Adult Neurogenesis and Mental Illness

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Several lines of evidence suggest that adult neurogenesis, the production of new neurons in adulthood, may play a role in psychiatric disorders, including depression, anxiety, and schizophrenia. Medications and other treatments for mental disorders often promote the proliferation of new neurons; the time course for maturation and integration of new neurons in circuitry parallels the delayed efficacy of psychiatric therapies; adverse and beneficial experiences similarly affect development of mental illness and neurogenesis; and ablation of new neurons in adulthood alters the behavioral impact of drugs in animal models. At present, the links between adult neurogenesis and depression seem stronger than those suggesting a relationship between new neurons and anxiety or schizophrenia. Yet, even in the case of depression there is currently no direct evidence for a causative role. This article reviews the data relating adult neurogenesis to mental illness and discusses where research needs to head in the future.

Neuropsychopharmacology Reviews (2015) **40**, 113–128; doi:10.1038/npp.2014.230; published online 24 September 2014

INTRODUCTION

Mental illness is debilitating not only to those afflicted with various disorders but to mankind as a whole. It has been estimated that 26% of the adult population have a diagnosable mental disorder (Kessler *et al*, 2005), and the economic burden of serious mental illness yearly has been estimated at 193 billion dollars because of annual loss of earnings alone (Kessler *et al*, 2008). More effective and innovative treatment options are necessary for battling this terrible burden.

The hippocampus has long been associated with psychiatric disorders (Antonova *et al*, 2004; Geuze *et al*, 2005; Sapolsky, 2000). The hippocampus is highly plastic throughout life and is particularly sensitive to changes in the environment, making it a promising research target for mental illness. Developmental lesions of the ventral hippocampus produce an animal model of schizophrenia (Lipska *et al*, 2002; Swerdlow *et al*, 2001). Hippocampal volume reductions are reported in patients suffering from various mental disorders such as depression, anxiety, and schizophrenia (Campbell *et al*, 2004; Nelson *et al*, 1998; Sheline *et al*, 2003; Vythilingam *et al*, 2002), as well as in animal models of these diseases (Gilbert-Juan *et al*, 2013; Golub *et al*, 2011; Kaae *et al*, 2012; Kalisch *et al*, 2006). Understanding how the hippocampus is changed in the

context of mental disorders will provide clues to their etiology and new avenues for prevention and treatment of these diseases.

One unusual feature of the hippocampus is that it contains a population of neuronal precursor cells in the dentate gyrus that generate large numbers of new granule neurons throughout adulthood. The mechanisms, stages, and time course of adult neurogenesis in the dentate gyrus have been extensively studied (Aimone *et al*, 2014; Lepousez *et al*, 2013). New dentate gyrus neurons generate action potentials (van Praag *et al*, 2002) and are activated by functionally relevant experiences (Belarbi *et al*, 2012; Kee *et al*, 2007; Schoenfeld *et al*, 2013; Snyder *et al*, 2009a, 2009c, 2012; Tashiro *et al*, 2007), suggesting that new neurons play a role in functions associated with this region.

The generation of new neurons in the adult brain has been of particular interest to researchers investigating the etiology and treatment of mental illness (Eisch, 2002; Jacobs *et al*, 2000; Lucassen *et al*, 2009; Samuels and Hen, 2011a), because of a number of similarities between the factors regulating adult neurogenesis and affecting psychiatric disease. Evidence that new neurons are important for mental health could come from: (1) factors that trigger or increase likelihood of developing mental illness and inhibit neurogenesis; (2) drugs and other treatments that improve mental illness or its symptoms and enhance neurogenesis; (3) behavioral changes mimicking features of illness that occur following inhibition of adult neurogenesis in animals; and (4) changes in adult neurogenesis in patients with disease. In this review, we will discuss each of these types of evidence, focusing on the potential links between adult neurogenesis and major depression, anxiety disorders, and schizophrenia.

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Received 11 April 2014; revised 28 August 2014; accepted 28 August 2014; accepted article preview online 2 September 2014

GENETIC AND ENVIRONMENTAL EFFECTS ON ADULT NEUROGENESIS AND MENTAL ILLNESS

One argument for a role of new neurons in the adult mammalian brain in positive mental health is that a number of behaviors and experiences that affect mental health also alter adult neurogenesis (Eisch, 2002; Jacobs *et al*, 2000; Lucassen *et al*, 2009; Samuels and Hen, 2011a). Typically, negative experiences, such as stress, sleep deprivation, and inflammation, adversely affect mental health and decrease the generation of new neurons. Conversely, positive experiences, such as exercise and environmental enrichment, tend to have beneficial effects on mental health and increase adult neurogenesis. Genetic predispositions and developmental insults also tend to affect adult neurogenesis and development of mental illness in parallel.

Effects of Early-Life Experiences on Adult Neurogenesis and Mental Illness

There is growing interest in the long-lasting effects of childhood trauma on mental health into adulthood. Among the general population, people with a history of childhood trauma, including physical, emotional, and/or sexual abuse, are predisposed to anxiety and depression (Chapman *et al*, 2004; McCauley *et al*, 1997; Moffitt *et al*, 2007). Adults who have had hallucinations are also more likely to have suffered from childhood physical or sexual abuse (Whitfield *et al*, 2005). In patients with diagnosed schizophrenia, there is also a positive association between childhood abuse and specifically dissociative symptoms in adulthood (Holowka *et al*, 2003; Sar *et al*, 2010; Schäfer *et al*, 2012). In addition, traumatic events not involving abuse, such as parental loss early in life, are associated with developing major depression, anxiety disorders, and schizophrenia in adulthood (Agid *et al*, 1999; Kendler *et al*, 1992). Even prenatal stress, because of infection, malnutrition, or maternal psychological stress, is a significant risk factor for developing mental illness in adulthood (Brown *et al*, 2000, 2004; St Clair *et al*, 2005; Stein *et al*, 2009; Watson *et al*, 1999). In women with major depression, childhood abuse is correlated with smaller hippocampal volume, suggesting long-lasting effects of developmental experience on hippocampal structure in humans (Vythilingam *et al*, 2002).

In animal models, early-life stress increases behavior suggestive of psychiatric illness in adulthood. Rodents born to mothers experiencing stress during pregnancy show behavioral deficits thought to model depression, anxiety, and schizophrenia. Maternal infection, stress, and malnutrition increase schizophrenia-like behavior in adult offspring (Borrell *et al*, 2002; Fortier *et al*, 2007; Koenig *et al*, 2005; Palmer *et al*, 2004). Elevated anxiety-like behavior is seen in mice and rats exposed to prenatal infection and stress (Enayati *et al*, 2012; Fride and Weinstock, 1988; Hava *et al*, 2006; Walf and Frye, 2007). Prenatal infections and stress also increase depression-like behavior in adult rodents (Abe

et al, 2007; Enayati *et al*, 2012; Lin and Wang, 2014; Tamura *et al*, 2011). During the early postnatal period, maternal separation, a commonly used experimental early-life stress, leads to increased anxiety-, depression-, and schizophrenia-like behavior in adulthood (Chen *et al*, 2011; Ellenbroek *et al*, 1998; Huot *et al*, 2001; Martisova *et al*, 2012; Romeo *et al*, 2003). In addition, juvenile rodents exposed to stressful events after weaning show increased depression- and anxiety-like behavior in adulthood (Jacobson-Pick and Richter-Levin, 2010; Pohl *et al*, 2007; Wilkin *et al*, 2012).

Early-life stress typically inhibits the production of new neurons in adulthood. Prenatal stress produces long-lasting deficits in the production and survival of new neurons into adulthood (Koo *et al*, 2003; Lemaire *et al*, 2000; Zueva *et al*, 2008). A recent study indicates that infection during pregnancy reduces cell proliferation and neurogenesis in both juvenile and adult offspring (Lin and Wang, 2014). Undernourished mothers produce offspring with lower rates of cell proliferation and neuronal survival in adulthood (Matos *et al*, 2011). Prenatal stress and maternal separation even decreases the size and complexity of the new neurons that are born in adulthood in the dentate gyrus (Leslie *et al*, 2011; Tamura *et al*, 2011). Stress during the early postnatal period produced by maternal separation reduces cell proliferation, neurogenesis, and the survival of new neurons in adult rodents in the dentate gyrus (Aisa *et al*, 2009; Leslie *et al*, 2011; Mirescu *et al*, 2004; Sachs *et al*, 2013).

The evidence that enriching experiences during early life lead to positive effects on adult mental health and neurogenesis in the dentate gyrus is more mixed. One study reported that housing pregnant dams in an enriched environment led to decreased anxiety-like behavior in adult offspring (Friske and Gammie, 2005). However, environmental enrichment for neonates and juvenile rodents had anxiolytic- and antidepressant-like effects on adult behavior in some studies (Baldini *et al*, 2013; Benaroya-Milshtein *et al*, 2004; Urakawa *et al*, 2013; Workman *et al*, 2011) but not others (Ishihama *et al*, 2010; Workman *et al*, 2011; Yildirim *et al*, 2012). Early-life wheel running also appears to have little effect on adult anxiety-like behavior (Ishikawa *et al*, 2014). Evidence is similarly sparse and mixed on lasting effects of early-life and prenatal enrichment on adult neurogenesis (Boehme *et al*, 2011; Schaefer, 2013). Given that the effects of early-life enrichment on neurogenesis and behavior are similarly mixed, this might still indicate parallels. It may be that animal models of environmental enrichment, which were developed for adult animals, are simply not as enriching for juveniles or pregnant dams. It is also possible that standard experimental housing, with plenty of food and an absence of predators, provide an optimal environment for emotional/cognitive development of rodents. In any case, it is unclear from animal studies whether positive events, or simply the lack of negative events, during development affect neurogenesis and behavior into adulthood. However, the data make a strong case that adverse experiences in early development can inhibit

neurogenesis and increase mental illness-related behaviors in adulthood.

Adverse Experiences in Adulthood

Stressful experiences have long been linked as potential contributors to the development of psychiatric disorders (Anisman and Zacharko, 1982; Kessler *et al*, 1985). Prolonged stress in humans can lead to an overloading of the stress response system, leaving people at risk for the development of illness, both physical and psychiatric (McEwen, 2004). Chronic exposure to stress has been implicated as a predisposing factor for developing major depressive disorder, anxiety disorders, posttraumatic stress disorder, and schizophrenia (Davidson and Baum, 1986; Gold *et al*, 1988; Pêgo *et al*, 2010; Pollin, 1972; Southwick *et al*, 2005). Chronic stress is frequently used in animals to produce behavioral states modeling depression, anxiety, and schizophrenia (Bahi, 2013; Brzózka *et al*, 2011; Katz, 1982; Taliaz *et al*, 2011). The hippocampus is a key brain region for linking stress and behavior. Hippocampal neurons express high levels of glucocorticoid and mineralocorticoid receptors, receptors for stress hormones, and the hippocampus provides negative feedback of the stress response, inhibiting the hypothalamic–pituitary–adrenal (HPA) axis in response to an increase in circulating stress hormones (Gerlach and McEwen, 1972; Jankord and Herman, 2008; McEwen *et al*, 1968; Roozendaal *et al*, 2001). New neurons in the adult dentate gyrus have receptors for stress hormones and are activated by stress, and hence they could play a direct role in stress response (Cameron *et al*, 1993; Schoenfeld and Gould, 2013). The effects of stress on adult neurogenesis are complex (reviewed in Schoenfeld and Gould, 2012), but it is clear that in at least some situations, chronic stress can reduce cell proliferation and survival of new neurons in the dentate gyrus (Czeh *et al*, 2007; Dayte *et al*, 2009; Ferragud *et al*, 2010; Pham *et al*, 2003).

Prolonged sleep deprivation has been suggested to be a risk factor for developing mood disorders like depression and anxiety disorders (Kahn-Greene *et al*, 2007; Taylor *et al*, 2005; Tkachenko *et al*, 2014), and patients with schizophrenia show impairments in various stages of sleep (Ferrarelli *et al*, 2010; Keshavan *et al*, 1998). Similarly, in animal studies, sleep deprivation can increase anxiety-like behavior in mice (Silva *et al*, 2004), and rodent models of anxiety, depression, and schizophrenia produce fragmented sleep (Grønli *et al*, 2004; Jakubcakova *et al*, 2012; Oliver *et al*, 2012; Phillips *et al*, 2012; Popa *et al*, 2006). The production of new neurons in the dentate gyrus is also inhibited by chronic sleep restriction or fragmentation (Mirescu *et al*, 2006).

A proinflammatory state has been associated with mental disorders, including major depression, anxiety, and schizophrenia (Dowlati *et al*, 2010; Fan *et al*, 2007; Rohleder *et al*, 2004). Increased inflammation has been suggested as a risk factor for developing a mood or psychotic disorder (Pervanidou *et al*, 2007; Reichenberg *et al*, 2001; Stojanovic

et al, 2014; Wichers *et al*, 2007), and anti-inflammatory medication reduces symptoms of depression in antidepressant-resistant populations (Raison *et al*, 2012). In rodents, activating inflammation in the brain, by genetic means or injection of endotoxins, induces behavioral phenotypes of depression, anxiety, and schizophrenia (Fahey *et al*, 2007; Takao *et al*, 2013; Wohleb *et al*, 2011), and suppresses proliferation and survival of new neurons in the dentate gyrus (Ekdahl *et al*, 2003; Goshen *et al*, 2007; Monje *et al*, 2003; Vallières *et al*, 2002).

Effects of Rewarding Experiences on Adult Neurogenesis and Mental Illness

Physical exercise can reduce symptoms in patients suffering from major depression, anxiety disorders, and schizophrenia (Beebe *et al*, 2005; Blumenthal *et al*, 1999; Herring *et al*, 2011), and can reduce feelings of anxiety and depression in healthy adults as well (Blumenthal *et al*, 1982; DiLorenzo *et al*, 1999). Similarly, exercise in the form of voluntary wheel running also ameliorates depressive- and anxiety-like symptoms in naive animals (Duman *et al*, 2008; Schoenfeld *et al*, 2013) as well as in animal models of mental illness (Lapmanee *et al*, 2013; Maniam and Morris, 2010; Wolf *et al*, 2011). Wheel running robustly enhances adult neurogenesis in experimental animals, increasing the proliferation, maturation, and survival of new neurons in the dentate gyrus (Schoenfeld *et al*, 2013; Snyder *et al*, 2009b; Stranahan *et al*, 2006; van Praag *et al*, 1999).

Another experimental manipulation used to bolster the proliferation and survival of new neurons in the adult dentate gyrus is enrichment of the animals' housing environment through the addition of toys, tunnels, greater space, social interactions, and other means to make home cages more complicated and stimulating (Kempermann *et al*, 1997; van Praag *et al*, 1999; Veena *et al*, 2009a). These environmental enrichments also reduce anxiety-, depressive-, and schizophrenic-related behaviors in animal models of illness (Jha *et al*, 2011; McOmish *et al*, 2008; Veena *et al*, 2009b). The effects of housing environments on adult neurogenesis and behavior in animals may parallel environmental effects on mental illness in humans, although it is unclear exactly what type of experience is modeled by enrichment of rodent cages. One possibility is that impoverished standard rodent cage environments model low socioeconomic status (Milgram *et al*, 2006). It has long been thought that socioeconomic status contributes to mental health, with higher prevalence of depression, anxiety, and schizophrenia in lower-income populations (Hemmingson, 2014; Holzer *et al*, 1986; Kessler *et al*, 1994; Zimmerman and Katon, 2005). The specific environmental features responsible for the risk are difficult to delineate, however. For example, one factor that has been a focus of attention in human studies, income inequality (Pickett and Wilkinson, 2010), is unlikely to apply directly to rodent-enriched environment models, but dominant and subordinate

rodents may have unequal access to preferred toys or shelters in enriched environments.

EFFECTS OF PSYCHIATRIC MEDICATIONS AND TREATMENTS ON ADULT NEUROGENESIS

In addition to looking for parallels between factors that regulate neurogenesis and those that predispose humans to psychiatric disorders, a great deal of work has investigated the relationship between neurogenesis and treatments for mental illness (Figure 1). Demonstrating an effect of a psychiatric medication on neurogenesis provides intriguing but relatively weak evidence for a link between new neurons and disease, but the finding that drugs with different direct targets and nonpharmacological treatments have similar neurogenic effects begins to make a stronger, if still indirect, case for a causative connection.

Depression

The past decade and a half of research on the role of adult neurogenesis in mental disorders has focused mainly on depression. The neurogenesis hypothesis of depression (Duman *et al*, 1999; Madsen *et al*, 2000; Sahay and Hen, 2007; Sapolsky, 2000) postulates that the production of new neurons may be causally related to depressive behaviors, based primarily on findings that stress inhibits adult neurogenesis and increases vulnerability to depression, that

the time course of the differentiation, maturation, and integration of new neurons into dentate gyrus circuitry parallels the timing of antidepressant efficacy, and that antidepressant treatments increase the rate of adult neurogenesis in the dentate gyrus (Duman *et al*, 1999; Madsen *et al*, 2000).

Many classical antidepressant drugs and therapeutic interventions have positive effects on the rates of cell proliferation and neurogenesis in the dentate gyrus of adult mammals. This was demonstrated first by showing that electroconvulsive shock treatment, a clinically effective tool to treat major depression, increased neurogenesis in adult rodents (Madsen *et al*, 2000; Scott *et al*, 2000), an experiment likely inspired by earlier findings that chemical and electrically induced seizures increase granule cell precursor proliferation (Bengzon *et al*, 1997; Parent *et al*, 1997). Malberg *et al* (2000) significantly extended this finding, demonstrating that chronic treatment with classic antidepressants fluoxetine, reboxetine, and tranylcypromine, as well as electroconvulsive shock, increased neurogenesis in the adult rodent. This research importantly showed that different antidepressants that target different neurotransmitters, that is, serotonin and norepinephrine, have the same effect on adult neurogenesis (Malberg *et al*, 2000). Chronic fluoxetine and electroconvulsive shock also increase adult neurogenesis in non-human primates (Perera *et al*, 2007, 2011). Additional studies have since shown that additional SSRIs (citalopram and escitalopram), tricyclics (imipramine), and mood stabilizers (lithium) all enhance

Figure 1. Summary of the effects of psychiatric drugs and other therapies on different processes involved in neurogenesis. The processes, shown below, include division of stem and precursor cells to generate additional neuronal progenitors (proliferation), development of neuronal morphology and functional synapses (maturation), and avoidance of cell death that normally eliminates a large fraction of new neurons (survival).

cell proliferation and neurogenesis in the adult rodent (Chen *et al*, 2000; Jaako-Movits *et al*, 2006; Jayatissa *et al*, 2006; Surget *et al*, 2008). Atypical antidepressants, such as AMPA-receptor potentiators, agomelatine, and other 5HT-2C antagonists, increase production of new neurons in the rodent as well (Bai *et al*, 2003; Banasr *et al*, 2006; Dekeyne *et al*, 2008; Soumier *et al*, 2009). Similarly, transcranial magnetic stimulation, like ECS, increases proliferation of granule cell precursors (Zhang *et al*, 2014). Acute, but not chronic (see above), sleep deprivation also rapidly increases granule cell precursor proliferation and improves symptoms of depression (Grassi Zucconi *et al*, 2006), although the speed of these behavioral changes make it unlikely that they are related to the birth of the still very immature neurons.

Most studies of antidepressant treatment on adult neurogenesis have focused on changes in proliferation, but recent findings indicate that antidepressants can alter maturation and survival of new neurons as well. Chronic fluoxetine treatment hastens maturation of new neurons and enhances LTP of new neurons (Wang *et al*, 2008). Agomelatine increases survival of new neurons and enhances their maturation, as seen by their more rapid loss of the immature marker PSA-NCAM (Soumier *et al*, 2009). Electroconvulsive shock, deep brain stimulation, and transcranial magnetic stimulation also hasten new neuron maturation, enhancing dendritic growth and inducing mature spine formation in newly born neurons and increasing their survival (Schmuckermair *et al*, 2013; Zhang *et al*, 2014; Zhao *et al*, 2012).

The slow time course of maturation and integration of new neurons into dentate gyrus circuitry was also part of the initial rationale for the neurogenesis hypothesis of depression, as the well-accepted delay in therapeutic onset of antidepressants suggests that some neuroplastic change is required. There is typically a delay of at least 2 weeks between the start of antidepressant treatment and positive effects on depressive behavior (Bodnoff *et al*, 1988; Duman *et al*, 1997; Porsolt *et al*, 1978; Wang *et al*, 2008; Willner *et al*, 1987). It also requires at least 2–3 weeks for granule cells in the rodent dentate gyrus to become functionally integrated into existing circuitry, showing electrophysiological activation and behavioral relevance (Schmidt-Hieber *et al*, 2004; Shors *et al*, 2001; Snyder *et al*, 2005, 2009a). Other studies have suggested a somewhat longer time course of new neuron maturation (Denny *et al*, 2012; Espósito *et al*, 2005; Ge *et al*, 2007; Gu *et al*, 2012; Kee *et al*, 2007; van Praag *et al*, 2002; Zhao *et al*, 2006), a difference that may reflect different methods of assessing integration and functionality (eg, physiological profiles of neurons *vs* behavioral effects), species differences between mice and rats (Snyder *et al*, 2009a), and differential housing or other environmental conditions, such as running, that affect the time course of new neuron maturation (Piatti *et al*, 2011; Snyder *et al*, 2009b). Altogether, rodent studies suggest that new neurons require between 1 and 8 weeks to become mature.

The novel antidepressant ketamine has recently demonstrated very rapid therapeutic effects, within hours (Browne and Lucki, 2013), suggesting a need for reevaluation of the parallel time course idea. Moreover, despite the long-standing belief that classical antidepressants require several weeks to show therapeutic efficacy, a recent meta-analysis suggests that their effects also begin more rapidly than previously thought (Lam, 2012). Very rapid effects of antidepressants seem unlikely to be mediated by increased birth of new neurons, but this is not necessarily a blow to the neurogenesis hypothesis of depression, as the proliferative effects may be important for prolonged or maximal effects of treatment, and the effects of antidepressants on maturation and survival of new neurons, which are only beginning to be examined, could have more rapid functional effects.

Anxiety

Although the role of adult neurogenesis in anxiety disorders has not been intensively investigated as it has in depressive disorders, the high comorbidity seen between anxiety and depression (Hirschfeld, 2001; Lamers *et al*, 2011) suggests that any role that neurogenesis in the dentate gyrus might have in depression is likely to affect anxiety disorders as well. Indeed, animal models of depression often produce anxiogenic-like effects as well (David *et al*, 2009; Fahey *et al*, 2007; Rainer *et al*, 2012), and chronic administration of antidepressants and deep brain stimulation tend to decrease anxiety-like behaviors in animal models (David *et al*, 2009; Dulawa *et al*, 2004; Schmuckermair *et al*, 2013).

Classic anxiolytics typically mimic the effects of the inhibitory neurotransmitter GABA (Tallman and Gallagher, 1985). These medications produce their anxiolytic effects very rapidly, unlike antidepressants, indicating that their mechanism of action is unlikely to involve slow processes such as the generation or survival of new neurons (see above). Chronic use of anxiolytics, however, could potentially have effects on adult neurogenesis that interact with those of antidepressants when coadministered. Studies have shown mixed results of acute anxiolytic or GABAergic drugs on neurogenesis. The benzodiazepine diazepam had no effect on cell proliferation in the dentate gyrus in male mice or male rats (Sun *et al*, 2013; Wu and Castrén, 2009), but increased granule cell precursor proliferation in a third study that used female mice and a 10-fold higher dose of the drug (Petrus *et al*, 2009). There is general agreement that diazepam does not affect survival of the young dentate gyrus neurons in mice or rats (Karten *et al*, 2006; Sun *et al*, 2013; Wu and Castrén, 2009). However, activating GABA-A receptors with barbiturates over several days reduced cell proliferation and increased cell survival in mice in one study (Tozuka *et al*, 2005). This difference between barbiturates and benzodiazepines, both of which act as agonists on the same GABA-A receptor, could potentially be explained by actions of barbiturates at several additional targets (Löscher and Rogawski, 2012). Importantly,

although diazepam has few, if any, effects on adult neurogenesis on its own, it prevents the proneurogenic effects of fluoxetine on adult neurogenesis and behavior (Sun *et al*, 2013; Wu and Castrén, 2009), suggesting that although these drugs are frequently used in combination at the start of clinical treatment, this coadministration may be detrimental if neurogenesis plays a role in human depressive illness.

Anxiolytics might be expected to enhance new granule cell maturation, because endogenous GABAergic signaling has been proposed to have this function (Schoenfeld and Gould, 2013). The first synaptic inputs onto new granule neurons are GABAergic, and running, which accelerates granule cell maturation, enhances GABA in the dentate gyrus (Markwardt *et al*, 2011; Schoenfeld *et al*, 2013; Snyder *et al*, 2009b). In fact, the anxiolytic-like effects of running are blocked by GABA receptor antagonists in mice (Schoenfeld *et al*, 2013), suggesting that running and anxiolytic drugs may share the same mechanism. Little is known about the effects of anxiolytic medications on granule neuron maturation, but pentobarbital increases dendritic length in young granule neurons, whereas the GABA-A receptor antagonist picrotoxin inhibits maturation, decreasing both spine density and dendritic length (Sun *et al*, 2009). In addition to any effects on maturation, the finding that running increases GABAergic signaling in the dentate gyrus and decreases the activation of new granule neurons by stress (Schoenfeld *et al*, 2013) suggests that anxiolytic medications may alter the functioning of new neurons in stressful situations. This mechanism would be very different from the increase in the number of new neurons proposed as a mechanism for antidepressants, but it is consistent with very rapid time course of anxiolytic effects.

Several studies have found that synthetic cannabinoids can reduce anxiety (Fabre and McLendon, 1981; Grant *et al*, 2011; Schindler *et al*, 2008). Cannabinoid effects on anxiety-like behavior in rodents have recently been described (Braida *et al*, 2007; Jiang *et al*, 2005; Patel and Hillard, 2006). Cannabinoids and cannabinoid receptor agonists increase the proliferation of new neurons in the adult dentate gyrus (Avraham *et al*, 2014; Campos *et al*, 2013; Jiang *et al*, 2005) and increase new granule cell survival (Wolf *et al*, 2010). However, the rapid time course of cannabinoid effects on behavior, and dissociations between behavioral and neurogenic effects of different cannabinoids (Wolf *et al*, 2010), argue against the anxiolytic effects of cannabinoids being mediated by adult neurogenesis.

Schizophrenia

Animal behavior models and human genetic studies have implicated the hippocampus in the etiology of schizophrenia. One of the best-characterized animal models of schizophrenia is the neonatal ventral hippocampal lesion model that produces periadolescent onset of schizophrenic-like behaviors in rats (O'Donnell, 2012; Tseng *et al*, 2009). Because schizophrenia has a heritable component, researchers

have long sought for genetic abnormalities that may lead to a predisposition to developing schizophrenia. Genetic analysis of a Scottish family with a high prevalence of schizophrenia indicated a mutation in the *DISC1* (*disrupted in schizophrenia 1*) gene (Millar *et al*, 2000) that codes for a scaffolding protein that interacts with different protein partners to promote development and growth (Soares *et al*, 2011). The locations and time course of *DISC1* expression suggest a role in neurogenesis; in the postnatal brain, it is localized primarily to the hippocampus (Austin *et al*, 2004; Schurov *et al*, 2004). Downregulation of *DISC1* gene in mice has been shown to impair cell proliferation in the adult dentate gyrus (Mao *et al*, 2009). *DISC1* has been suggested to guide migration of new neurons in the dentate gyrus (Namba *et al*, 2011) and, indeed, knockdown of *DISC1* protein in mice leads to accelerated maturation and abnormal morphology of new neurons in the adult dentate gyrus (Duan *et al*, 2007). These new neurons appear to be misplaced in circuitry and show aberrant physiological characteristics. Another gene, *NPAS3*, a member of a family of transcription factors known to be involved in a wide array of functions, including neurogenesis (Crews, 1998), has been shown to be affected in schizophrenia (Kamnasaran *et al*, 2003). Similarly, *NPAS3* knockout mice show impaired neurogenesis in adulthood (Pieper *et al*, 2005).

Research into the effects of antipsychotic medications on adult neurogenesis, however, provide little evidence for a role for adult neurogenesis in treatment for schizophrenia. The classical antipsychotic haloperidol effectively reverses deficits in prepulse inhibition in animal models of schizophrenia (Mansbach *et al*, 1988). However haloperidol had no effect on neurogenesis in the adult dentate gyrus in several studies, using several doses and treatment regimens and examining long-term survival of new neurons as well as their generation (Halim *et al*, 2004; Malberg *et al*, 2000; Wakade *et al*, 2002; Wang *et al*, 2004). Similarly, atypical antipsychotics like olanzapine, risperidone, and clozapine were also ineffective at altering adult neurogenesis in several studies (Green *et al*, 2006; Meyer *et al*, 2010; Wakade *et al*, 2002; Wang *et al*, 2004). One study demonstrated an increase in proliferation with clozapine treatment, but the new cells were lost within 3 weeks, likely before becoming functional, despite ongoing clozapine treatment (Halim *et al*, 2004). Another found that olanzapine increased cell proliferation (Kodama *et al*, 2004), in contrast to other studies (Green *et al*, 2006; Wang *et al*, 2004); the observed increase was only 20% over baseline levels, suggesting that there may be a modest and variable effect of this drug on neurogenesis. One group found increased precursor cell proliferation with risperidone and increased survival of new granule cells with both haloperidol and risperidone (Keilhoff *et al*, 2010a, b). It is unclear why these findings diverge from those of the majority of studies, as the doses, species, and time courses of the studies all overlap. Despite the lack of clear data suggesting effects of antipsychotic medications on adult neurogenesis, it is possible that such effect would emerge when structural changes underlying

schizophrenia are elucidated and animal models of such changes are generated.

BEHAVIORAL EFFECTS OF INHIBITING ADULT NEUROGENESIS

Depression

Short of real-time imaging to track neurogenesis levels in humans, which is not currently possible, the best evidence for a causal role of new neurons in depression will likely come from studies demonstrating depressive-like behavior in animal models of reduced neurogenesis. Rapid or prolonged immobility in the forced swim test (FST), long latency to eat in the novelty-suppressed feeding (NSF) test, and decreased sucrose preference in the sucrose preference test (SPT) are the most commonly used rodent behavioral analogs of depressive behavior. Inhibiting adult neurogenesis, using brain irradiation or the mitotic blocker methylazoxymethanol acetate (MAM), produce no change in immobility in the FST (Airan *et al*, 2007; Bessa *et al*, 2009; Holick *et al*, 2008); however, one study using pharmacogenetic methods to eliminate adult neurogenesis found increased FST immobility (Snyder *et al*, 2011). One possible explanation for these differential findings is that Snyder *et al* (2011) measured immobility during the early phase of testing, when animals are least likely to be immobile, whereas other studies followed a common drug testing protocol and measured immobility during the latter part of the test and/or after a pretest. In the NSF test, or related 'cookie test,' several studies found no effect of inhibiting neurogenesis (Meshi *et al*, 2006; Revest *et al*, 2009; Santarelli *et al*, 2003; Surget *et al*, 2011; Wang *et al*, 2008; Zhu *et al*, 2010). Bessa *et al* (2009) found increased latency to eat under similar conditions; however, the dose of MAM used to inhibit neurogenesis may decrease motivation to eat independent of its effects on neurogenesis (Dupret *et al*, 2005; Shors *et al*, 2001). A study using pharmacogenetic methods showed decreased latency to eat, that is, decreased

depressive-like behavior, in rats lacking new neurons relative to controls. However, this group found a similar difference in transgenic animals without drug treatment to inhibit neurogenesis, suggesting a transgene insertion effect (Groves *et al*, 2013). Fewer studies have examined the effects of increasing, as opposed to inhibiting, adult neurogenesis, but mice with increased neurogenesis because of genetic deletion of a cell death gene also show no baseline change in forced swim or NSF behavior (Sahay *et al*, 2011).

The only study to date to report an effect on NSF found no effect of new neurons under naive conditions but found that acute stress immediately before NSF testing increased latency in animals without neurogenesis but had no effect in controls—suggesting that new neurons can affect depressive-like behavior by buffering the effects of stress (Snyder *et al*, 2011). This effect on stress response may explain why these mice show depressive-like behavior in the FST under baseline/naive conditions—this test, unlike the NSF test, is very stressful, and hence mice may be responding to the stress of the test itself. These stress response effects are intriguing, given the strong relationship between stress and mental health (described above), and suggest that having low levels of adult neurogenesis might increase susceptibility to the effects of stress on mental health (Figure 2). Interestingly, chronic mild stress does not differentially affect depressive-like behavior in mice with inhibited and intact neurogenesis (David *et al*, 2009; Surget *et al*, 2008). This could reflect a role for new neurons only in moderate to severe stress, regardless of duration. Alternatively, as corticosterone treatment and stress inhibit adult neurogenesis, the nonirradiated/nontransgenic control mice in these studies may have decreased numbers of new neurons like the ablated mice, resulting in a lack of behavioral difference.

Although most studies show no change in depressive-like behavior in naive rodents following manipulation of neurogenesis, removal of new neurons alters the behavioral effects of antidepressants. Santarelli *et al* (2003) were the first to show that eliminating adult neurogenesis via irradiation blocked the antidepressant effect of fluoxetine

Figure 2. Diagram showing a potential role for new neurons in maintaining mental health. Genetic, developmental, physiological, experiential, and therapeutic interventions can upregulate or downregulate adult neurogenesis. The population of functioning new neurons may protect an individual from negative or inappropriate effects of stress, increasing resilience and thereby promoting mental health.

on NSF behavior in mice. Since then, several studies have replicated and extended this finding, showing adult neurogenesis is required for the effects of antidepressants on the FST and cookie test as well as on the NSF test (Airan *et al*, 2007; Surget *et al*, 2011; Wang *et al*, 2008). Elimination of adult neurogenesis via irradiation also blocks the beneficial effect of fluoxetine on anhedonia in non-human primates (Perera *et al*, 2011), indicating that this new neuron requirement holds for primates as well and may be relevant in humans. Inhibiting adult neurogenesis in rodents also prevents the antidepressant effects on LTP and HPA axis reactivity to stress (Surget *et al*, 2011; Wang *et al*, 2008). Bessa *et al* (2009) found that decreasing neurogenesis did not prevent antidepressant effects on anhedonia and learned helplessness in rodents, but the MAM treatment used in this study only partially arrested adult neurogenesis, suggesting that greater inhibition of neurogenesis might be necessary to block the antidepressant effects. The antidepressant effects of fluoxetine in the FST were unaffected by irradiation in a strain of highly anxious mice (Holick *et al*, 2008), perhaps fitting with the lack of effect of new neurons on anxiety (see below).

Anxiety

Anxiety-like behavior is generally tested in rodents using exploratory tests like the open field test and elevated plus maze. Lesions of the hippocampus, in particular the ventral hippocampus, decrease anxiety-related behavior, indicating a role for the hippocampus in generating anxiety (Bannerman *et al*, 2014; Deacon *et al*, 2002), suggesting that neurogenesis might also play a role in anxiety. However, several studies have failed to find any effect of genetic or irradiation-induced ablation of adult neurogenesis on anxiety-like behavior in the open field test or elevated plus maze, either in naive animals (Jaholkowski *et al*, 2009; Saxe *et al*, 2006; Snyder *et al*, 2011; Wei *et al*, 2011) or after acute stress (Snyder *et al*, 2011). A recent meta-analysis of open field and elevated plus maze behavior data from 25 studies also found no significant effects of adult neurogenesis (Groves *et al*, 2013). Increasing the survival of new neurons also has no effect on anxiety-like behavior in these tasks (Sahay *et al*, 2011). One study found that deleting the brain-derived neurotrophic factor TrkB receptors from new neurons increased anxiety-like behavior on the open field and elevated plus maze (Bergami *et al*, 2008). It is surprising that deleting a single gene in this neuronal population would have a greater behavioral impact than eliminating the cells altogether. This paradoxical finding suggests that the deletion of this gene may not be limited to new neurons in this model or that changes in TrkB in these neurons has downstream effects in other cell types. In contrast to the lack of effect of adult neurogenesis on anxiety-like behavior, Roughton *et al* (2012) showed that irradiation during the juvenile period in rodents increased anxiety-like behavior on the open field in adulthood, suggesting that postnatal

neurogenesis, and the primary granule cell population that is born during this period, are more important for anxiety than adult-born granule cells.

The NSF test is sensitive to both antidepressants and anxiolytics in rodents, and hence changes in behavior in this test can be interpreted as reflecting anxiety and/or depression (Samuels and Hen, 2011b). Snyder *et al* (2011) found increased latency to feed after acute stress in mice lacking adult neurogenesis, as described above, potentially suggesting increased anxiety-like behavior. However, because the mice showed no behavioral differences in the elevated plus maze but did behave differently in multiple tests of depressive-like behavior, this NSF test behavior appears more likely to reflect depressive-like than anxiety-like behavior.

It is not known whether new neurons are required for the effects of classic anxiolytics. Cannabinoids, however, have anxiolytic-like effects in elevated plus maze and the NSF test that are blocked by ablation of new neurons (Campos *et al*, 2013; Jiang *et al*, 2005). Adult neurogenesis is required for the anxiolytic-like effects of cannabinoids in a chronic stress model of anxiety as well as under baseline conditions (Campos *et al*, 2013). More studies are needed to test the role of new neurons in mediating behavioral effects of cannabinoids and classical anxiolytics.

Schizophrenia

Schizophrenia-associated symptoms may be the most difficult to model in rodent behavior tests. Diminished prepulse inhibition of startle behavior, which is believed to reflect sensory gating deficits, is often described as a biological marker of schizophrenia, although it is not specific to this condition (Braff *et al*, 2001). Rats lacking adult neurogenesis, because of irradiation or MAM treatment, show impairments in prepulse inhibition of acoustic startle (Iwata *et al*, 2008; Maekawa *et al*, 2009). Irradiated rats also show behavioral abnormalities in social interactions and working memory that are also impaired in human schizophrenia (Iwata *et al*, 2008). These findings suggest a potential role for new neurons in schizophrenia-related behavior, although a great deal of work is still clearly needed. The effects of antipsychotics in animals following ablation of new neurons has not been tested, but the apparent lack of effects of these medications on the rate of neurogenesis in rodents suggests that the effects on adult neurogenesis are unlikely to underlie their effects. That said, the lack of baseline effects of antipsychotics on neurogenesis does not preclude the effects in models of schizophrenia.

FUTURE RESEARCH DIRECTIONS

Human Studies

The most direct evidence for a relationship between adult neurogenesis and mental illness has to come from studies of human patients, even though these studies can at best only

offer correlational data—and can currently only provide postmortem snapshots. No studies have examined cell proliferation or neurogenesis in patients with anxiety disorders and very few have looked at the rates of neurogenesis in subjects with schizophrenia. One study of postmortem tissue found a decrease in cell proliferation in the dentate gyrus of adults suffering from schizophrenia compared with controls (Reif *et al*, 2006), although the reported discarding of several samples that had high numbers of Ki67-positive cells suggests potential immunostaining problems in the included samples. It is impossible to make any conclusions about the relationship between adult neurogenesis and schizophrenia or anxiety disorders based on the scant evidence to date.

There have been more studies looking into the role of adult neurogenesis in human depressive disorder. Decreased numbers of MCM-expressing dividing cells were found in postmortem tissue from depressed patients (Boldrini *et al*, 2009; Lucassen *et al*, 2010), although no changes have been found in cell expressing two other cell division markers, PH3 and Ki67, or the stem cell marker nestin (Boldrini *et al*, 2012; Lucassen *et al*, 2010; Reif *et al*, 2006). The current data, therefore, do not strongly support an effect of major depressive disorder on cell proliferation. Examination of antidepressant effects have produced similarly mixed results, showing strong ($6\text{--}20\times$) increases in nestin-expressing precursor cells in two studies (Boldrini *et al*, 2009; 2012) but no change in cell division in another (Lucassen *et al*, 2010). Taken together, these findings suggest a possible association between neurogenesis and depressive disorder, but they also point to several difficulties with postmortem studies. First, immunostaining in human postmortem tissue is difficult, and the resulting staining is generally of much lower quality than immunostaining in perfused rodent brain. Second, the variability in these studies is quite high, and hence even $10\times$ differences across means can just barely reach statistical significance. Third, without injecting BrdU before death, which is rarely done in human studies (Eriksson *et al*, 1998), there is no way to follow new cells and compare rates of true mature neuron production.

There is clearly a need for innovative and reliable *in vivo* methods of identifying new neurons in humans, both in postmortem tissue and, ideally, in the living brain. Live imaging of neuronal precursor cells or recently generated neurons in humans has been discussed, but the available techniques do not yet have the sensitivity and specificity required to detect adult neurogenesis (Couillard-Despres and Aigner, 2011). The advancement of such technology would allow for studies that can address critical questions, such as whether the rate of neurogenesis changes over the course of disease and whether there is a within-subject change in the rate of neurogenesis with treatment. Technology that enables live imaging of adult neurogenesis would be invaluable for resolving basic questions about whether adult neurogenesis plays a role in mental illness.

Animal Models

Because of the difficulties in studying adult neurogenesis in humans, described above, the vast majority of information on the interplay between adult neurogenesis and mental illness comes from work on rodents. Although work in rodent models has generated many new ideas about potential roles for new neurons in the etiology and treatment of mental disorders, the limitations of studying very complex human thought processes in rodents are clear (Donaldson and Hen, 2014; Hyman, 2014). A handful of studies have investigated the role of new neurons in antidepressant treatment in non-human primates, but these studies are tremendously costly, and it is largely unknown how well non-human primate psychiatric models reflect conditions in humans.

There is a clear need for better rodent models of mental illness. The term ‘animal models’ of psychiatric disease is used to mean both tests of behaviors that model symptom and manipulations that increase disease-related behaviors in these tests. Both of these need improvement. It is unclear which aspects of mental illness rodents are capable of reproducing. Clearly, ‘mice will never have guilty ruminations [or] suicidal thoughts’ (Donaldson and Hen, 2014), although they (if rats are included) do show evidence of some mental processes related to psychiatry, such as motivation and empathy (Ben-Ami Bartal *et al*, 2011; Der-Avakian and Markou, 2012; Simpson *et al*, 2012). But even if rodents could experience many features of human mental illness, it would be difficult to determine with any certainty because of their inability to communicate with us. It is very difficult to imagine, for example, how we would know if a mouse had hallucinations. But the problems with modeling psychiatric illness are not all due to shortcomings of rodents; incomplete understanding of the constellations of symptoms associated with mental illness in humans hinders development of animal models as well. Improved understanding of human symptoms, for example the key features of anhedonia or the relationship between anxiety and depression, will enable generation of better tests of rodent behaviors modeling these symptoms. Although the current rodent models may seem to lead in circles as far as drug development is concerned (Donaldson and Hen, 2014; Hyman, 2014), any improvement on the human or the rodent side could potentially produce a positive feedback loop in which an improved rodent model might generate a new hypothesis about human illness that could then inspire an even better rodent model.

Improvement is also needed in animal models of the other type, that is, manipulations that increase behaviors resembling psychiatric symptoms. There are models of schizophrenic-like behavior in rats, but for the reasons discussed above, it is difficult to determine how well they truly model the disease. Developmental insults and/or chronic stress in adulthood have been used to increase depressive-like behavior in rodents. However, the majority of experiments looking at effects of psychiatric medications

on neurogenesis or the effects of neurogenesis on mental illness-related behavior have used naive animals, under baseline conditions. Even if animals lacking neurogenesis show no change in psychiatric disease-related behavior under baseline conditions, behavioral changes may result from a combination of altered neurogenesis and a particular adverse experience. In the case of depressive-like behavior, this idea is supported by the finding that mice lacking adult neurogenesis show normal behavior in the NSF test if they are naive but increased depressive behavior following acute stress (Snyder *et al*, 2011).

Animal models used for work on the role of adult neurogenesis in psychiatric disorders should attempt to model risk factors for developing those diseases rather than focusing on naive animals. Because traumatic life events are so strongly associated with many forms of mental illness, future research should investigate the role of new neurons on the development of behaviors associated with mental illness in various stress models. To date, no studies have looked at the long-lasting effects of acute traumatic events in rodent models of neurogenesis ablation. It is possible that adult-born neurons in the hippocampus may facilitate recovery and general resiliency to salient stressors, whereas animals with impaired or ablated neurogenesis may show heightened and prolonged ill effects of traumatic events (Figure 2). In addition, it is unknown how neurogenesis is functionally involved in behavioral changes produced by stressors occurring prenatally or in early life. Combinations of genetic predispositions, prenatal illness/inflammation, early-life stress, chronic stress in adulthood, and/or single traumatic events may produce behavioral phenotypes that provide insight into the role of neurogenesis in development of and recovery from anxiety, depression, and schizophrenia.

Neurogenesis in Other Regions

Finally, although the vast majority of research on adult neurogenesis in psychiatric disease has been aimed at the dentate gyrus, new neurons generated in other brain regions could play a role in mental health as well. The brain region that adds the largest number of neurons in adulthood is the olfactory bulb. Although the olfactory bulb may not come to mind as a key region for mental illness, the depressive-like state produced in rodents by removal of the olfactory bulbs and the olfactory changes in depressed human patients suggests a potential association between olfaction and depression (Schablitzky and Pause, 2014; Yuan and Slotnick, 2014). Olfactory deficits are observed in schizophrenia as well (Nguyen *et al*, 2010; Rupp, 2010). The effects of antipsychotic and anxiolytic medications on cell proliferation in the subventricular zone (SVZ), the source of olfactory bulb neurons, have been examined in a handful of studies, but with mixed results (Green *et al*, 2006; Kippin *et al*, 2005; Kodama *et al*, 2004; Wakade *et al*, 2002; Yamaguchi and Mori, 2005).

The olfactory epithelium generates new neurons throughout life and therefore offers a source of neural stem cells that is relatively easily accessed in humans. These cells are often studied as potential markers for neurogenic activity in the brain (Féron *et al*, 1999), although these sensory neurons are not very closely related to the neurons generated in the brain and may not reflect pathological changes in central nervous system stem cells.

Adult neurogenesis has also been reported in other brain areas believed to be involved in depression, anxiety, and schizophrenia, including the amygdala and prefrontal cortex. Adult neurogenesis has been reported in the amygdala of rodents and monkeys (Bernier *et al*, 2002; Jiang *et al*, 2014; Takemura, 2005), although the evidence for double labeling of the proliferation marker BrdU and mature neuronal markers is not especially strong. Effects of olfactory bulbectomy, fear conditioning, and fluoxetine have been observed on the numbers of adult-born cells in the amygdala (Jiang *et al*, 2014; Keilhoff *et al*, 2006; Okuda *et al*, 2009), but it is unclear how many of the affected cells are neurons.

Adult neurogenesis has also been reported in the prefrontal cortex of adult rats and primates (Dayer *et al*, 2005; Gould *et al*, 1999a, b, 2001). The new neurons are small interneurons and make up only a fraction of the newborn cells in this region (Dayer *et al*, 2005; Gould *et al*, 2001). In mice, neocortical adult neurogenesis appears to be almost nonexistent (Snyder *et al*, 2009a). In rats, the number of new neurons generated in neocortex is quite small relative to the number in the dentate gyrus, but the fraction of neurons produced (of small interneurons or granule cells, respectively) is equivalent in the two regions (Cameron and Dayer, 2008). Nevertheless, the small number of neurons produced across a large volume of cortex in rats makes quantitative studies of new neurons in the adult neocortex very difficult. Several studies have investigated the effects of factors related to mental illness on cell proliferation in the prefrontal cortex. Glucocorticoid treatment and stress inhibit proliferation of NG2-expressing cells, the proposed neuronal precursors, in the prefrontal cortex, and antidepressant treatments, including electroconvulsive shock and fluoxetine, increase proliferation in this region (Alonso, 2000; Banasr *et al*, 2007; Czéh *et al*, 2007; Dayer *et al*, 2005; Madsen *et al*, 2005). Olanzapine also increases proliferation in the prefrontal cortex (Green *et al*, 2006; Kodama *et al*, 2004; Wang *et al*, 2004). However, as most new daughter cells in the neocortex do not appear to differentiate into neurons (Dayer *et al*, 2005), it is unclear whether any of these changes reflect effects on neurogenesis. One recent study has reported that chronic fluoxetine treatment increases the generation of GABAergic interneurons in the rodent neocortex (Ohira *et al*, 2013), although this finding will need to be replicated.

Despite the importance of the amygdala and prefrontal cortex to mental health, the potential contributions of adult neurogenesis in these regions has largely been ignored. This is most likely because of the small numbers of neurons

generated in these regions, the difficult nature of neurogenesis experiments in these regions, and the poor quality of much of the resulting data. Although the number of neurons produced in these regions is low, production of even small numbers of interneurons is likely to have functional effects (Cameron and Dayer, 2008). Better methods for identifying the particular types of neurons born in the amygdala and neocortex could potentially lead to identification of some of the previously unidentifiable cells generated in these regions as neurons (Dayer *et al*, 2005). Even without this, better methods for long-term labeling of newborn cells could increase the numbers of new neurons that can be detected, allowing quantitative studies of how these neurons are affected by factors that trigger or treat mental illness. Future studies should also investigate the functional effects of specific ablation of or increases in these new neuron populations. Identifying the location and identity/protein expression pattern of the precursor cells generating new neurons in each brain region will aid in specific targeting of these pools by focal irradiation and pharmacogenetic methods. So little is known about adult neurogenesis in these important regions that this presents a challenge but also a tremendous opportunity for uncovering new links between adult neurogenesis and mental illness.

FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the Intramural Program of the National Institute of Mental Health, National Institutes of Health, USA, 1ZIAMH002784 (to HAC).

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