticosterone (CORT) or exposure to social defeat stress (SS), unpredictable chronic mild stress (UCMS), and restraint stress – and then examined the effect on mood-related behaviors. This approach has been used in 8 publications (light green rows, Table 1) for a total of 19 behavioral tests in animal models of depression. Generally these studies find no behavioral effect of ablating neurogenesis (15 of the 19, or 79%, of tests show no change). This suggests that as in non-stressed animals, decreasing neurogenesis in animal models of depression is not sufficient to result in or exacerbate a depressive- or anxiety-like phenotype.

However, Table 1 also lists 4 of the 19 published tests (21%) in which decreasing neurogenesis in animal models of depression is sufficient to drive a depressive- or anxiety-like phenotype. What might explain these conflicting data? One explanation is that the relationship between behavioral performance on mood-related tests and adult neurogenesis may be dependent on the method, timing, or extent of neurogenesis disruption. A good example of behavioral performance being reliant on the method, timing, or extent of neurogenesis disruption is evident from review of publications that inducibly alter neurogenesis and then examine behavior on the NSF test. When neurogenesis was ablated via cranial irradiation prior to the start of UCMS, there was no change in latency to feed in the NSF test (Surget et al., 2008). In contrast, when neurogenesis was ablated via MAM treatment 3 weeks after the onset of UCMS, there was an increased latency to feed (Bessa et al., 2009). The contradictory nature of these results could be due the non-specific nature of the experimental interventions (e.g. systemically administered MAM disrupts cell division throughout the body in contrast to cranially-delivered radiation) and encourages for development of more specific ways to ablate neurogenesis. However since most transgenic approaches result in less efficient ablation than more global approaches like irradiation, it remains to be seen how the quantity and extent of ablation will also influence behavioral responses in animals. These conflicting data could also be due to differences in the lag time between testing for functional deficits and the time after UCMS or ablation of neurogenesis. Another area that warrants additional study is whether these studies are all utilizing similar measures of neurogenesis, and whether there are cell stage-specific changes that are currently unappreciated. One example of this is with another animal model of depression, social isolation. Dranovsky and colleagues found that social isolation induced an accumulation of the putative Type 1 neural stem cells in the mouse hippocampus, but not neurons (Dranovsky et al., 2011). This emphasizes the need to continually advance our understanding of neurogenesis.

3.2. Do antidepressant or antianxiety therapeutics require adult hippocampal neurogenesis for their effects?

The second postulate of the neurogenesis hypothesis (Fig. 2) was first hinted at in a study showing that antidepressants reversed the decrease in proliferation induced by the learned helplessness model of depression (Malberg and Duman, 2003). The reliance of antidepressant efficacy on intact neurogenesis was also supported in the NSF test in non-stressed mice with ablated neurogenesis (Santarelli et al., 2003). As shown in Table 2, there are 14 publications that have examined the requirement for neurogenesis in antidepressant or antianxiety efficacy in behavioral tasks via ablation approaches (Airan et al., 2007; Bessa et al., 2009; David et al., 2009; Fuss et al., 2010b; Holick et al., 2008; Jiang et al., 2005; Meshi et al., 2006; Perera et al., 2011; Santarelli et al., 2003; Schloesser et al., 2010; Surget et al., 2008; Surget et al., 2011; Wang et al., 2008; Zhu et al., 2010). As with Table 1, the publications in Table 2 are grouped by behavioral test, with each publication appearing multiple times for each test examined. However, here an additional column is added to allow

presentation of animal models of depression, antidepressant/antianxiety therapeutics and manipulations, and the combined approach.

3.2.1. Is intact neurogenesis required for efficacy of antidepressants? Studies in non-stressed animals—

So far a total of 10 studies (pink rows, Table 2) have used naïve animals, disrupted neurogenesis, and explored whether adult-generated neurons are required for antidepressant efficacy of antidepressant compounds like fluoxetine or antidepressant stimuli like environmental enrichment or running. In the studies that assess performance on the NSF and FST (9 publications, 10 individual tests reported), there is 80% consensus that neurogenesis is required for antidepressant-induced alterations in behavior. These data from the NSF and FST suggest that, in general, intact neurogenesis is required for the antidepressant effects that can be produced by either pharmacological (antidepressants) or environmental (environmental enrichment) manipulation. When all the behavioral tests are considered (e.g. all pink rows, Table 2), there is less agreement. For example, there are 6 tests across three publications that show antidepressant efficacy is not reliant on intact neurogenesis: environmental enrichment in the NSF (Meshi et al., 2006), fluoxetine in the FST and novelty-induced hypophagia (Holick et al., 2008), and running in the open field, light/dark, and O maze (Fuss et al., 2010b). While inclusion of running here as an “antidepressant” is controversial, since in this particular study running induced an anxious and depressive-phenotype (Fuss et al., 2010b), it remains notable that irradiation did not influence the performance on tests of depression or anxiety. Still, when all the pink rows in Table 2 are considered together, there is a slight majority - 57% - of behavioral data that support the second postulate: intact adult neurogenesis is required for antidepressant efficacy, at least in the basal context (e.g. not in animal models of depression). The next section will address whether the second postulate holds in animal models of depression.

3.2.2. Is intact neurogenesis required for efficacy of antidepressants? Studies in animal models of depression—

The dependency of antidepressant action on intact adult neurogenesis also has been assessed in many studies using a variety of animal models of depression, such as UCMS, CMS, SS, and Cort (purple rows, Table 2, Table 8 publications, 38 individual tests reported). There is support for the second postulate in animal models of depression, with 20 of the 38 tests (53%) showing the reliance of antidepressant efficacy on intact neurogenesis in the context of animal models of depression. For example, antidepressants fail to “work” in the NSF test an animal model of depression (UCMS) after cranial irradiation; fluoxetine, for example, does not lead to decreased latency to feed in the NSF test in stressed, irradiated mice (Surget et al., 2008). This is similar to the original finding that antidepressants fail to work in the NSF test after just cranial irradiation (Santarelli et al., 2003).

However, 18 of 38 individual tests (47%) from a variety of publications do not support the idea that adult neurogenesis is required for antidepressant-associated changes in behavior in animal models of depression. For example, latency to feed in the NSF test was reduced in MAM-treated animals even when antidepressants were administered (Bessa et al., 2009), suggesting that antidepressants can improve mood independently of adult neurogenesis. In addition, genetic ablation of adult neurogenesis in nestin-tk+ mice did not prevent antidepressant action in the TST (Singer et al., 2009). These studies, which are cited in Table 2, fit with other studies that did not inducibly ablate neurogenesis. For example, a study the same year as Malberg et al. 2003 reported that a reduced number of actively dividing progenitors did not correlated with performance in the learned helplessness task (Vollmayr et al., 2003). Similarly in BALB/cJ mice, which have high levels of basal anxiety, the behavioral effects of antidepressants (chronic fluoxetine) also did not require adult neurogenesis and were not associated with changes in proliferation or differentiation (Holick et al., 2008; Huang et al., 2008). Taken together, Table 2 shows that there is an almost even

division between those results that support and those that oppose a role for intact neurogenesis in antidepressant efficacy when using an animal model of depression (purple rows).

While there are only 14 publications total in Table 2, there are sufficient results to ask the question: what might explain these differing perspectives on whether or not antidepressants require intact neurogenesis in laboratory animals? One hypothesis is that the basal level of anxiety or activation of the stress axis plays a critical role in whether or not antidepressants rely on intact neurogenesis. Indeed, antidepressants increased adult neurogenesis in animals subjected to stress (David et al., 2009); however, fail to do so in unstressed ones (Couillard-Despres et al., 2009). Similarly, stressed nonhuman primates who lack neurogenesis fail to show the behavioral response of antidepressants (Perera et al., 2011). The hippocampus itself has long been known to be important in regulation of the stress axis, and even more recent data have begun to elegantly dissect the role of adult-generated neurons in stress-induced surges in serum and fecal corticosterone (Schloesser et al., 2009; Snyder et al., 2011; Surget et al., 2011). Second, behavioral tests appear sensitive to the animal strain used (Alahmed and Herbert, 2008), and animal strains have long been known to display enormous differences in levels of hippocampal proliferation and adult neurogenesis (Kempermann, 2002; Kempermann and Gage, 2002), which fits with strain-dependent differences in brain morphology and metabolism (e.g. Penet et al., 2006). Therefore, it is important to consider mouse strain when interpreting basic research studies that examine the relationship between neurogenesis, stress, and antidepressants (e.g. Table 1 in David et al., 2010). A final hypothesis is that the ablation approaches themselves might produce confounds in these behavioral experiments. Adult-generated neurons for example provide more than just new hippocampal neurons; they also provide structural support and cell-cell contact, and ablation of new neurons is akin to pulling a support beam out from a scaffolding platform in that it can have wide reaching and unintended effects no matter how cell-specific the ablation strategy is. This possibility can be resolved by a gain of function approach, which, opposite to ablation of neurogenesis, induces a specific upregulation of adult neurogenesis. Excitingly, recent work showed specific upregulation of adult neurogenesis using a genetic approach resulted in improved pattern separation in spatial memory in mice (Sahay et al., 2011). Highly relevant for this review, this same publication showed a lack of effect of increasing neurogenesis on NSF, FST, and another test relevant for anxiety (open field exploration in both low and high anxiety conditions) (Sahay et al., 2011). As this study was performed in non-stressed animals (e.g. not in an animal model of depression), it will be important to see if selective increase in neurogenesis in an animal model of depression results in normalized mood-related behaviors or response to antidepressants. It is also possible that the antidepressant aspects of neurogenesis come from normalization of levels, not increasing levels neurogenesis beyond basal levels. This is in part supported by postmortem work showing the level of proliferation in patients with MDD on antidepressants (SSRIs) was higher than in patients with MDD not on antidepressants, but not significantly different from age-matched healthy controls (Boldrini et al., 2009). Clearly, more work with such selective and inducible manipulation of neurogenesis is warranted to more fully understand how increasing – or decreasing – hippocampal neurogenesis influences antidepressant responsivity. One particularly interesting tool in this regard is application of inducible yet reversible reduction in neurogenesis (e.g. Massa et al., 2011). It will also be important to explore the signaling and molecular mechanisms mediating antidepressant-induced regulation of neurogenesis and behavior. One molecular candidate in this regard is TrkB, the receptor for the neurotrophin BDNF (Li et al., 2008). Interestingly, inducible ablation of TrkB from nestin-expressing cells and their progeny did not decrease basal levels of neurogenesis, but rather prevented the antidepressant-induced increase in indices of neurogenesis and antidepressant-induced alterations in behavior on the NSF and TST (Li et al., 2008). Given the long line of research linking BDNF, antidepressant

efficacy, and neurogenesis, deeper exploration of how precisely TrkB on adult-generated neurons mediates antidepressant-induced changes in neurogenesis and behavior is warranted.

If adult-generated neurons do indeed play a critical role in antidepressant efficacy, there are some interesting clinical implications. For example, adult neurogenesis decreases with age (Kuhn et al., 1996). If antidepressant action requires neurogenesis, one could reason that antidepressants should not be as effective in aged individuals as in young ones. This seems to be true, as aging abolishes the positive effects of fluoxetine of hippocampal proliferation and pro-neuronal differentiation in mice (Couillard-Despres et al., 2009). Also, antidepressant efficacy decreases dramatically in elderly patients (Schatzberg and Roose, 2006; Tollefson et al., 1995), and antidepressants fail to stimulate adult neurogenesis in old age (Lucassen et al.; however, see Zhao et al., 2008b). This aspect of the neurogenesis hypothesis of depression also raises important considerations for anti-cancer chemotherapy that targets mitotically active cells, including the hippocampal neuronal progenitors (Fig. 1). Since adult neurogenesis is proposed to be critical for mood control (DeCarolis and Eisch, 2010), anti-cancer therapies may have direct effects on affect and mood. Consistent with this, antidepressant treatment was able to reverse memory and proliferation impairments after chemotherapy in rats (Lyons et al., 2011).

3.3. Implications of the neurogenesis hypothesis of affective and anxiety disorders for the understanding of the neurobiology of resilience

One tenet of the neurogenesis hypothesis is that a stress-induced decrease in neurogenesis may contribute to the onset or exacerbate stress-related disorders (e.g. Bremner et al., 2008), making decreased neurogenesis a “vulnerability factor” for disorders like PTSD. In support of this, stress is used to mimic clinically-relevant symptoms in animals models of MDD or PTSD (Greenwood and Fleshner, 2008; Krishnan and Nestler; Stam, 2007; Takemura and Kato, 2008), in models as diverse as the social defeat stress (e.g. Van Bokhoven et al., 2011) and UCMS (e.g. Surget et al., 2009). SGZ proliferation and neurogenesis are robustly inhibited in these and other stress models and after administration of stress hormones (e.g. Gould and Tanapat, 1999; Joels, 2007; Joels et al., 2008; Pittenger and Duman, 2008; Schmidt and Duman, 2007; Van Bokhoven et al., 2011; Zhao et al., 2008a). Several correlative studies have also suggested that stress is associated with decreased hippocampal neurogenesis and depressive- or anxious-like phenotypes (e.g. Ho and Wang, 2010; Lucassen et al., 2010a; Pittenger and Duman, 2008; Vollmayr et al., 2007), and that antidepressants can reverse the behavioral or cellular phenotype (e.g. Dwyer et al., 2011; Veena et al., 2011). The message from most of these studies is that “stress decreases neurogenesis”.

However, a growing number of publications suggest the message is much more complex than “stress decreases neurogenesis”. For example, while there is decreased SGZ proliferation during or immediately after stress, there is no change in survival of cells that were dividing prior to stress (Heine et al., 2004). In addition, decreased neurogenesis might be thought to result in decreased hippocampal volume; however, there is no change in granule cell layer volume reported in many stress studies (Czeh et al., 2001; Jayatissa et al., 2006; Yap et al., 2006). Also, there are many correlative studies in which stress-induced decrease in some index of neurogenesis does not correlate with an anhedonic or anxious phenotype (e.g. Jayatissa et al., 2010). Finally, there are a few recent studies that suggest stress does not decrease neurogenesis but actually can increase neurogenesis, and that this increase is functionally relevant (Lagace et al., 2010; Lyons et al., 2010; Parihar et al., 2011). What do these recent findings mean for the neurogenesis hypothesis of affective and anxiety disorders?

There are two messages that these recent studies have for us about the neurogenesis hypothesis. First, contrary to stress always being “bad”, it has long been appreciated that stress has an important biological role, and recent research supports that some amount of stress at the right time is actually useful for learning and memory (Joels et al., 2006). For example, in a study of non-human primates, successful coping with intermittent social stress was associated with enhanced neurogenesis (as assessed by BrdU given during the stressor) and hippocampal function (as assessed by spatial learning, Lyons et al., 2010). A study in rats came to a similar conclusion, where predictable chronic mild stress enhanced neurogenesis and hippocampal-dependent memory as well as diminished depressive- and anxiety-like behaviors (Parihar et al., 2011). These studies suggest that as in humans, predictability confers a positive aspect to stress, and that successful coping with a stressor may actually serve to enhance brain function. In contrast, unpredictable stressors are potentially more damaging and difficult to cope with.

A second, related message relevant to the neurogenesis hypothesis evident from another recent study is the importance of the behavioral response to stress. In humans, some “susceptible” individuals exposed to stress develop symptoms of MDD and PTSD, while other “resilient” individuals do not. There are some personality traits (optimism) and situational variables (whether the stress is controllable) that appear to be important in determining whether someone is either susceptible or resilient to a given stress (Duman, 2009; Feder et al., 2009). Assessment of “resilience” can also be examined in preclinical research. The social defeat model, for example, is a model of stress-induced social avoidance that produces multiple features of stress susceptibility in approximately half of subjects (Krishnan et al., 2007). In mice exposed to this prolonged stressful psychosocial experience, susceptible mice will display behavioral and physiological indices reminiscent of MDD and PTSD and will avoid an aggressor mouse in a social environment, while resilient mice will not. A notable difference between the social defeat model and other animal models of stress is the ability to measure the behavioral response to stress. In other tests, like separation or restraint stress, the animal is merely exposed to the stress. In the social defeat model, the animal’s behavioral response to stress is calculated by their performance on an interaction test with an aggressor. As such, it is an ideal model in which to probe the neural mechanisms contributing to an organism’s response to chronic severe stress.

Using the mouse model of social defeat, and exploiting the diversity of stress response in this model, we recently discovered that adult hippocampal neurogenesis is functionally important for stress-induced social avoidance (Lagace et al., 2010). There are two key findings from this study that are relevant to the neurogenesis hypothesis of affective disorders. First, we found that enhanced neuronal survival occurs only in mice with persistent social avoidance. We did not see this effect when all defeated mice were analyzed irrespective of behavioral response to this stressor. This emphasizes the importance of considering the behavioral response to stress, rather than just exposing an animal to stress, as is common with animal models of depression. It is possible that some of the studies presented in Tables 1 and 2 would yield a different answer if the animal’s response to stress was taken into consideration. Second, using focused cranial X-Ray irradiation to ablate neurogenesis, we found that decreased neurogenesis led to a greater proportion of the mice displaying resilience. This emphasizes that the time window after cessation of stress is a critical period for the establishment of persistent cellular and behavioral responses to stress, and therefore is a very good target for therapeutic intervention. If, as our data suggest, adult-generated neurons store the memory of a stressful experience, targeting adult-generated neurons after a stressful experience may provide some translational approaches to dealing with abnormally strong or stressful memories.

Two additional intriguing speculations emerge from our work in regards to treatment of or even prevention of PTSD. Since the survival of adult-generated neurons is functionally important in social avoidance, it is possible that modern approaches to visualize neurogenesis in the living brain (e.g. Manganas et al., 2007) could be used to help correlate behavioral responses to stress in humans and levels of neurogenesis. With this information, strategies could be used to selectively increase or decrease neurogenesis appropriately to help augment or diminish particular memories of stressful experiences, similar to those approaches suggested for other brain neuroadaptations (e.g. Blundell et al., 2008; Ressler et al., 2004). In regards to treatment, there are several novel strategies that have been shown to prevent the behavioral response to stress in laboratory animals, including exercise and regulation of diet (e.g. Finger et al., 2011a, b; Greenwood and Fleshner, 2008), which are also known to alter hippocampal neurogenesis. It would be interesting to dissect the involvement of hippocampal neurogenesis in these protective strategies.

4. New scaffolding needed to keep up with construction

When reviewed as a whole, the published literature relevant to the neurogenesis hypothesis of affective and anxiety disorders has been built logically, study by study, with many of the results supporting prior work and allowing a true hypothesis-driven approach to test whether new neurons are important in mood disorders. In addition, the work on this topic is not complete, so there is no sense in dismantling the scaffolding of the hypothesis now; this is when the workers need the support provided by these hypotheses the most. However, the great speed at which these studies are being generated puts the field at risk for, in Goethe's words, mistaking the scaffolding for the building. What can we learn from examining the scaffolding – the neurogenesis hypothesis of depression and anxiety – that might help us restructure it to best guide future studies?

It seems we have discounted the first postulate that decrease in hippocampal adult neurogenesis is related to the pathophysiology of depression in the “basal” or nonstressed state. Indeed, as summarized in Table 1 and Figure 2, most studies do not find that reduced adult neurogenesis yields depression behavior (Bessa et al., 2009; Jayatissa et al., 2009; Meshi et al., 2006; Shors et al., 2002). This fits with human post-mortem work that does not find decreased neurogenesis in the hippocampi of depressed patients (e.g. Boldrini et al., 2009; Reif et al., 2006). The lack of a clear-cut effect – decreased neurogenesis leads to depression – also fits with the fact that even though adult neurogenesis is dramatically decreased in older age (Hwang et al., 2007; Jinno; Knott et al.; Kuhn et al., 1996; McDonald and Wojtowicz, 2005), the majority of aged animals and elderly patients are not depressed. The work on the neurobiology of resilience from our laboratory and others also fits into this; a stress-induced decrease in neurogenesis may not result in depression, but it could influence the behavioral response to future stressors and the ability to cope with them in an adaptive manner.

The second postulate proposing that hippocampal neurogenesis is required for the behavioral effects of antidepressants is and will likely remain a great source of controversy and intensive research. As shown in Table 2 and Figure 2, while many studies support a role for intact neurogenesis in antidepressant efficacy, others do not. Thus additional research is needed to resolve these differences. In addition, the entire field is challenged – or perhaps distracted – by the fact that “antidepressants” are for the most part monoaminergic modulating agents that are effective for a wide variety of disorders (and arguably more effective for anxiety disorders than depression), and “models of depression” are actually models of stress. This type of generalization or simplification has been extremely beneficial for some aspects of research in the field, but likely is holding back progress in other areas. Nevertheless, the studies that provided conflicting evidence to the original hypothesis that

hippocampal neurogenesis is required for the behavioral effects of antidepressants raise several interesting questions. For example, how does the basal anxiety level affect adult neurogenesis if the anxiety level is important for the adult neurogenesis to confer antidepressant effects (e.g. David et al., 2009; Fuss et al., 2010a; Fuss et al., 2010b; Onksen et al., 2011)? Are the experimental animals living in non-enriched environment the best model for the neurogenesis hypothesis of depression since their neurogenesis may be underscored by non-stimulating environment (Hauser et al., 2009)? Why do antidepressant effects on adult neurogenesis influence only some depression-like behavior tests and not others? Is it because many of the behavioral tests for estimating depression and anxiety are not mutually compatible (Belzung and Le Pape, 1994) or were developed for drug screening (Krishnan and Nestler, 2008) and thus do not reflect the complex etiology of depression and/or anxiety? Or is it possible that differences in results came from experimental differences in animal species and handling, timing of the antidepressant administration and other factors as it was shown before (Crabbe et al., 1999; Wahlsten et al., 2003)?

As we near the end of this review it is worth stressing a point we made in the introduction: depression and anxiety are not defined or diagnosed via etiology but rather by symptom presentation. Indeed, depression and anxiety may share etiology. This is an additional factor that has likely made it difficult to delineate the role of neurogenesis through the lens of depression or anxiety models. With this in mind, it is also important to stress that a common approach for many studies in this field – inducible ablation of adult neurogenesis – itself will alter the neuronal circuitry responsible for controlling mood. Indeed, very recent results show the particular power that adult-generated neurons have over physiological response to stress (Snyder et al., 2011), thus providing a functional link to the long-known anatomical connections between the hippocampus and the stress axis, and provides a mechanistic avenue to explore how new neurons might regulate mood. This work by Cameron's group also clarifies how the first postulate should be stated in the future: reduced neurogenesis may result in increased-depressive like behavior when the individual is stressed. However, since the neurobiology of depression relies on many different aspects of brain functioning and involves many proposed cellular and molecular mechanisms including changes in neurotrophic factors, synaptic plasticity, and even cell proliferation and survival outside of hippocampus (Castro et al., 2010; Krishnan and Nestler, 2008; Laverne and Jay, 2010), it is unlikely that the adult hippocampal neurogenesis would influence them all. Similarly, antidepressants modulate a wide spectrum of brain functions and processes besides adult neurogenesis (Berton et al., 2006). While it is likely that adult-generated neurons play some role in antidepressant efficacy (e.g. Li et al., 2008), it is highly unlikely that all antidepressants would have a single common denominator in requirement of adult neurogenesis. This fits well with the concept of a circuit- or behavioral-level endophenotype of depression and anxiety (e.g. Airan et al., 2007; Cryan and Slattery, 2007; Garner et al., 2009; Leuner and Gould, 2010), where hippocampal plasticity as a whole is disrupted, and neurogenesis is just one facet that can help normalize this disruption. This concept has worked well with other complex psychiatric disorders (Frankland et al., 2008; Kobayashi, 2009; Tamminga et al., 2010; Yamasaki et al., 2008), and can be applied to depression-related disorders. It may also help to explain some discrepancies in results, for example, as adult neurogenesis is capable of compensating for some endophenotypes but not others.

We believe that taking this hard look at the current structure of the neurogenesis hypothesis will result in a beneficial restructuring of it. For example, we posit that the neurogenesis hypothesis is not at odds with the complexity of affective and anxiety disorders, nor is it in conflict with the preexisting scaffolding or hypotheses that have long supported active and fruitful research into these disorders, such as the neurotransmitter and endocrine hypotheses. Instead the neurogenesis hypothesis fits extremely well with overarching “neuroplasticity” hypothesis of affective and anxiety disorders (e.g. Fossati et al., 2004; Fuchs et al., 2004;

Kempermann, 2011a; McEwen and Chattarji, 2004; Nissen et al.). In fact, the neurogenesis hypothesis is well positioned to be interdigitated into other existing hypotheses, particularly the hypotheses that involve the endocrine and stress systems, providing a broader and more flexible base from which to work towards improving our understanding of these disorders. The current challenge is for scientists working from distinct scaffolding to continue their work upwards but also work across hypotheses to construct a clinically-relevant understanding of affective and anxiety disorders. This scrutiny is critical, since if we “mistake the scaffolding for the building” we miss an opportune time to thoughtfully craft the neurogenesis hypothesis of affective and anxiety disorders, and to reveal the potential clinical relevance behind it.

In conclusion, while the neurogenesis hypothesis of depression offers new perspective into the etiology of MDD and anxiety disorders, it needs to be reformulated. As scaffolding, it does not fit the building that is emerging from recent results. Its first postulate – decreased neurogenesis in the “basal” state leads to depression – does not fit the evidence from literature. Rather, decreased neurogenesis may lead to depression when animal models of depression or stress are invoked. In fact, given the historically strong connection between the hippocampus, depression, anxiety, and stress and given the more recent links between these things and adult hippocampal neurogenesis, it is interesting to consider that this newly-appreciated connection between neurogenesis and stress regulation may have been discovered much earlier if it were not obscured by the scaffolding supporting the construction of the “neurogenesis hypothesis of depression”. As an extension of this, the restructured neurogenesis hypothesis should aim to clarify the relationship between adult-generated neurons and the production or regulation of stress and anxiety. This may have tremendous clinical relevance in allowing, for example, dissection of levels of resilience to stress and to *in vivo* levels of neurogenesis (e.g. Manganas et al., 2007). This restructured emphasis on stress and anxiety fits well with the second and still somehow valid postulate – adult neurogenesis is required for beneficial actions of antidepressants. If stress resilience or stress levels both influence adult neurogenesis and can in turn be regulated by levels of adult neurogenesis, these likely are dynamic factors in the efficacy of antidepressants. Thus, considering neurogenesis-related stress resilience may offer a new perspective – and even more supportive scaffolding – in the search to develop and test novel antidepressants and perhaps even prevent or at least diminish the severity of mood-related disorders.

Acknowledgments

This work was supported by grants from the National Institutes of Health (R01 DA016765 and K02 DA023555 to AJE), NASA (NNX07AP84G to AJE), NSERC (371716 to DCL), a Young Investigator Award (DCL) and an Independent Investigator Award (AJE) from the National Alliance for Research on Schizophrenia and Depression, and a postdoctoral research fellowship from the Canadian Institute of Health Research (DCL). Special thanks to Dr. Jason Snyder for permission to use his blog (<http://www.functionalneurogenesis.com/blog/>) as inspiration for Tables 1 and 2 of this review.

Abbreviations

AVb1	arginine vasopressin receptor type 1b
BrdU	bromodeoxyuridine
CMS	chronic mild stress
Cort	corticosterone
CRF1	corticotropin releasing hormone type 1 receptor
DG	dentate gyrus

GFAP	glial fibrillary acidic protein
MAM	methylazoxymethanol acetate
MDD	major depressive disorder
PTSD	post traumatic stress disorder
SGZ	subgranular zone
SS	social defeat stress
SSRI	selective serotonin reuptake inhibitor
tk	thymidine kinase
UCMS	unpredictable chronic mild stress

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Figure 1. Adult hippocampal neurogenesis and the neurogenesis hypothesis of depression

(A) Dissection of the rodent telecephalon reveals a cross-section through the hippocampus (colored lines) with the dentate gyrus – the site of adult-generated hippocampal neurons – depicted in red. (B) Enlarged schematic of the dentate gyrus shows the superior and inferior blades of the granule cell layer (GCL, brown) and the subgranular zone (SGZ, red) where the hippocampal neurogenesis occurs in the postnatal period through adulthood. (C) Higher magnification of the boxed region from (B) displays the phases of adult hippocampal neurogenesis as a function of time. The neural stem cells (NSCs, green) putatively give rise to the transiently-amplifying progenitors (blue and violet) whose progeny differentiate into immature neurons (dark violet) and finally into fully mature dentate gyrus GC neurons (red). (D) Under normal, physiological conditions, the process from NSCs to mature GC takes approximately 4–6 weeks. (E) The first postulate of the neurogenesis hypothesis of depression states that reduced neurogenesis should result in a depressive phenotype. (F) The second postulate of the neurogenesis hypothesis of depression states that antidepressants require adult neurogenesis for effects in improving mood. As discussed in the text, Figure 2, and Tables 1 and 2, published work supports aspects of the second, but not the first, hypothesis.

Figure 2. Is the efficacy of antidepressants reliant on intact adult hippocampal neurogenesis? (A) This question is often addressed by depletion adult-generated neurons by cranial irradiation or antimetabolic agents (methylazoxymethanol or MAM is shown; see Tables 1, 2 for more approaches) and subsequent administration of antidepressant compounds or environmental manipulations known to have antidepressant efficacy (like running or environmental enrichment). As highlighted in Table 2, the results from these studies are conflicting. Some studies show that after disruption of neurogenesis, antidepressants still produce antidepressant or anxiolytic effects in behavioral tests, here summarized as “improved mood”. However, other studies show that after disruption of neurogenesis, antidepressants fail to result in antidepressant or anxiolytic effects in behavioral tests, here summarized as “impaired mood”. (B) The conflicting results summarized in (A) may in part be explained by the many factors that influence whether adult-generated neurons are required for antidepressant efficacy or not. Stress or anxiety levels of the experimental animals, difference in animal strain that may influence the basal level of adult neurogenesis, and the type of ablation strategy utilized (such as gancyclovir in tk+ mice) are just some of the factors that appear to influence whether or not antidepressants influence mood regulation via adult-generated neurons.

Table 1
Effect of ablation of adult neurogenesis on depression- and anxiety-related behaviors

Inspired by Dr. Jason Snyder's online catalog of papers relevant to neurogenesis (www.functionalneurogenesis.com/blog/), Table 1 highlights studies that have genetically (via knockout mouse) or inducibly ablated neurogenesis (via irradiation, MAM, or inducible transgenic mice) and assessed how specific behavioral tests have been used in various mood-related rodent models. Depression- and anxiety-related behavior tasks that have been assessed in studies that have ablated or disrupted adult neurogenesis are listed in chronological order and divided by two categories. Yellow highlighted studies were performed in "naïve" or non-stressed animals (e.g. suppression of neurogenesis was employed but no animal model of depression or anxiety (Unpredictable cited, 42 individual test results shown). Light green highlighted studies were performed using animal model of depression or anxiety (Unpredictable Chronic Mild Stress, UCMS; Corticosterone Treatment, Cort; social stress, SS; or Restraint stress, Restraint, n=8 publications cited, 19 individual test results shown). In answer to the question "How is depression/anxiety-related behavior altered by disrupted neurogenesis?" (Column 2), behavioral test results are classified as no change (nc) or increased or decreased depression/anxiety-related behavior. As the focus of this table is on depression- and anxiety-related behaviors, it does not address other aspects of physiology that have been linked to neurogenesis and the stress response (e.g. cortisosterone levels in serum or fecal boli (e.g. Surget et al., 2011), body weight (e.g. Surget et al., 2011), and normalization of corticosterone levels after stress or dexamethasone suppression (e.g. Snyder et al., 2011; Surget et al., 2011)).

Depression model	How is depression/anxiety-related behavior altered by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
Novelty Suppressed Feeding					
-	nc	mouse	irradiation	Santarelli et al., 2003	Figure 5A
-	nc	mouse	irradiation	Meshi et al., 2006	Figure 3A
-	nc	mouse	irradiation	Surget et al., 2008	Figure 2C
-	nc	mouse	irradiation	Wang et al., 2008	Figure 6
-	increased	rat	MAM	Bessa et al., 2009	Figure 1C
-	nc	mouse	nestin-Bax mice	Revest et al., 2009	Figure 5A
-	nc	rat	irradiation	Zhu et al., 2010	Figure 4E
-	nc	mouse	hGFAPtk mice	Snyder et al., 2011	Figure 4A–B
UCMS	nc	mouse	irradiation	Surget et al., 2008	Figure 2C
UCMS	increased	rat	MAM	Bessa et al., 2009	Figure 1C
Cort	nc	mouse	irradiation	David et al., 2009	Figure 3E–G
Restraint	increased	mouse	hGFAPtk mice	Snyder et al., 2011	Figure 4A–B
Forced Swim Test					
-	nc	rat	irradiation	Airan, Melzter et al., 2007	Figure 4E
-	nc	mouse	irradiation	Holick et al., 2008	Figure 3

Depression model	How is depression/anxiety-related behavior altered by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
-	nc	rat	MAM	Bessa et al., 2009	Figure 1B
-	nc	mouse	nestin-Bax mice	Revest et al., 2009	Figure 5C-D
-	nc	rat	irradiation	Zhu et al., 2010	Figure 4B
-	increased	mouse	GFAP-tk	Snyder et al., 2011	Figure 4C-D
UCMS	nc	rat	MAM	Bessa et al., 2009	Figure 1B
Cort	nc	mouse	irradiation	David et al., 2009	Figure 3H
Restraint	nc	mouse	GFAP-tk	Snyder et al., 2011	Figure 4C-D
Coat State					
-	nc	mouse	irradiation	Surget et al., 2008	Figure 2A
-	nc	mouse	irradiation	Surget et al., 2011	Supp Figure 2B,D
UCMS	nc	mouse	irradiation	Santarelli et al., 2003	Figure 5C
UCMS	nc	mouse	irradiation	Surget et al., 2008	Figure 2B
CMS	nc	rat	irradiation	Zhu et al., 2010	Figure 5B
UCMS	nc	mouse	irradiation	Surget et al., 2011	Supp Figure 2B,D
Splash Test					
-	nc	mouse	irradiation	Surget et al., 2008	Figure 2B
UCMS	nc	mouse	irradiation	Santarelli et al., 2003	Figure 5C
UCMS	nc	mouse	irradiation	Surget et al., 2008	Figure 2B
Sucrose Preference					
-	nc	rat	MAM	Bessa et al., 2009	Figure 1A
-	increased	mouse	hGFAPtk mice	Snyder et al., 2011	Figure 4E,F
UCMS	nc	rat	MAM	Bessa et al., 2009	Figure 1A
Restraint	increased	mouse	hGFAPtk mice	Snyder et al., 2011	Figure 4E,F
Elevated Plus Maze					
-	nc	rat	MAM	Shors et al., 2002	Figure 5
-	nc	mouse	irradiation	Saxe et al., 2006	Figure 4 (online)

Depression model	How is depression/anxiety-related behavior altered by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
-	increased	mouse	nestin-Bax mice	Revest et al., 2009	Figure 2B-2D
-	nc	mouse	hGFAPtk mice	Snyder et al., 2011	Supp Figure 7
Restraint	nc	mouse	hGFAPtk mice	Snyder et al., 2011	Supp Figure 7
Open Field					
-	nc	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 2D
-	nc	mouse	irradiation	Fuss et al., 2010	Figure 4A
-	nc	mouse	hGFAPtk mice	Snyder et al., 2011	Supp Figure 3D
Cort	nc	mouse	irradiation	David et al., 2009	Figure 3A-D
Light/Dark Test					
-	nc	mouse	irradiation	Saxe et al., 2006	Figure 4 (online)
-	increased	mouse	nestin-Bax mice	Revest et al., 2009	Figure 2E-G
-	nc	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 2E
-	increased	mouse	irradiation	Fuss et al., 2010	Figure 5
Social Interaction/Avoidance					
SS	increased	mouse	irradiation	Lagace et al., 2010	Figure 4I
Novelty-Induced Hypophagia					
-	nc	mouse	irradiation	Holick et al., 2008	Figure 5
-	decreased	mouse	ATR mice	Onksen et al., 2011	Figure C,D
Predator Avoidance					
-	increased	mouse	nestin-Bax mice	Revest et al., 2009	Figure 3A-B
Sucrose/Saccharine Consumption					
-	nc	rat	MAM	Jayatissa et al., 2009	Figure 1B
-	nc	rat	irradiation	Noonan et al., 2010	Figure 5
-	nc	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 2F

Depression model	How is depression/anxiety-related behavior altered by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
-	nc	mouse	hGFAP ^{tdk} mice	Snyder et al., 2011	Supp Figure 9
Cookie Test					
-	nc	mouse	irradiation	Surget et al., 2011	Figure 2B,C
UCMS	nc	mouse	irradiation	Surget et al., 2011	Figure 2B,C
O Maze					
-	nc	mouse	irradiation	Fuss et al., 2010	Figure 4B
-	decreased	mouse	ATR mice	Onksen et al., 2011	Figure 3A,B
Tall Suspension Test					
-	nc	mouse	nestin-tdk mice	Singer et al., 2009	Figure 8B
Marble Burying					
-	decreased	mouse	ATR mice	Onksen et al., 2011	Figure 4A,B

Table 2
Effect of ablation of adult neurogenesis on the efficacy of antidepressant compounds and antidepressant physiological manipulations in depression- and anxiety-related behavior task

As with Table 1, Table 2 was inspired by Dr. Jason Snyder's online catalog of papers relevant to neurogenesis (www.functionalneurogenesis.com/blog/). However, this table specifically addresses the question "Is antidepressant efficacy diminished by disrupted neurogenesis"? Depression- and anxiety-related behavior tasks that have been assessed in studies that have ablated or disrupted adult neurogenesis (via irradiation, MAM, or inducible transgenic mice) are listed in chronological order and divided into two categories. In pink highlighted studies, animals were given a compound or manipulation that has antidepressant efficacy (e.g. antidepressant compounds including fluoxetine, imipramine, AV1b or CRF1 receptor antagonists; environmental enrichment; the cannabinoid receptor [CB] agonist HU210; intermittent hypoxia; and running,) in addition to the disruption of neurogenesis (n=10 publications, 14 individual test results shown). Purple highlighted studies were performed using animal models of depression or anxiety (Unpredictable Chronic Mild Stress, UCMS; Corticosterone Treatment, Cort; Chronic Mild Stress, CMS; social stress, SS; or Restraint stress, Restraint), and also received an additional treatment such as a pharmacological treatment or environmental modification (n=8 publications, 38 individual test results shown). In answer to the question "Is antidepressant efficacy diminished by disrupted neurogenesis?" (Column 3), behavioral test results are classified as *No* or *Yes*. As the focus of this table is on the reliance of the behavioral effects of antidepressant on intact neurogenesis, it does not address other aspects of physiology that have been linked to neurogenesis and the stress response (e.g. antidepressant-induced synaptic plasticity, Wang et al., 2008).

Depression model	Pharmacological or environmental manipulation	Is antidepressant efficacy diminished by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
Novelty Suppressed Feeding						
-	Fluoxetine	Yes	mouse	irradiation	Santarelli et al., 2003	Figure 5A
-	Imipramine	Yes	mouse	irradiation	Santarelli et al., 2003	Figure 5A
-	CB agonist	Yes	rat	irradiation	Jiang et al., 2005	Figure 8E
-	Envir Enrichment	No	mouse	irradiation	Meshi et al., 2006	Figure 3A
-	Fluoxetine	Yes	mouse	irradiation	Wang et al., 2008	Figure 6C,D
-	Intermittent Hypoxia	Yes	rat	irradiation	Zhu et al., 2010	Figure 4E
UCMS	Fluoxetine	Yes	mouse	irradiation	Surget et al., 2008	Figure 3C
UCMS	Imipramine	No	mouse	irradiation	Surget et al., 2008	Figure 4C
UCMS	CRF1 antag	No	mouse	irradiation	Surget et al., 2008	Figure 5C
UCMS	AV1b antag	No	mouse	irradiation	Surget et al., 2008	Figure 6C
UCMS	Fluoxetine	Yes	rat	MAM	Bessa et al., 2009	Figure 1C
UCMS	Imipramine	Yes	rat	MAM	Bessa et al., 2009	Figure 1C
UCMS	CRF1 antag	Yes	rat	MAM	Bessa et al., 2009	Figure 1C
UCMS	AV1b antag	Yes	rat	MAM	Bessa et al., 2009	Figure 1C
Cort	Fluoxetine	Yes	mouse	irradiation	David et al., 2009	Figure 3E

Depression model	Pharmacological or environmental manipulation	Is antidepressant efficacy diminished by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
CMS	Intermittent Hypoxia	Yes	rat	irradiation	Zhu et al., 2010	Figure 5C
Forced Swim Test						
-	CB agonist	Yes	rat	irradiation	Jiang et al., 2005	Figure 8F
-	Fluoxetine	Yes	rat	irradiation	Airan, Melzter et al., 2007	Figure 4E
-	Fluoxetine	No	mouse	irradiation	Holick et al., 2008	Figure 3
-	Intermittent Hypoxia	Yes	rat	irradiation	Zhu et al., 2010	Figure 4B
UCMS		No	rat	MAM	Bessa et al., 2009	Figure 1B
UCMS	Imipramine	No	rat	MAM	Bessa et al., 2009	Figure 1B
UCMS	CRF1 antag	No	rat	MAM	Bessa et al., 2009	Figure 1B
UCMS	AV1b antag	No	rat	MAM	Bessa et al., 2009	Figure 1B
Cort	Fluoxetine	No	mouse	irradiation	David et al., 2009	Figure 3H
Coat State						
UCMS	Fluoxetine	Yes	mouse	irradiation	Santarelli et al., 2003	Figure 5C
UCMS	Fluoxetine	Yes	mouse	irradiation	Surget et al., 2008	Figure 3B
UCMS	Imipramine	Yes	mouse	irradiation	Surget et al., 2008	Figure 4B
UCMS	CRF1 antag	No	mouse	irradiation	Surget et al., 2008	Figure 5B
UCMS	AV1b antag	No	mouse	irradiation	Surget et al., 2008	Figure 6B
UCMS	Fluoxetine	Yes	mouse	irradiation	Surget et al., 2011	Supp Figure 2B
UCMS	CRF1 antag	No	mouse	irradiation	Surget et al., 2011	Supp Figure 2D
Splash Test						
UCMS	Fluoxetine	Yes	mouse	irradiation	Santarelli et al., 2003	Figure 5D
UCMS	Fluoxetine	Yes	mouse	irradiation	Surget et al., 2008	Figure 3B
UCMS	Imipramine	Yes	mouse	irradiation	Surget et al., 2008	Figure 4B
UCMS	CRF1 antag	No	mouse	irradiation	Surget et al., 2008	Figure 5B
UCMS	AV1b antag	No	mouse	irradiation	Surget et al., 2008	Figure 6B
Sucrose/Saccharine Preference						

Depression model	Pharmacological or environmental manipulation	Is antidepressant efficacy diminished by disrupted neurogenesis?	Species	Approach to disrupt neurogenesis	Reference	Figure in reference
UCMS	Fluoxetine	No	rat	MAM	Bessa et al., 2009	Figure 1A
UCMS	Imipramine	No	rat	MAM	Bessa et al., 2009	Figure 1A
UCMS	CRF1 antagon	No	rat	MAM	Bessa et al., 2009	Figure 1A
UCMS	AV1b antagon	No	rat	MAM	Bessa et al., 2009	Figure 1A
SS	Envir Enrichment	Yes	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 4I
Open Field						
-	Running	No	mouse	irradiation	Fuss et al., 2010	Figure 4A
Cort	Fluoxetine	No	mouse	irradiation	David et al., 2009	Figure 3A-D
SS	Envir Enrichment	Yes	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 4H
Light/Dark Test						
-	Running	No	mouse	irradiation	Fuss et al., 2010	Figure 5
SS	Envir Enrichment	Yes	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 4J
Social Interaction/Avoidance						
SS	Envir Enrichment	Yes	mouse	hGFAPtk mice	Schloesser et al., 2010	Figure 4D-G
Novelty-Induced Hypophagia						
-	Fluoxetine	No	mouse	irradiation	Holick et al., 2008	Figure 5
Anhedonic Behaviors						
SS	Fluoxetine	Yes	bonnets	irradiation	Perera et al., 2011	Figure 1
O Maze						
-	Running	No	mouse	irradiation	Fuss et al., 2010	Figure 4B
Cookie Test						
UCMS	Fluoxetine	Yes	mouse	irradiation	Surget et al., 2011	Figure 2B