

The Contribution of Adult Hippocampal Neurogenesis to the Progression of Psychiatric Disorders

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Abstract

New neurons are continuously formed in the adult hippocampus of the human, nonhuman primate, and rodent throughout life though rates of neurogenesis precipitously decline with age to near zero levels at the end of the natural life span. Since its discovery in the 1960s, a large number of studies have documented numerous environmental and genetic factors which regulate adult neurogenesis. Chief among the positive regulators of neurogenesis are exercise and antidepressant drugs. Chief among the negative regulators of neurogenesis besides age are stress and inflammation. To the extent that many psychiatric disorders are comorbid with or causally related to stress and inflammation, decreased neurogenesis could be a partial contributor to the pathophysiology of the disorders. However, the functional significance of new neurons in behavior has yet to be established and is currently a hotly debated topic. Therefore, it is not clear whether changes in neurogenesis that occur alongside psychiatric illnesses are a cause or a consequence of the mediating factors such as stress, drug abuse, and inflammation, which are complexly involved in the disorders. It

will be important moving forward to use modern technologies capable of instantaneously inactivating cohorts of new neurons to test their functional significance in behavior and the etiology of mental illnesses.

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Introduction

In this chapter, we consider the recent literature on the role of adult hippocampal neurogenesis (and lack thereof) in psychiatric illnesses. We first carefully define adult hippocampal neurogenesis and briefly review the current understanding of the functional significance of adult neurogenesis in behavior, a topic that is still under considerable debate. Followed by a brief review of the positive regulators of neurogenesis, the majority of the chapter emphasizes known risk factors of psychiatric illnesses that are confirmed to negatively regulate neurogenesis, including the effects of stress and inflammation. Lastly, we discuss the

evidence in support of a role of adult hippocampal neurogenesis in schizophrenia and major depressive disorder as well as currently employed pharmacological treatments.

Adult Hippocampal Neurogenesis

Prior to the 1960s, it was generally thought that new neurons were not formed in the adult human brain [1]. Instead, it was thought that a person was born with all the neurons they would ever have and that all one could do as an adult was to lose neurons through environmental exposures and experiences [2]. However, it was not until the late 1980s to early 1990s when immunohistochemical technologies became available that convinced the entire scientific community that neurogenesis continues to occur in certain regions of the adult human brain throughout life (Fig. 1) [3]. Remarkably, in two regions of the brain, levels of neurogenesis can be quite high, such as in the hippocampus and the olfactory bulb [4]. Because of the crucial importance of the hippocampus in learning and memory, since the 1990s, much attention has been devoted to understanding the regulatory factors and functional significance of adult hippocampal neurogenesis. Therefore, in the remainder of this chapter when we use the term adult neurogenesis, we are referring to adult hippocampal neurogenesis unless otherwise noted.

The mammalian hippocampus is crucially important for associative learning [5]. This has been demonstrated extensively in human and animal lesion and functional imaging studies [6, 7]. The hippocampus is well positioned for a function in forming associations between different types of stimuli because it is the first place in the brain that receives information from all the sensory modalities [5]. The information first converges on a region of the hippocampus known as the dentate gyrus. The granule neurons of the dentate gyrus receive the information through their dendrites

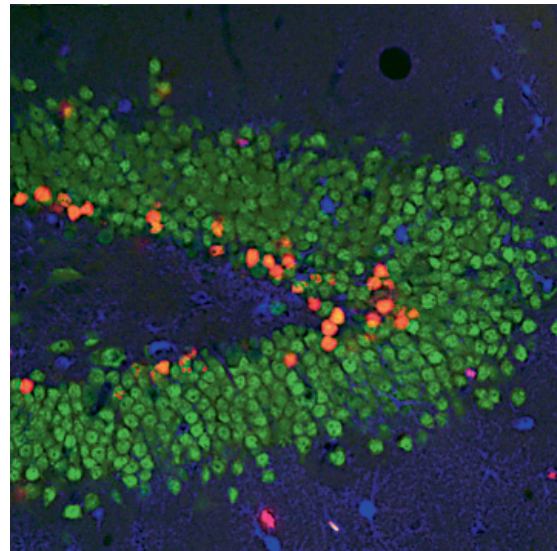


Fig. 1. Measuring adult hippocampal neurogenesis. Photograph of a section through the granule cell layer of the dentate gyrus of the hippocampus of a mouse, triple fluorescently stained to visualize adult neurogenesis. The mouse was given an intraperitoneal injection of bromodeoxyuridine (BrdU) to label dividing cells approximately 1 month before the mouse was euthanized. The brain was then sectioned and stained using immunohistochemistry. The red fluorescent label was conjugated to an antibody against BrdU and, therefore, detects newly formed cells approximately 1 month old. The green label was conjugated to an antibody against neuronal nuclear protein, to detect mature neurons. The blue label was conjugated to an antibody against S100 β to detect mature astrocytes. The cells in the inside layer adjacent to the hilus that are yellow/orange have both the BrdU indicating newly formed cell that subsequently differentiated into a mature neuron, an episode of neurogenesis. A few cells outside the granule layer labeled purple indicate newly formed astrocytes.

which contact terminals of afferent entorhinal cortical neurons (Fig. 2). The entorhinal cortical neurons carry processed sensory information that is segregated by modality.

One of the features of the mapping from the entorhinal cortex to the dentate that is thought to be critical for its function as an integrator of information is that the granule neurons are far more numerous than the relatively sparse inputs

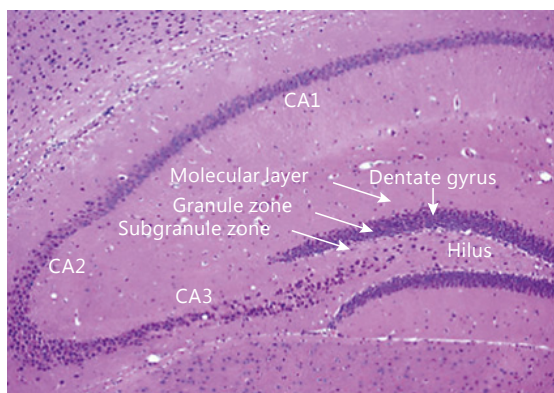


Fig. 2. Anatomy of the hippocampus. The hippocampus is composed of the dentate gyrus, CA1–CA3 fields. Information flowing into the hippocampus makes first contact on dendrites of granule neurons of the dentate gyrus which project into the molecular layer. Axons of granule neurons project to CA3 through the hilus.

from the entorhinal cortex [8]. This feature of few to many mapping is thought to enable unique representations even for very similar contexts or pairings of multiple related stimuli. This ability to distinguish subtle differences between similar contexts is referred to as pattern separation. The idea that the granule neurons of the dentate gyrus play a crucial role in pattern separation has recently received a great deal of attention [9–12]. The granule neurons, primarily excitatory and glutamatergic, project to the CA3 region of the hippocampus, a region of the hippocampus that has been widely studied for its role in long-term potentiation and integration of the sensory information into unique representations [5].

For the purposes of this review, an episode of adult hippocampal neurogenesis will be defined as an event in which a cell is born in the subgranule zone of an adult organism AND subsequently survives AND differentiates into a granule neuron AND functionally integrates into the hippocampal circuitry. The entire process from proliferation to integration is estimated to take approximately 4 weeks or longer [13]. The inside layer of the dentate gyrus adjacent to the hilus is referred

to as the subgranule zone; it contains the stem cells and progenitor cells that asymmetrically divide to produce one daughter cell that has the potential to differentiate into a neuron or glial cell while the other cell retains its regenerative capacity for additional cycles of asymmetric division (Fig. 2). Eventually, the progenitor cell differentiates into an astrocyte [14]. A majority of the newly formed daughter cells do not survive [15]. Of the remaining cells that survive, a majority differentiate into granule neurons (approximately 80–90%) [16]. As they mature, they move to the outer edges of the granule cell layer. Approximately, 10–15% of the surviving cells differentiate into astrocytes, and remaining cells differentiate into oligodendrocytes or remain undifferentiated for an extended period [17]. Using methods which label the cells in vivo (e.g., by expressing green fluorescent protein), it has been estimated that it takes approximately 3–4 weeks for a newly divided cell to differentiate into a functional neuron [13]. Because the process of adult hippocampal neurogenesis involves multiple steps, a treatment or factor can affect adult hippocampal neurogenesis by affecting any or multiple stages in the process. For example, a treatment might increase proliferation of dividing cells but have no influence on survival or vice versa. Alternatively, a treatment might have no influence on proliferation or survival but might increase differentiation and integration. In all cases, net neurogenesis would increase.

Neurogenesis across the Life Span

Perhaps the most crucial factor to consider when evaluating levels of adult hippocampal neurogenesis is the age of the animal at the time when the measurement was taken. Age is crucially important to consider when interpreting group differences in neurogenesis because even slight differences in age distribution will confound the response unless measures are taken to account

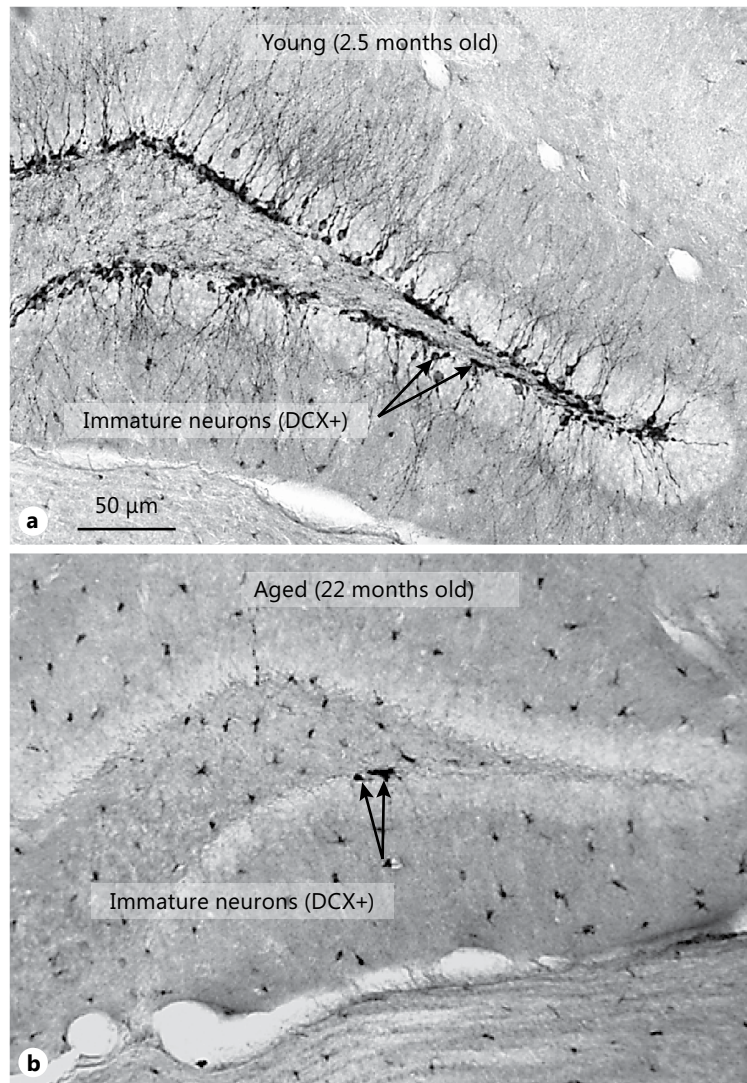


Fig. 3. Adult hippocampal neurogenesis dramatically declines with age. Photographs of the granule layer of the dentate gyrus stained for the doublecortin (DCX) marker of immature neurons of a young adult (a) and an aged mouse (b).

for the effect of age using statistical methods (Fig. 3). Levels decrease dramatically from young adult to middle aged to aged, with barely detectable levels at the end of the life span [18–20]. This has important implications for understanding the functional significance of adult hippocampal neurogenesis because neurogenesis is at such low levels in aged relative to younger subjects, yet aged subjects' brains are still broadly functional. Further, neurogenesis would be predicted to play a differential role in psychiatric

illnesses depending on the time point during development that the psychiatric illness presents itself.

Functional Significance of Adult Hippocampal Neurogenesis

Because of the large literature establishing the role of the hippocampus in learning and memory, it is often assumed that adult hippocampal

neurogenesis serves a specific function in learning and memory. It is well established that new neurons are more excitable than older neurons and have lower thresholds for displaying long-term potentiation [13, 21, 22]. Moreover, the idea that a new neuron might be more moldable to experience than an older neuron is intuitive and consistent with much of the evidence. However, the idea that adult neurogenesis plays a specific role in learning and memory as opposed to merely a result of prolonged development of a brain region is debatable [23–30]. One piece of evidence consistent with the latter idea is the precipitous drop-off in neurogenesis with age, much faster than any decline in learning and memory. Hence, if neurogenesis plays a specific role in a learning function, then aged subjects would be expected to be completely impaired in that domain, but no such complete impairment occurs with aging.

One method that has been used to evaluate whether neurogenesis plays a specific function in learning and memory is to abolish neurogenesis and measure the response on a learning and memory task. Older studies used crude methods to abolish neurogenesis that likely induced side effects that impaired learning and memory, such as administering chemotherapy or exposing the brain to irradiation [25, 31–33]. Modern approaches to specifically ablate neurogenesis include transgenic models. For example, in one version of these models, the nestin promoter is used to drive the expression of a viral-derived enzyme that converts exogenously administered ganciclovir into a product that incorporates into the DNA of dividing cells. The incorporation of the phosphorylated ganciclovir into the DNA drives the cell toward programmed cell death. Using these methods, neurogenesis can be specifically ablated without inducing high levels of inflammation or other side effects [34]. Recently, a meta-analysis concluded that when neurogenesis is ablated using these more specific methods, no impact on learning and memory is detected [30].

One possible explanation is that the hippocampus is able to compensate for the loss of neurons by extending synapses in older neurons, hence masking the true contribution of the new neurons to the learning and memory performance. One way to get around the problem of compensation is to use optogenetics to label cohorts of new neurons with inhibitory opsins [35] or to use inhibitory designer receptors such as inhibitory DREADDs to inactivate cohorts of new neurons instantaneously, on command [36], when the animal is acquiring a task or recalling a memory. The advantage of this method is that rather than being completely eliminated, new neurons are allowed to integrate into the circuit and are then manipulated directly during the learning or memory event. This way, the hippocampus has no time to compensate for the loss of the function of these new neurons, so it is expected to more robustly reveal their functional significance. One such study reports that inactivating a small cohort of new neurons labeled with 2 injections of retrovirus using an optogenetics strategy can completely abolish learning and memory performance on the Morris water maze spatial learning task [35]. These data are certainly incredible, if true, but will have to be replicated before any strong conclusions can be drawn at this time.

Positive Regulators of Neurogenesis

Exercise

Besides the youthfulness of the animal, the factor that arguably produces the most robust increases in levels of adult hippocampal neurogenesis is aerobic exercise [37]. This has been established in rodents [16, 38, 39] with supportive data in humans [40]. Allowing mice access to a running wheel increases adult hippocampal neurogenesis by 2- to 5-fold depending on the mouse strain and amount of running performed by the mouse [16]. Importantly, the effect of running on increasing neurogenesis is not a result of the

environmental enrichment of having a wheel or sensory deprivation of not having any enrichment. Multiple studies have now confirmed that a highly enriched environment does not increase adult hippocampal neurogenesis by very much unless it includes an aerobic exercise component [41, 42]. Aerobic exercise itself strongly activates the hippocampus, which is likely related to the induction of neurogenesis detected in this region [43, 44]. These discoveries have a few important implications for understanding the relationship between adult hippocampal neurogenesis and psychiatric illnesses. First, if the illness is associated with changes in physical activity, then parallel changes in neurogenesis would be expected to follow. Second, if the illness is associated with differential activation of the dentate gyrus independent of physical activity, then corresponding changes in neurogenesis would also be expected to follow.

Antidepressant Drugs

It has been established that antidepressants increase adult hippocampal neurogenesis in rodents [45–49]. There has been some speculation that the increased neurogenesis that occurs from antidepressants is related to their therapeutic effect for treating major depression [46, 47]. This is largely because it takes approximately 3–4 weeks for a new neuron to integrate into the circuit and establish functional connections in rodent models, which is approximately how long it takes for antidepressants to ameliorate depressive symptoms in humans. However, it must be remembered that the 3- to 4-week differentiation/integration time is for mice not humans. In at least one nonhuman primate, the crab-eating macaque monkey, it was estimated that the time for a newly formed cell to differentiate into a functional neuron takes more than 6 months [50]. Hence, if the differentiation time in humans is on a similar timescale as the macaque, then increased neurogenesis is unlikely to contribute to the ameliorating effects of antidepressants.

Genetics

Mouse studies have established that adult hippocampal neurogenesis is strongly influenced by genotype [16, 51]. Certain mouse strains display much higher levels of neurogenesis than others under the same environmental conditions. The implication for psychiatric disorders is that genetic predisposition for mental illnesses would be expected to covary with levels of neurogenesis to the extent that the individuals with the illness are genetically defined.

Negative Regulators of Neurogenesis

Drugs of Abuse

Extensive literature has established that repeated administration of drugs of abuse, such as alcohol [52–55], cocaine [56–59], and opiates [60–62], decreases adult hippocampal neurogenesis, as reviewed elsewhere [63–65]. However, therapeutic doses of amphetamines increase neurogenesis in at least one mouse model [66]. The implication for a role in psychiatric illnesses is that psychiatric illnesses are often comorbid with drug abuse, and hence reduced neurogenesis would be expected to follow.

Stress

One of the first factors discovered to regulate levels of adult hippocampal neurogenesis was psychological stress [67, 68]. Unlike brief physical stress, which occurs, for example, with exercise, psychological stress decreases neurogenesis [69]. This has potentially important implications for understanding the relationship between adult neurogenesis and psychiatric disorders, as psychological stress often accompanies mental illness. The body's physiological response to stress is mediated by the hypothalamic pituitary adrenal (HPA) axis (see section on depression) and the sympathetic nervous system. Collectively, these systems coordinate the endocrine and autonomic responses through the release of cortisol,

epinephrine, and norepinephrine, which mobilize the necessary resources to handle and subsequently recover from a stressful event. Generally, activation of the stress response is adaptive, but exposure to intense and/or prolonged stressful experiences can have detrimental effects.

Psychological stressors have a well-established link to the development of psychiatric disorders, as stressful experiences often precede the onset of a depressive or psychotic episode [70]. Given that not all individuals exposed to chronic and/or extreme stressors go on to develop a psychiatric disorder, the general consensus is that a genetic predisposition, environmental factors, or other causes of intrinsic vulnerability create a subgroup of at-risk individuals [70]. Therefore, stressful experiences likely act in combination with preexisting states to impair mental health. Evidence of alterations in the stress response have been demonstrated in multiple psychiatric diseases. A sizable proportion of depressed individuals show elevated plasma levels of cortisol compared to nondepressed controls [71]. Stress is commonly used to induce symptoms of depression in animal models, as chronic stress is known to recapitulate depression-like symptoms such as anhedonia, which is often assessed by sucrose consumption [70]. In schizophrenia, measurement of salivary cortisol levels has shown that cortisol is elevated during the first schizophrenic episode [72]. At-risk subjects and those experiencing their first psychotic episode also report higher levels of perceived stress compared to controls [72]. Moreover, imaging studies have shown that the volume of the pituitary is increased during the first episode as well as in individuals that are considered at high risk of developing schizophrenia, indicating abnormalities in a key structure of the HPA axis [72]. Interestingly, the increased pituitary volume is only detected in high-risk individuals that later go on to develop psychosis. Schizophrenic individuals generally do not show increased pituitary volume compared with controls, indicating that alterations in the HPA axis

may occur as the disease progresses [72]. Accompanying these basal changes are an increased responsiveness to stressful events. Schizophrenics were shown to experience an elevated emotional reaction and higher cortisol levels in response to daily life stress [73].

Stress has been convincingly shown to negatively impact the hippocampus, as chronic elevations in cortisol are associated with atrophy of the hippocampus [74]. This vulnerability is related to the hippocampal role in regulating activation of the HPA axis, as the hippocampus has a high density of the corticosterone glucocorticoid and mineralocorticoid receptors [70]. The presence of these receptors may make the hippocampus particularly reactive to stress. For instance, overwhelming evidence has shown that stress impairs hippocampal neurogenesis [70], as a number of studies, utilizing various stressors, report decreases in cell proliferation, survival, and differentiation [75–80]. In nonhuman primates, social isolation for 1 or 3 weeks has been shown to decrease new cell proliferation as well as the number of new cells that differentiate into new neurons, as shown by decreased colabeling of bromodeoxyuridine (BrdU) and doublecortin (DCX) [81]. Further, exposure to a social defeat paradigm has shown that defeated rats continue to display a reduced number of DCX-positive cells 3 months after stress exposure [82]. Ultimately, the evidence demonstrates that hippocampal neurogenesis is susceptible to stress-induced alterations.

While numerous types of stressors can reduce hippocampal neurogenesis, variations in the predictability and controllability of the stressor have been shown to modulate the effects of stress on neurogenesis. For instance, exposure to uncontrollable foot shocks has been shown to decrease cell proliferation [78]. However, if the animal can learn to avoid the foot shock, no deficits in cell proliferation or new cell survival are observed [83]. Whereas if the stressor is predictable, even if it is chronic in nature, there is evidence that neurogenesis may actually be stimulated. Parihar

et al. [84] reported that exposing rats to 5 min of daily restraint stress at the same time of the day for 28 days produced a decrease in anxiety- and depression-like behaviors. Moreover, predictable chronic stress increased proliferation of new cells in the subgranular zone and increased the proportion of DCX-positive cells, indicating enhanced new neuron production. This increase in neurogenesis may relate to stress-induced memory enhancement, as glucocorticoids can enhance memory under select conditions [85]. These results demonstrate that the nature of the stress exposure alters the effects of the stressor on hippocampal neurogenesis, as the ability to predict or even control exposure to the stress helps buffer the negative effects.

Exposure to pre- or perinatal stress can have enduring effects on hippocampal neurogenesis [80]. For example, Mirescu et al. [86] found that perinatal stress in the form of daily maternal separation for 2 weeks produced a prolonged reduction in new cell proliferation. Maternal separation occurred on postnatal days 1–14, but BrdU was not administered to the offspring until they were 60–70 days old. Assessment of cell proliferation 2 h after BrdU administration showed a reduction in the number of BrdU-positive cells in the offspring that experienced maternal separation for 180 min for 2 weeks. New cell survival was also reduced 1 week after BrdU administration, but this deficit was no longer present 3 weeks after BrdU administration. No changes in cell proliferation or survival were seen if the maternal separation only lasted for 15 min, indicating that the severity of the stressor is a key factor in determining whether persistent deficits in proliferation develop [86]. Moreover, Mirescu et al. [86] stated that perinatal stress modulated the response to a stressor in adulthood (i.e., fox odor), as deficits in cell proliferation were evident in the nonstressed control offspring whereas stressed offspring failed to show a further reduction in proliferation. This lack of a decrease in proliferation may relate to the fact that proliferation in the

perinatal-stress group was already attenuated in the absence of an additional stressor and may be indicative of a comprised response to adulthood stress [86]. Prenatal stress has been reported to produce similar deficits in neurogenesis. Exposing pregnant nonhuman primates to a 6-week period of stress (i.e., random acoustic startle) during either the early or late stage of pregnancy produced enduring changes in behavior, elevated cortisol levels, and a decrease in the number of BrdU-positive cells in the offspring. Assessment of the behavioral and physiological changes in the prenatally stressed and nonstressed offspring occurred when the animals were 2.5–3 years of age, indicating the prenatal effects persisted for an extended length of time confirming long-lasting changes following early-life stressors. Potentially, early-life stressors that predispose individuals to psychiatric disorders may set the stage for altered neurogenesis that persists well beyond the initial exposure.

Stress-induced reductions in neurogenesis may develop through multiple mechanisms. Direct administration of corticosterone to rats has been reported to decrease cell proliferation, as measured by the number of Ki-67-positive cells and the density of DCX-positive cells in the granular cell layer [87]. Further, corticosterone injections decreased the proportion of new cells that differentiated into neurons, as the proportion of cells that colabel with BrdU and the mature neuron marker NeuN (neuronal nuclei) is reduced in corticosterone-treated rats [88]. Interestingly, the influence of corticosterone on neuronal differentiation appears to depend on the timing of exposure, and 9 daily injections of corticosterone reduced neuronal differentiation when it was administered later in cell development (i.e., days 18–27 after division), whereas treatment during days 0–8 or 9–17 after BrdU incorporation did not affect cell differentiation. However, longer corticosterone (i.e., 27 days) treatment administered at any point after a cell was born was found to decrease the proportion of BrdU- and NeuN-

colabeled cells [88]. These data potentially indicate that subchronic exposure to corticosterone has differential effects on neuronal differentiation depending on the age of the cell, whereas chronic elevations in corticosterone are able to reduce new neuron production independent of the age of the cell. Moreover, removal of the adrenal gland which prevents the stress-induced increase in corticosterone was shown to block the decrease in new cell proliferation following exposure to fox odor [89]. These data confirm a role for glucocorticoids in mediating the effects of stress on neurogenesis.

An additional route through which stress may inhibit hippocampal neurogenesis is through alterations in neurotrophic factors, which typically enhance the proliferation and survival of new cells [70]. Exposure to either acute or chronic stress has been found to decrease levels of brain-derived neurotrophic factor (BDNF) [70, 90, 91]. These effects are believed to result from glucocorticoids acting directly within the hippocampus, as direct administration of corticosterone has been shown to decrease BDNF expression in the hippocampus via mineralocorticoid and glucocorticoid receptor activation [92]. Acute immobilization stress was also found to decrease hippocampal expression of nerve growth factor (NGF) and neurotrophin-3 as well as decrease expression of the tyrosine protein kinase receptors TrKA, TrKB, and TrkC that mediate the effects of these neurotrophins [91]. Similarly, exposure to chronic unpredictable stress was found to decrease protein levels of vascular endothelial growth factor [93]. Given the central role neurotrophic factors play in sustaining hippocampal neurogenesis, stress-induced reductions in neurotrophic factors and their cognate receptors are likely a major contributor to the alterations in neurogenesis.

Lastly, stress-induced increases in inflammation have been implicated in mediating the effects of stress on neurogenesis. Prior work has shown that activation of the immune system can inhibit aspects of hippocampal neurogenesis (see section

on inflammation) [94]. Research by Koo and Duman [95] demonstrated that stress-induced release of the proinflammatory cytokine interleukin (IL)-1 β contributes to the inhibitory effects of stress on hippocampal neurogenesis. Inactivating IL-1 β , by administering an antagonist to the IL-1 receptor, was found to block the stress-induced decrease in new cell proliferation. In agreement, IL-1 receptor-knockout mice were protected from stress-induced reductions in cell proliferation [95]. Similar protective effects were found with pharmacological inhibition of nuclear factor (NF)- κ B, which is a transcription factor that regulates expression of multiple inflammatory-related genes. Inhibition of NF- κ B prevented the reductions in new cell proliferation following acute or chronic stress exposure [96]. Collectively, these data highlight activation of the immune system as an additional mechanism through which stress may inhibit hippocampal neurogenesis.

Inflammation

Psychiatric disorders have been traditionally viewed as diseases of neurons, but recent advances have demonstrated that glial cells, such as microglia and astrocytes, likely contribute to psychiatric conditions. Microglia are the innate immune cells that mediate the inflammatory response within the brain (i.e., neuroinflammation). In the healthy brain, microglia express a ramified or resting phenotype that allows the cells to monitor the surrounding microenvironment for signs of injury or cellular distress [97]. If an infection or injury is detected, these cells become activated and express the classic inflammatory phenotype often referred to as M1 activation. Expression of the M1 phenotype is characterized by increased cell proliferation and physical transformations that include retraction of the long processes and an increase in the size of the cell body [97, 98]. Additionally, M1 microglia secrete a variety of inflammatory molecules, including cytokines, chemokines, and reactive oxygen species [98, 99]. These chemical mediators produced by microglia

aid in coordinating the neuroinflammatory response by activating and attracting other cells to the site of injury as well as altering the activity of nonimmune cells including neurons [97]. While not considered an immune cell, astrocytes contribute to the neuroinflammatory response. Astrocytes are activated by inflammatory molecules produced by microglia and subsequently release cytokines and chemokines, upregulate expression of glial fibrillary acidic protein (GFAP), and proliferate [100, 101]. During injury or infection, temporary activation of the neuroinflammatory response is largely beneficial, but prolonged activation can disrupt normal cellular function and even cause cell death [102, 103].

In regard to neurogenesis in adulthood, neuroinflammation has been shown to disrupt the production, survival, and integration of new neurons born into the granule cell layer of the hippocampus [104]. The initial evidence that inflammation impaired hippocampal neurogenesis was provided by Monje et al. [94] and Ekdahl et al. [105]. Both reports employed the bacterial endotoxin lipopolysaccharide (LPS) to simulate a bacterial infection and induce an inflammatory response. Ekdahl et al. [105] found that chronic intracortical administration of LPS significantly decreased survival of new neurons in the hippocampus but had no effect on the proliferation of new cells. In agreement, Monje et al. [94] discovered that intraperitoneal administration of LPS had no effect on cell proliferation, but significantly reduced survival and neuronal differentiation, as shown by decreased DCX expression. Though the routes of LPS administration varied between these experiments, in both instances a neuroinflammatory response would develop as activation of immune cells within the periphery is readily transmitted to the brain and stimulates M1 activation in microglia [106]. Ekdahl et al. [105] described a negative correlation between the number of activated microglial cells and new hippocampal neurons. Moreover, administration of a microglial cell inhibitor (minocycline) was found

to negate the inflammation-induced reductions in neurogenesis [105]. Collectively, these studies provided the foundational evidence that inflammation can negatively regulate hippocampal neurogenesis.

More recent work indicates that there are dose-dependent and individual factors that influence the effects of LPS on hippocampal neurogenesis. For instance, administration of a lower dose of LPS to young and aged mice selectively decreased the number of new neurons in the aged mice but had no effect on the young mice [107]. Given that aged subjects display prolonged microglial cell activation following an immune challenge [108, 109], aged subjects may be more vulnerable to inflammation-induced deficits in hippocampal neurogenesis. Exposure to an immune challenge can further suppress the already low levels of neurogenesis in the aged brain. Further, early-life immune activation was reported to increase sensitivity to adulthood exposure to LPS [110]. Mice that received an LPS injection on postnatal day 14 and a 2nd injection in adulthood had significantly fewer DCX-positive cells compared with saline-treated controls, whereas mice that received a single LPS injection at either time point showed no reductions in DCX-positive cells. Moreover, Bastos et al. [111] reported that lower doses of LPS (i.e., 0.1 and 0.5 mg/kg) had no effect on new cell survival assessed by BrdU-positive cells, whereas administration of a 1 mg/kg dose of LPS significantly decreased survival of new cells in adult mice. Taken together, these data indicate that the effects of immune activation are dose dependent, and that individual differences that alter immune activation may heighten sensitivity to inflammation-induced deficits in neurogenesis. Whether a similar sensitivity exists in psychiatric disorders has yet to be determined.

In addition to alterations in the rates of survival and cell differentiation, inflammation has been reported to alter the function and integration of new neurons into existing neural networks. Prior research has found that new neurons

that undergo maturation and integration during chronic inflammation show an increase in inhibitory synaptic inputs compared with new cells developing under normal conditions and, as a result, show an increased rate and amplitude of spontaneous inhibitory postsynaptic currents [112]. Moreover, maturation during chronic inflammation caused changes in the structure of the inhibitory synapses located on the distal dendrites of new neurons that may indicate enhanced inhibitory connections [112]. These alterations in the balance of inhibitory and excitatory inputs may have enduring effects on the functional activity of new neurons that mature during chronic inflammation. However, the effects of chronic inflammation on synaptic development appear to have a short window to alter new neurons, as exposing new neurons to inflammation during the late phase of synaptic development (i.e., 4 weeks after birth) has minimal effects on excitatory and inhibitory inputs [113]. In contrast, alterations in synaptic inputs and an increase in the number of thin dendritic spines were confirmed if inflammation occurred early on in synaptic development, indicating that new neurons are more vulnerable to inflammation early in the maturation process. In accordance, Belarbi et al. [114] stated that new neurons produced during chronic inflammation show reduced ability to participate in hippocampal networks. Specifically, in the control group, exploration of a novel environment induced expression of the immediate-early gene *Arc* in a greater proportion of new neurons relative to the preexisting mature granule neurons. In contrast, new neurons that matured in chronic inflammation presented similar levels of *Arc* expression as mature neurons, indicating that inflammation may decrease the ability of new neurons to participate in hippocampal networks that respond to spatial information [114]. Exposing new neurons to inflammation during early phases of integration may have the potential to impact the normal functions mediated by the granule cell layer.

The deficits in hippocampal neurogenesis seen following immune activation are likely mediated by the chemical messengers secreted by activated microglia and astrocytes. Prior research has shown that overexpression or direct administration of individual cytokines can impair hippocampal neurogenesis. For instance, administration of the proinflammatory cytokines IL-1 β , IL-6, or tumor necrosis factor (TNF)- α inhibits proliferation, survival, and neuronal differentiation of new cells in the hippocampus [94, 95, 115–118]. These chemical messengers may act directly on neural progenitor cells (NPCs), as NPCs express several cytokine receptors, including IL-1 β and TNF- α [115, 119]. A recent study reported that exposing rat hippocampal NPCs to IL-1 β *in vitro* produced a significant reduction in the number of new cells that differentiated into serotonergic neurons [120]. Research by Green and Nolan [121] indicates that IL-1 β negatively regulates NPC proliferation in culture by increasing levels of glycogen synthase kinase (GSK)-3 β and decreasing levels of the orphan nuclear receptor *tailless* homologue (TLX). Overexpression of GSK-3 β has been shown to degrade β -catenin which participates in stimulating proliferation of NPCs [122]. TLX is expressed on cells undergoing division, and its overexpression increases neuronal differentiation. Inhibiting GSK-3 β via a small-molecule inhibitor was found to block the IL-1 β -induced reductions in TLX expression and NPC proliferation, indicating that GSK-3 β participates in IL-1 β -induced deficits in neurogenesis [115]. In addition, exposing differentiating cells to TNF- α in culture decreases the proportion of cells that differentiate into new neurons and increases the proportion that become astrocytes [119]. However, these effects are only seen if cells are exposed to TNF- α during differentiation and not during proliferation, indicating differential effects depending on the timing of exposure. Overall, findings indicate elevated levels of proinflammatory cytokines disrupt various stages of hippocampal neurogenesis.

Inflammation has been implicated as a risk factor for several psychiatric disorders [123, 124]. For instance, research in humans and animal models indicates that early-life infection increases the risk of developing schizophrenia [123, 125–128]. Moreover, adults that suffer from a severe infection or an autoimmune disorder are at greater risk for developing schizophrenia [129]. The specific mechanisms through which these immune events increase susceptibility for schizophrenia is still a matter of debate, but the data have repeatedly confirmed that immune activation is a clear risk factor that may contribute to the onset and/or symptoms expressed in the disease.

Beyond being a risk factor, abnormalities in immune activation appear to be present during the course of schizophrenia. Several studies have noted increased peripheral levels of inflammatory molecules as measured in serum samples from schizophrenics [130]. A meta-analysis by Miller et al. [131] delineated the role of the disease status and antipsychotic treatment in the expression of peripheral inflammation. Schizophrenic individuals experiencing an acute relapse or their first episode of psychosis show increased serum levels of several proinflammatory cytokines, including IL-6 and TNF- α , and reduced levels of anti-inflammatory cytokines. In contrast, stable medicated schizophrenics did not show higher IL-6 levels versus controls. Moreover, levels of IL-6 were found to be positively correlated with psychopathology scores and were reduced by treatment with antipsychotic medication, though only a limited number of studies have reported such results [131]. Taken together, these findings indicate that peripheral inflammation occurs in schizophrenia, but that the current status of the disease likely modulates the inflammatory profile.

Similar immune disturbances have been noted in the brains of schizophrenics. Levels of IL-6 have been reported to be increased in the cerebrospinal fluid of schizophrenics compared with controls [132, 133]. Additionally, increased microglial cell and astrocyte activation has been shown in schizo-

phrenics, potentially indicating the presence of neuroinflammation [124, 134, 135]. However, this increase in inflammation is only detected in a subset of schizophrenic individuals. In a recent meta-analysis of the levels of neuroinflammation in postmortem samples from schizophrenics, half of the published studies found increased microglial cell activation, whereas the remaining studies found a decrease or no change. These differences in findings may relate to the clinical status of the disease as high levels of paranoia were associated with greater microglial activation, and a similar relationship was noted for peripheral inflammation [131, 135]. In accordance, heterogeneity in the presence of astrogliosis has also been reported in postmortem brains from individuals with schizophrenia [135]. Work by Catts et al. [134] demonstrated that astrogliosis was only detected in schizophrenics that showed other indices of inflammation, whereas in the absence of neuroinflammation expression of glial fibrillary acidic protein and astrocyte morphology did not differ between schizophrenics and controls. Lastly, elevated levels of IL-6 in the cerebrospinal fluid were found to be specific to schizophrenics that showed a delayed response to antipsychotics, suggesting that the presence of neuroinflammation may affect treatment responsiveness [133]. Though factors such as disease status and treatment responsiveness, for example, may help explain the differential expression of inflammation in schizophrenia, what remains unclear is how the presence or absence of inflammation contributes to the progression of the disease and symptom severity.

Inflammation has also been implicated in the pathophysiology of major depressive disorder (MDD) [136]. Similar to schizophrenia, the risk of developing MDD is greater in individuals with a chronic disease characterized by immune activation. For instance, individuals diagnosed with an autoimmune disease, such as multiple sclerosis or rheumatoid arthritis, are more likely to experience MDD [137, 138]. Moreover, 20–40% of individuals treated with the cytokine interferon- α

for chronic hepatitis C subsequently develop MDD, and symptoms of depression are reduced following treatment with standard antidepressants [139]. Indeed, aspects of the behavioral changes associated with immune activation, commonly known as sickness behavior, parallel the symptoms such as altered sleep, lethargy, reduced appetite, and impaired cognitive function commonly seen in depressed individuals [139]. Animal research has demonstrated that stimulating an immune response increases expression of depression-like symptoms, as an acute immune challenge is reported to increase behavioral indices of depression in several tests of emotionality, including the forced swim test and tail suspension test [140]. Additionally, acute immune activation has been shown to produce anhedonia-like behavior, as transient inflammation has been shown to decrease consumption of an appetitive sucrose solution 24 and 48 h after the inflammatory response has dissipated [141]. In accordance, research with healthy adults has shown that transient immune activation produces an increase in anxiety and depressed mood [142]. Taken together, these data indicate that inflammation may elicit symptoms of MDD. Whether inflammation only elicits a depressive episode when it interacts with other risk factors (e.g., genetic/life stress) of MDD or whether inflammation can indiscriminately predispose individuals to MDD is presently unclear. However, a few studies indicate polymorphisms in select genes, such as IL-6 and serotonin, may alter susceptibility to cytokine-induced depression [143, 144]. Clarifying whether inflammation triggers MDD primarily in vulnerable individuals may aid in identifying populations that may benefit from anti-inflammatory therapeutics as well as facilitate preventative measures.

Assessment of peripheral markers of inflammation has shown that approximately a third of individuals with MDD have elevated levels of several inflammatory markers. For example, meta-analyses have shown that serum levels of the in-

flammatory molecules C-reactive protein, IL-6, and TNF- α are elevated in individuals with MDD [145, 146]. However, several studies have reported no changes in cytokine levels with MDD [145, 147], potentially indicating that inflammation may define a subgroup of individuals with MDD. There is some evidence that the presence of inflammation may negatively affect treatment responsiveness, as elevated levels of IL-6 and TNF- α were associated with treatment resistance [148, 149], although these findings have not been consistently reported [136]. More research is needed to elucidate whether the presence of inflammation represents a unique MDD phenotype and how inflammation may alter the response of the patient to antidepressant interventions.

While the precise role of inflammation in the onset and progression of psychiatric disorders is complex, the evidence points to the existence of clusters of individuals within these disease entities that show clear evidence of inflammation. This persistent increase in inflammatory molecules in these individuals likely represents a route through which deficits in neurogenesis may develop. Inflammation has clear effects on survival and neuronal differentiation, as even acute induction of an inflammatory response has been shown to inhibit hippocampal neurogenesis. Given the ability of inflammatory molecules to act directly on NPCs and negatively regulate their proliferation, the expression of a chronic inflammatory state likely creates an environment that suppresses neurogenesis. Gaining a clear understanding of whether inflammation is a causal or consequential factor of these diseases may aid in clarifying the role of inflammation in the pathophysiology of psychiatric diseases.

Neurogenesis in Schizophrenia

Schizophrenia is a chronic neuropsychiatric disease that is estimated to affect approximately 1% of the total population [150]. Schizophrenia is

characterized by the presentation of negative symptoms (i.e., flat affect and social withdrawal), positive symptoms (i.e., delusions, hallucinations, and disordered thought), and cognitive deficits [150]. Abnormalities in neural development have been proposed to contribute to the disorder, as early life events, or being born with select genetic risk factors has been associated with an elevated risk of developing schizophrenia [151]. The first psychotic episode typically occurs in late adolescence or early adulthood [151]. The delayed onset of schizophrenia likely indicates the involvement of a second event (e.g., stress and/or substance abuse) that interacts with genetic and/or other etiological risk factors to trigger the expression of the disease [151].

Neurochemical abnormalities in the production or signaling mechanisms of key neurotransmitters, such as dopamine and glutamate, in select regions of the brain are believed to mediate many of the positive and negative symptoms in schizophrenia [151]. The majority of the current antipsychotic compounds are aimed at normalizing these neurochemical imbalances; while beneficial these drugs often have aversive side effects and fail to fully alleviate all of the symptoms of schizophrenia [150]. Beyond altered neurochemistry, schizophrenia is believed to be a connectivity disorder, as abnormal neural activity has been noted in the default mode network as well as a loss of white matter [152, 153]. Additionally, structural abnormalities have been noted in several regions of the brain, as enlargement of the ventricles and volumetric reductions in the prefrontal cortex, thalamus, hippocampus, and other structures have been reported [151, 154]. Collectively, these structural and neurochemical abnormalities likely contribute to dysfunctional communication within and across regions of the brain. Gaining an understanding of how these diffuse neural changes contribute to disease development and expression of individual symptoms is expected to aid in identifying alternative or additional therapeutic treatments to prevent

and/or alleviate symptoms in schizophrenic individuals.

Alterations in hippocampal structure and/or function are common in many psychiatric disorders. In schizophrenia, for instance, the overall volume of the hippocampus is reduced versus healthy controls [154]. While these volume reductions are not found in all schizophrenics, reduced hippocampal volume is the most common structural abnormality reported [152, 154]. There is some evidence that the volume changes predominantly occur in the anterior division of the hippocampus and less so in the posterior division, but these regional differences are not consistently observed [152]. The changes in hippocampal volume are often present early in the disease, as volume reductions are noted in individuals experiencing their first episode of schizophrenia [155, 156]. How far in advance of disease onset the volume reductions are present is unclear, though a smaller hippocampal volume in children with schizophrenic parents has been reported to be predictive of the schizophrenia risk, potentially indicating these changes may exist long before the first episode [152]. While the volume reductions are often present at the onset of the disease, there is some evidence that hippocampal volume loss is progressive. In a study by Chakos et al. [155], hippocampal volume was significantly reduced in individuals presenting with schizophrenia for 10 or more years versus those with a disease duration of less than 5 years. A recent study reported that early volume loss in schizophrenia occurs in the CA1 and the dentate gyrus of the hippocampus [157]. Individuals diagnosed with schizophrenia 10 or more years earlier show volume reductions in all subregions of the hippocampus, indicating the volume loss may become widespread with increased disease duration [157]. Currently, the cause of these volume reductions is debated, but there is support for white matter loss as well as modest changes in gray matter that may contribute [152].

Accompanying these volume reductions are deficits in hippocampal neurogenesis. Analysis of

cell proliferation in hippocampal samples from postmortem brains of schizophrenics and matched controls has demonstrated that schizophrenics show reductions in Ki-67-positive cells, indicating lower rates of proliferation [158, 159]. These deficits in new cell proliferation appear to be independent of disease duration as well as the age of onset, as no differences in Ki-67-positive cells were noted between those diagnosed at an early or later age [159]. While the decrease in hippocampal neurogenesis does not appear to be the primary mediator of the reduced volume, these changes may relate to the functional deficits seen in schizophrenic individuals. Several reports have linked the abnormalities in hippocampal function to the declarative memory deficits seen in schizophrenics [154]. For instance, imaging studies have shown that activation of the hippocampus is reduced in schizophrenics relative to controls when recalling information, indicating that the hippocampus is not being engaged during memory retrieval. Moreover, abnormalities in the interactions between the hippocampus and the prefrontal cortex have been proposed to contribute to the expression of delusions and hallucinations [154], as the hippocampus along with other regions shows increased activation prior to the onset of a visual hallucination [160]. The precise role of hippocampal neurogenesis in mediating the cognitive deficits associated with schizophrenia has yet to be fully elucidated. However, Schreiber and Newman-Tancredi [161] have suggested that the delusions seen in schizophrenics may relate to abnormalities in the ability to distinguish present from prior experiences that may contribute to the distortion of reality. As noted, hippocampal neurogenesis has been implicated in participating in pattern separation [162]. Inhibition of hippocampal neurogenesis via irradiation has been shown to impair performance on a spatial discrimination task when the two stimuli were located close together, whereas no deficits were seen if the stimuli were spaced farther apart [162]. These data indicate that new neurons in the

dentate gyrus may aid in partitioning stimuli or events that have overlapping information, thus allowing the formation of separate memories for similar experiences. The potential side effects of using irradiation to inhibit hippocampal neurogenesis must be considered when evaluating these data. Though limited, recent evidence has shown deficits in pattern separation in schizophrenic individuals. However, further work is needed to dissociate whether these impairments result from a true deficit in pattern separation or alterations in basic recognition and/or response bias in schizophrenics [163, 164]. Based on the putative link between hippocampal neurogenesis and memory function, it seems plausible that the reduction in hippocampal neurogenesis could contribute to the cognitive impairments associated with schizophrenia. However, as our understanding of the role of hippocampal neurogenesis in memory function continues to evolve with future research, the selective emphasis on the role of neurogenesis in cognitive function in schizophrenia will have to be revisited.

The existing animal models of schizophrenia have also confirmed deficits in hippocampal neurogenesis. While modeling a complex disorder like schizophrenia in a rodent is challenging, current approaches are based on known neurochemical abnormalities and environmental factors associated with schizophrenia in humans. For instance, based on the higher rates of schizophrenia following maternal infection, one animal model employs the use of the viral mimetic polyribonucleosinic-polyribocytidylic acid [poly(I:C)] to stimulate an inflammatory response in pregnant dams. Offspring from poly(I:C)-exposed dams show cognitive deficits and behavioral abnormalities associated with schizophrenia that can be attenuated by antipsychotic treatment [165, 166]. Assessment of hippocampal neurogenesis in the rodent maternal infection model has shown that offspring from poly(I:C)-treated dams show decreased new cell survival as measured by the number of

BrdU-positive cells 21 days after administration [167]. Further, the density of granule cells was reduced in the poly(I:C) offspring relative to controls on postnatal day 100, potentially indicating the reduced cell survival may have long-term effects on the granular cell layer. Work by Zhang and Van Praag [165] confirmed that poly(I:C) offspring show reductions in new cell survival and overall volume of the dentate gyrus. Further, the dendritic morphology of new neurons was less complex in poly(I:C) offspring relative to controls. In addition, mature and adult-born granule cells of poly(I:C) offspring showed abnormal intrinsic properties, as cells showed a decreased threshold to generate an action potential as well as a decline in the overall number of action potentials produced while input resistance was increased relative to control offspring. These data collectively indicate that animal models that mimic the behavioral and structural changes in schizophrenia also provide evidence of attenuated hippocampal neurogenesis and persistent abnormalities in granular cell activity. Further work is needed to determine whether the cognitive deficits resulting from prenatal immune activation relate to the depression of hippocampal neurogenesis.

Additional support for a potential role of neurogenesis in the pathology of schizophrenia arises from genetic studies. One of the main genes associated with an increased risk of developing schizophrenia, namely DISC1 (disrupted-in-schizophrenia 1), participates in new cell integration [168]. During embryonic development, DISC1 is widely expressed within the brain, but as the brain completes maturation, DISC1 expression is primarily localized to the hippocampus, including the dentate gyrus [169]. Moreover, assessment of cell-specific expression of DISC1 in the hippocampus demonstrated that DISC1 was present in cells expressing the proliferation marker Ki-67 or the early postmitotic neuron marker calretinin [170]. Use of virus-mediated RNA interference to selectively inhibit DISC1 in hippo-

campal neurons revealed that DISC1 plays a key role in new neuron integration. Selective knock-down of DISC1 in newly born neurons was found to alter cell migration, as new neurons deficient in DISC1 migrated farther than normal cells as well as showed abnormal orientation within the granule cell layer [170]. Additionally, DISC1-deficient neurons showed morphological abnormalities and accelerated development, as cells showed faster synapse formation and enlarged cell bodies compared to new neurons with normal DISC1 expression [170]. These data indicate that DISC1 normally acts as a regulator of new cell integration in terms of the rate of development and cell migration, removing the brakes from this process by downregulating DISC1 appears to adversely affect new neuron integration that may have long-lasting implications on the functional capacity of these cells.

Research has also shown that DISC1 regulates progenitor cell proliferation [171]. DISC1 has been shown to influence cell proliferation via its effects on GSK-3 β , which is a serine/threonine protein kinase that is expressed at high levels in the brain [172]. GSK-3 β is expressed when a cell is at rest; via phosphorylation, GSK-3 β inhibits the activity of several signaling molecules and transcription factors such as β -catenin [172]. β -catenin is known to regulate the pool of progenitor cells, as deletion of β -catenin was found to reduce NPCs, whereas continuous expression increased the progenitor pool [122]. In its normal state, DISC1 directly inhibits GSK-3 β , which releases β -catenin from the inhibitory control of GSK-3 β and stimulates progenitor cell proliferation. In instances where DISC1 activity is impaired, GSK-3 β is continually active, and the ability of β -catenin to induce proliferation is suppressed. Research has shown that the decrease in progenitor cell proliferation in DISC1-knock-down mice can be reversed by administration of a GSK-3 β inhibitor or continuous β -catenin expression, indicating that a failure to inhibit GSK-3 β mediates the deficits in progenitor cells in case

of disrupted DISC1 [171]. Alterations in the DISC1 gene may represent one route through which hippocampal neurogenesis is impaired in schizophrenia.

In addition to DISC1, other genetic risk factors of schizophrenia are reported to disrupt hippocampal neurogenesis. Select single nucleotide polymorphisms of the G-protein-coupled receptor SREB2 (superconserved receptor expressed in brain 2) are associated with a higher risk of developing schizophrenia [173]. Transgenic mice that overexpress SREB2 show behavioral indices of schizophrenia, including deficits in cognitive function and sensorimotor gating [173]. Chen et al. [174] have reported that selective overexpression of SREB2 decreased new cell survival, as the number of BrdU-positive cells was significantly reduced 30 days after BrdU administration in the SREB2 transgenic mice. Further, the number of DCX-positive cells was also reduced with overexpression of SREB2, indicating deficits in neuronal differentiation. As complementary evidence, SREB2-knockout mice showed increased neuronal survival as indicated by higher numbers of BrdU-positive cells and colocalization of BrdU and NeuN. Alterations in SREB2 levels were also found to alter performance in behavioral tasks associated with hippocampal neurogenesis, as mice overexpressing SREB2 showed impaired pattern separation at a medium distance in a spatial task compared with control mice. In contrast, SREB2-knockout mice showed enhanced performance in the spatial pattern separation task at the closest distance compared with control mice [174]. These data confirm a role for SREB2 as a negative regulator of hippocampal neurogenesis and support the contention that alterations in neurogenesis contribute to schizophrenia.

Chromosomal deletions that dysregulate the function of several genes have also been reported to increase the risk of schizophrenia. For instance, monoallelic microdeletions on chromosome 22 at the 22q11.2 region have been associated with a higher incidence of schizophrenia as

approximately one fourth of the individuals with this deletion develop schizophrenia [175]. It is estimated that the activity of the 28 genes that reside within this chromosome segment are disrupted by this deletion. Dgcr8 (DiGeorge syndrome chromosomal region 8) is one of the genes affected by this chromosomal deletion, which has been shown to regulate production of microRNA and has been implicated in the risk of developing schizophrenia [176]. Research has demonstrated that knockdown of Dgcr8 in male mice produced deficits in spatial working memory as measured by spontaneous alternation in the Y-maze test and a trend towards impaired retention of spatial memory in the water maze [176]. In addition, knockdown of Dgcr8 inhibited cell proliferation in the subgranular zone of the dentate gyrus, as measured by lower levels of Ki-67- and BrdU-positive cells. The proliferation deficits were accompanied by reductions in DCX-positive cells indicating reductions in new neuron production [176]. These data again confirm a link between genetic risk factors associated with schizophrenia and alterations in hippocampal neurogenesis and strengthen the argument that employing treatments that enhance hippocampal neurogenesis may have beneficial effects in the context of schizophrenia.

There is indication that parts of the beneficial effects of current pharmacological treatments used in schizophrenia relate to their ability to stimulate hippocampal neurogenesis. Current antipsychotics are subclassified into typical and atypical drugs. Typical antipsychotics, such as haloperidol, reduce positive symptoms of schizophrenia by antagonizing the D₂ dopamine receptor [161]. However, the development of motor abnormalities is common with these compounds given the role of dopamine in the initiation of movement. The atypical antipsychotics target both the positive and negative symptoms of schizophrenia by altering activity of multiple receptors, such as serotonin receptor subtypes, in addition to antagonizing the D₂ receptor [131].

The reduced incidence of motor abnormalities as well as the ability of these drugs to treat both positive and negative symptoms has made atypical antipsychotics the most commonly prescribed medication for schizophrenia. While research with haloperidol showed no effects on adulthood hippocampal neurogenesis, findings indicate that atypical antipsychotics may stimulate neurogenesis [177]. For example, in a mouse model of schizophrenia, maternal poly(I:C) decreased new cell survival, as measured by the number of BrdU-positive cells, in offspring up to postnatal day 57 but not at later time points. Risperidone treatment significantly increased cell survival in offspring of dams exposed to either poly(I:C) or saline [167]. Further, olanzapine was reported to increase cell proliferation in the hippocampus of adult rats [178]. The increase in proliferation was dependent on the duration of treatment, as subchronic administration lasting 7 days had no effect on cell proliferation, whereas 21 days of olanzapine administration increased cell proliferation [178]. Research by Halim et al. [179] confirmed that chronic (i.e., 28-day) treatment with the atypical drug clozapine, but not haloperidol, increased cell proliferation in the hippocampus. However, neither compound altered new cell survival when BrdU cells were assessed 3 weeks after BrdU administration. Both clozapine and olanzapine, but not haloperidol, were able to attenuate deficits in cell proliferation following phencyclidine administration [180, 181]. Though the data are limited and inconsistencies exist, taken together, the results indicate that atypical drugs may stimulate neurogenesis by increasing cell proliferation [90]. Further work is needed to clarify which features (e.g., dosage, duration of treatment, receptor subtype targeted, or model system) of atypical drugs may stimulate proliferation.

Collectively, the data support a role for the hippocampus in mediating some of the symptoms, particularly cognitive dysfunctions, seen in schizophrenic individuals. The precise link be-

tween specific reductions in hippocampal neurogenesis and cognitive dysfunction remains unclear. Regardless, the evidence indicates that schizophrenia is characterized by deficits in neurogenesis. Reductions in new cell proliferation and neurogenesis have been repeatedly demonstrated in both animal models and postmortem assessment of hippocampal neurogenesis. Some of the strongest evidence for the contribution of altered neurogenesis to the pathogenesis of schizophrenia comes from the established relationship between genetic risks of schizophrenia and the regulation of hippocampal neurogenesis. A sizable number of genes associated with developing schizophrenia have been shown to play a central role in the proliferation and survival of progenitor cells. While current antipsychotic drugs may support hippocampal neurogenesis by stimulating cell proliferation, whether the enhanced proliferation translates into lasting changes in survival or cell differentiation is unclear. Potentially, the use of alternative or additive interventions, such as aerobic exercise, that increase cell survival may have beneficial effects in alleviating cognitive deficits associated with schizophrenia. Prior work has shown that increasing aerobic fitness via regular exercise in schizophrenic individuals enhances cognitive function [182]. Given that exercise causes a potent increase in hippocampal neurogenesis, it is possible that enhancing neurogenesis is one mechanism through which exercise exerts its beneficial effects.

Neurogenesis in Major Depressive Disorder

MDD is estimated to affect 20% of individuals at some point in their lifetime and is characterized by recurrent episodes of enduring despair and behavioral abnormalities [183]. The symptoms of depression include changes in mood (e.g., excessive sadness, hopelessness, irritability, and anhedonia), physiological functions (e.g., sleep

disturbances and altered appetite), energy and motivation, and cognitive function (e.g., memory impairment and rumination) [70, 183]. Diagnosis requires that a constellation of depressive symptoms persists for at least 2 weeks. While several subtypes of depressive disorders have been described, the two major forms include unipolar depression (i.e., major depression) and bipolar depression, which is distinguished by episodes of mania or hypomania in addition to depressive episodes. Development of a depressive disorder appears to arise from a complex interaction between environmental factors, such as stress and childhood trauma, and genetic factors. While depression is a heritable disease, identification of reliable risk genes or chromosome regions has been challenging, although variations in serotonin transporters have been linked to a greater disease risk under select conditions [184]. This lack of consistent genetic risk factors highlights the poly-genetic nature of depression. Current pharmacological treatments target monoamine neurotransmitter systems (e.g., serotonin, dopamine, and norepinephrine), as deficits in monoamines are believed to be an underlying cause of depression. However, additional factors likely contribute to the pathophysiology of depression given that not all depressed individuals show improvements with antidepressant treatment, and treatment responsiveness is often delayed even though monoamine levels are rapidly altered [183]. Identifying the physiological changes that accompany the normalization of monoamine levels is expected to improve treatment effectiveness.

Along with other limbic system structures and regions of the prefrontal cortex, the hippocampus has been implicated in mediating depressive symptoms. Evidence for the involvement of the hippocampus in depression has come from imaging studies that often show reduced hippocampal volume in depressed individuals relative to controls [157]. Further, the decrease in hippocampal volume has been shown to be greater in individuals with longer periods of

time without treatment [185]. The precise mechanisms driving these volume changes are still under investigation, but increases in neuronal and glial cell death, deficits in hippocampal neurogenesis, and reductions in dendritic complexity likely contribute [95].

Additionally, the hippocampus has been associated with depression because of its role in regulating the stress response produced by the HPA axis [80]. The end result of HPA axis activation is the release of cortisol (corticosterone in rodents) into the bloodstream by the adrenal cortex. Stressful experiences stimulate the release of corticotrophin-releasing hormone and vasopressin from the paraventricular nucleus of the hypothalamus, which subsequently induces the release of adrenocorticotrophic hormone from the anterior pituitary. This hormone travels through the bloodstream to stimulate the release of cortisol from the adrenal gland [80]. The hippocampus is part of the negative feedback mechanism that limits HPA activation, as elevated levels of cortisol circulate throughout the body and act as a self-regulating factor by inhibiting further activation of the HPA axis, in part by binding to glucocorticoid receptors in the hippocampus [186]. Excessive and/or prolonged elevations in cortisol are known to induce atrophy in the hippocampus that ultimately impairs the negative feedback function and results in reduced inhibition of cortisol release [74]. Hyperactivity of the HPA axis is often observed in depression, as higher levels of circulating cortisol are detected in a large proportion of depressed individuals [91]. These elevated cortisol levels are believed to result from impaired negative feedback and contribute to volume reductions in the hippocampus and expression of depressive symptoms.

An additional abnormality within the hippocampus that has been linked with depression is a reduction in hippocampal neurogenesis. Stressful events are known to predispose individuals to MDD. The hippocampus is particularly sensitive to stress, as stress has been shown to interfere

with all aspects of hippocampal neurogenesis, including proliferation, cell differentiation, and survival (see section on stress) [80, 90]. Secondly, antidepressants increase hippocampal neurogenesis. For instance, several antidepressants have been shown to increase cell proliferation in rats, but this increase was only reported after chronic and not after acute treatment [187]. Additionally, chronic treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine increases new cell survival, as the number of BrdU-positive cells was elevated in fluoxetine-treated rats 4 weeks after BrdU administration [187]. Fluoxetine also increased hippocampal neurogenesis in nonhuman primates, as measured by the number of DCX-positive cells in both control and stress-exposed subjects [188]. Assessment of hippocampal neurogenesis in postmortem brains from individuals with MDD confirmed that antidepressants increased neurogenesis. Individuals that had been taking an SSRI within 3 months prior to death showed a significant increase in the number of NPCs compared to unmedicated depressed individuals and nondepressed controls [189, 190]. There was no difference in the number of NPCs between unmedicated depressed and nondepressed individuals. In a similar report, cell proliferation (measured by Ki-67-positive cells) did not differ between depressed and nondepressed individuals though the medication status was not reported in this study [158]. Deficits in hippocampal neurogenesis were originally proposed to mediate the pathogenesis of depression, but clear evidence of impaired neurogenesis in depressed individuals has not been found.

Moreover, animal models have demonstrated that induction of depression-like behavior may be independent of alterations in hippocampal neurogenesis. Surget et al. [79] ablated neurogenesis in the hippocampus by targeted irradiation which inhibits progenitor cell proliferation. After 5 weeks of recovery following irradiation, half of the mice experienced 5 weeks of chronic unpredict-

able stress (CUS). Assessment of behavioral changes revealed that, as expected, CUS increased depression-like behavior, regardless of whether mice were irradiated or not, showing that inhibiting hippocampal neurogenesis did not enhance the response to stress. Moreover, irradiated mice that were not exposed to CUS showed no evidence of depression-like behavior, indicating that suppression of hippocampal neurogenesis is insufficient to elicit depression-like symptoms [134]. In contrast, others report that a transient reduction of neurogenesis using a genetic mouse model was associated with an increase in depression-like behavior but only when under stress [191], indicating that under some conditions suppressing neurogenesis may increase stress reactivity. Evidence that a deficit in hippocampal neurogenesis is a contributing factor to the development of depression is generally lacking, though some inconsistencies exist in the literature [183, 192, 193].

Though the role of neurogenesis as an etiological factor in depression is debated, there is stronger evidence that hippocampal neurogenesis is required for the treatment effects of antidepressants [193]. Prior work has shown that the administration of fluoxetine or the tricyclic antidepressant imipramine can block the development of behavioral indices of depression induced by CUS. However, the protective effects of fluoxetine and imipramine were absent in irradiated mice, indicating that the beneficial effects of antidepressants necessitate a significant increase in hippocampal neurogenesis [79]. Similar effects were found in nonhuman primates, as ablation of neurogenesis via irradiation prevented the effects of fluoxetine on stress-induced depression-like behavior [188]. The majority of the original studies that indicated a link between stimulation of hippocampal neurogenesis and reductions in depression-like symptoms employed irradiation to inhibit neurogenesis, which can increase inflammation as well as other confounding side effects. However, similar results were reported by Santarelli et al. [46] who ablated hippocampal neuro-

genesis using a genetic approach and confirmed that inhibition of neurogenesis prevented the antidepressant effects of fluoxetine in mice. Though it is important to note that inconsistent findings have been reported, the lack of an effect may relate to using unstressed animals [194]. An additional point of support is the match between the time course of the therapeutic benefits of antidepressants and hippocampal neurogenesis. Even though monoamine levels are quickly altered by antidepressants, symptom alleviation often takes several weeks to develop. This delayed effectiveness maps onto the timing of new cell maturation that at least in rodents occurs over the course of 3–4 weeks. If cell maturation follows a similar time course in humans this may strengthen the argument that hippocampal neurogenesis mediates aspects of the antidepressant effects of current medications.

The requirement of neurogenesis may, however, be limited to compounds that target monoamines, such as SSRIs, tricyclics, and monoamine oxidase, as compounds that have alternative targets can alleviate depressive symptoms even in the absence of neurogenesis. Drugs that reduce HPA axis activation, namely, corticotrophin-releasing factor 1 and vasopressin 1b receptor antagonists, are able to reduce stress-induced depression-like behavior in irradiated mice [79]. These data indicate the need to enhance neurogenesis to observe antidepressant effects may be specific to select compounds that aim to normalize levels of monoamine neurotransmitters. One possibility is that increasing neurogenesis may aid in normalizing activation of the HPA axis, given that the hippocampus is a negative regulator of the HPA axis [186]. Prior research has shown that suppression of neurogenesis in a conditional transgenic mouse model is associated with alterations in stress responses [192]. Ablation of neurogenesis delayed the recovery from acute and chronic restraint stress, as levels of corticosterone were higher at select time points in the transgenic mice than the control mice. In ad-

dition, reducing neurogenesis attenuated the ability of dexamethasone to suppress corticosterone levels [170]. The role of new neurons in regulating the HPA axis is complex, as ablation of neurogenesis via irradiation did not alter basal activity of the HPA axis as measured by dexamethasone suppression of corticosterone [79]. However, neurogenesis was found to be required for fluoxetine to normalize HPA activation following CUS, indicating that new neurons may contribute to the inhibitory influence on the HPA axis. Though more work is needed to clarify the role of new neurons in regulating the stress response, the initial findings indicate that increasing neurogenesis may represent one mechanism through which antidepressants can regulate overactivation of the HPA axis. By the same token, treatments that circumvent the hippocampus and act directly within the HPA axis may produce antidepressant effects independent of hippocampal neurogenesis.

Research has also implicated hippocampal neurogenesis as a contributing factor to the anti-manic and antidepressant effects of lithium, a mood stabilizer commonly used to treat bipolar disorder [172]. Lithium has been reported to participate in the maintenance of the pool of NPCs by increasing progenitor cell proliferation [195]. In vivo work has shown that chronic lithium administration increased the number of BrdU-positive cells in the dentate gyrus [196]. Additionally, lithium has been shown to increase the total number of neurons in the dentate gyrus compared with control mice [197]. A likely mechanism through which lithium enhances hippocampal neurogenesis is through inhibition of GSK-3 β [172]. Though lithium may have a number of targets within the brain, research has confirmed that lithium directly inhibits GSK-3 β activity which, as noted, subsequently releases β -catenin from the inhibitory control of GSK-3 β and allows β -catenin to stimulate progenitor cell proliferation [122]. Inhibition of GSK-3 β likely mediates the ability of lithium to enhance neurogenesis, as

overexpression of GSK-3 β or deletion of β -catenin blocks lithium-induced increases in cell proliferation [172]. There is also evidence that reductions in GSK-3 β may contribute to the proneurogenic effects of antidepressants (e.g., SSRIs) [172]. Overall, the data highlight a role for neurogenesis in mediating aspects of the beneficial effects of lithium.

An additional effect that likely contributes to the antidepressant-induced increase in hippocampal neurogenesis is the induction of neurotrophic and growth factors. Chronic antidepressant treatment increases expression of multiple neurotrophic and growth factors including BDNF, vascular endothelial growth factor, insulin-like growth factor, and nerve growth factor, among others [70]. Each of these molecules has been reported to have positive effects on hippocampal neurogenesis. For instance, central administration of BDNF has been found to increase new cell survival [198]. Moreover, reducing BDNF levels blocked the survival-promoting effect of the antidepressant imipramine. Chronic imipramine increased the number of BrdU-positive cells that survived 21 days after BrdU administration compared with saline-treated mice, whereas imipramine had no effects on survival in BDNF-knockdown mice [198]. Given the central role these growth and neurotrophic factors play in stimulating hippocampal neurogenesis, the induction of these factors following antidepressant treatment likely contributes to the increase in neurogenesis.

While the role of hippocampal neurogenesis in the onset of depression is in question, a wealth of evidence indicates a role for neurogenesis in the recovery process, as the antidepressant effects of the commonly employed drugs are blocked by inhibition of neurogenesis. Elucidating the functions mediated by the dentate gyrus and the new neurons born within this region in the healthy brain is expected to clarify how alterations in this process that develop in disease states may contribute to the onset and progression of disorders

such as depression. Further, preclinical evidence indicates that enhancing hippocampal neurogenesis may aid in treatment-resistant cases [199]. Undoubtedly, more work is needed to elucidate the role of hippocampal neurogenesis in treatment responsiveness. Based on the existing knowledge, however, employing treatments aimed at stimulating hippocampal neurogenesis would be expected to have beneficial effects in the context of depression.

Concluding Remarks

New neurons are continuously formed in the human, nonhuman primate, and rodent adult hippocampus throughout life, though rates of neurogenesis precipitously decline with age to near zero levels at the end of the natural life span. Since its discovery in the 1960s, a large number of studies have documented numerous environmental and genetic factors which regulate adult neurogenesis. Chief among the positive regulators of neurogenesis are exercise and antidepressant drugs. Chief among the negative regulators of neurogenesis besides age are stress and inflammation. To the extent that many psychiatric disorders are comorbid with or causally related to stress and inflammation, decreased neurogenesis could be a partial contributor to the pathophysiology of the disorders. However, the functional significance of new neurons in behavior has yet to be established and is currently a hotly debated topic. Therefore, it is not clear whether changes in neurogenesis that occur alongside psychiatric illnesses are a cause or a consequence of the mediating factors such as stress, drug abuse, and inflammation which are complexly involved in the disorders. It will be important moving forward to use modern technologies capable of instantaneously inactivating cohorts of new neurons to test their functional significance in behavior and the etiology of mental illnesses.

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