HHS Public Access

Author manuscript

Nat Med. Author manuscript; available in PMC 2018 January 31.

Published in final edited form as:

Nat Med. 2016 November ; 22(11): 1239–1247. doi:10.1038/nm.4218.

Re-evaluating the link between neuropsychiatric disorders and dysregulated adult neurogenesis

Sanghee Yun[1], **Ryan P Reynolds**[1], **Irene Masiulis**[2], and **Amelia J Eisch**[1,2,3]

[1]Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[3]Department of Neuroscience and Mahoney Institute of Neuroscience, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

People diagnosed with neuropsychiatric disorders such as depression, anxiety, addiction or schizophrenia often have dysregulated memory, mood, pattern separation and/or reward processing. These symptoms are indicative of a disrupted function of the dentate gyrus (DG) subregion of the brain, and they improve with treatment and remission. The dysfunction of the DG is accompanied by structural maladaptations, including dysregulation of adult-generated neurons. An increasing number of studies using modern inducible approaches to manipulate new neurons show that the behavioral symptoms in animal models of neuropsychiatric disorders can be produced or exacerbated by the inhibition of DG neurogenesis. Thus, here we posit that the connection between neuropsychiatric disorders and dysregulated DG neurogenesis is beyond correlation or epiphenomenon, and that the regulation of adult-generated DG neurogenesis merits continued and focused attention in the ongoing effort to develop novel treatments for neuropsychiatric disorders.

By 2020, neuropsychiatric disorders are predicted to be the second highest cause of global disease burden[1]. Current treatment for disorders such as major depressive disorder (MDD), bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD) and substance-related or addictive disorders includes pharmacological intervention, which provides relief for many people. However, these therapies are ineffective for as many as 30% of individuals, and they are often accompanied by substantial side effects[2–4]. Equally concerning is that a high percentage of treated individuals relapse[5–8]. These facts call for aggressive expansion of the current neuropsychiatric-disorder treatment toolkit.

Clues to treatment and understanding of neuropsychiatric disorders come from the fact that many symptoms of these disorders are reminiscent of abnormal DG function. Similarly to

Correspondence should be addressed to A.J.E. (eischa@email.chop.edu).

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

the hippocampus that surrounds it, the DG has a role in memory and mood regulation, and it is also instrumental in the processing of contextual similarities and differences known as 'pattern separation,' as well as the processing of intrinsically positive or rewarding stimuli (Box 1)[9–16]. The DG is also highly sensitive to stressful experiences, and baseline DG function can be enhanced or inhibited by stress (Box 1)[17–19]. Illustrative of aberrant DG function, many people diagnosed with MDD, bipolar disorder, schizophrenia, PTSD or substance-related or addictive disorders have memory dysfunction and mood fluctuations or abnormalities[20–22]. Humans diagnosed with MDD, PTSD or schizophrenia show aberrant pattern separation[22–24], whereas those diagnosed with MDD, bipolar disorder, schizophrenia or substance-related and addictive disorders have abnormal processing of rewarding stimuli[25].

Furthermore, in humans and animal models, stressful experiences can enhance the susceptibility to and severity of these disorders and their symptoms[18,22,26,27], which also suggests a role for the DG in these disorders (Table 1). Finally, successful treatment of these disorders in humans and the application of similar therapies in animal models normalize or enhance DG function (Fig. 1). For example, brain-stimulation therapy is commonly applied to brain cortical regions to 'jump start' or recalibrate brain circuitry in MDD[28]. However, stimulation of the entorhinal cortex (Ent), a brain region functionally upstream from the DG (Box 1), improves memory in both humans and mice[29,30].

One aspect of DG physiology that has offered hope with regard to the normalization of DG function in neuropsychiatric disorders is its ability to give rise to new neurons throughout life (Fig. 1). These new neurons are found in the DG of mammals ranging from rodents to humans[31], and work in mice shows that new neurons are able to wire and fire correctly within the DG (Fig. 1a)[27,32–35].

New DG neurons are dynamically regulated by environmental and physiological factors[32,36–40]. Notably, the number of new neurons is increased by neuropsychiatric medications such as antidepressants and altered by drugs of abuse[41,42], and this correlative link between new DG neurons and neuropsychiatric disorders is a well-established concept (Table 1)[18,26,43–50].

However, in the past decade, new technologies have emerged that enable inducible manipulation of new DG neuron number, morphology or activity in mice and rats. As highlighted in Table 2 (full details in Supplementary Table 1), studies that employ these modern approaches indicate a role for new DG neurons in memory, mood, pattern separation and reward[29,51–68]. In addition, studies using animal models of depression coupled with these new technologies show that behavioral symptoms can be produced or ameliorated by select manipulation of new DG neurons. On the basis of this recent work in mice and rats, we posit that the connection between neuropsychiatric disorders and dysregulated DG neurogenesis is beyond correlation or epiphenomenon, and that the regulation of new DG neurons merits continued and focused attention in the ongoing effort to develop novel treatments for neuropsychiatric disorders.

Adult DG neurogenesis

Adult DG neurogenesis in laboratory animals and humans shares common features[69–71]. For example, new DG neurons occur throughout the hippocampal DG, from the dorsal (or septal) to the ventral (or temporal) DG (mouse DG shown in Fig. 1a), albeit with distinct functional contributions along the DG longitudinal axis[72–75]. Also, as with the process of embryonic neurogenesis, adult DG neurogenesis in humans and mice and rats is a process, not a timepoint, with maturing cells proceeding through "stages" (Fig. 1a)[27,71]. In general, the proliferation, differentiation and eventual survival to maturity of new DG neurons takes 2–4 weeks in mice and rats (Fig. 1a), but weeks longer in primates and humans, as revealed by postmortem studies[31,76]. New DG neurons in both rodents (mice, rats) and humans do not replace existing embryonic-generated DG neurons, but rather contribute to the ongoing turnover (addition and subtraction) of newborn neurons in a restricted part of the DG (Fig. 1a)[9,71,77–80].

In contrast to these shared traits, most of what is known about the specific development and afferent input of new DG neurons is understood in mice and rats. Once mature, new DG neurons become glutamatergic granule neurons that receive glutamatergic input from the upstream Ent and inhibitory GABAergic feedback from DG interneurons[81] and project to the downstream hippocampal CA3 region (Box 1)[16]. In this sense, fully mature adult-generated DG neurons are indistinguishable from embyronic-generated DG granule neurons. However, as they mature, new DG neurons receive specialized inputs and outputs and dynamically express key intrinsic ion channels and neurotransmitter receptors (Fig. 1a,b)[32,82,83]. For example, younger new DG granule neurons receive direct innervation from mature DG granule neurons and downstream hippocampal cornus ammonis region 3 (CA3) pyramidal neurons[84], and these inputs disappear as the new neuron matures. In addition, younger new DG granule neurons neither receive nor send feedback inhibition[81], whereas older new DG neurons do. The location of inputs to new DG neurons is crucial for determining their influence on new neuron function[33,35,83]. For example, most glutamatergic inputs are on the dendritic tree of new neurons, whereas inhibitory inputs are on or near the soma (Fig. 1a)[33,35]. These inputs form gradually over the >4 weeks that it takes for new neurons to mature (Fig. 1b), with nonsynaptic, ambient GABA as the first input and synaptic glutamate from Ent as the last[33,35,83]. Taken together with the fact that new neurons have a lower threshold for firing relative to embryonic-generated neurons and that they are sensitive to activity-dependent regulation[36,85–87], the emerging view is that immature adult-generated DG neurons are distinct from mature adult-generated and all embryonic-generated DG neurons in that they are "young and excitable"[88], function independently of inhibitory GABA circuits[89] and receive direct innervation from their glutamatergic "elders"[84]. In fact, some work suggests that adult-generated neurons remain functionally distinct from their embryonic-generated counterparts[90].

Neuropsychiatric disorders and adult DG neurogenesis

It has long been known that the development of new neurons is regulated by antidepressants and drugs of abuse[41,42]. In fact, treatments for neuropsychiatric disorders (including antidepressants, electroconvulsive treatment, antipsychotics and mood stabilizers, all of

which can improve DG functional output in humans diagnosed with or animal models of neuropsychiatric disorders) act on many of the very neurotransmitter systems that regulate new neurons (Fig. 1b)[26,91]. Such studies raise the idea that neuropsychiatric disorders are linked with fewer new DG neurons, and that treatment or remission is linked to more or a normalized number of new DG neurons.

Although this correlative relationship between new DG neurons and neuropsychiatric disorders relies on only a few human postmortem publications, there is much evidence in animal models that these disorders are linked to impaired generation or function of new DG neurons[26,47]. New DG neurons contribute to hippocampal volume and appropriate DG function and activity, and in humans, mice and rats, these disorders are also marked by impaired hippocampal volume and/or DG network activity (Table 1). For example, the relative activity between the DG and the downstream hippocampal CA1 region (Box 1) is decreased in stressed rats as compared to control rats[59], which is notable, given that stress is a major precipitating factor in the exacerbation of neuropsychiatric symptoms. In animal models of bipolar disorder and schizophrenia, the stress- or novelty-induced activity of the DG is diminished[92,93]. Additionally, humans with PTSD have decreased hippocampus and amygdala activity relative to undiagnosed, trauma-exposed controls[94]. Finally, long-term cocaine users have decreased hippocampal gray matter, and abstinent heroin-dependent users have enhanced connectivity among hippocampus and reward-related brain regions relative to individuals who do not use drugs[95,96].

Additional support for a correlation between the presence of fewer new DG neurons and the presence or exacerbation of neuropsychiatric symptoms comes from studies in both humans and rodents in which a decreased number of new neurons or lower DG volume is normalized or improved after treatment or during remission (Table 1). For example, postmortem studies show that chronic antidepressant treatment restores proliferation deficits in humans with MDD[97]. Chronic treatment with the mood stabilizer lithium increases new-neuron proliferation and differentiation in animal models, and the bipolar disorder medication valproate rescues aberrant DG activity and manic-like behavior in animal models[98,99]. Furthermore, anti-psychotic drugs, such as haloperidol, risperidone or clozapine, restore neurogenesis in animal models of schizophrenia, and antipsychotics can also ameliorate anxiety and restore new-neuron proliferation in an animal model of PTSD[100,101].

Neuropsychiatric symptoms and neurogenesis—a causative relationship?

Recently, techniques have emerged that enable more focused exploration of the correlative–causative relationship of neurogenesis and neuropsychiatric disorders (Table 2; see also Supplementary Table 1). These include studies in mice and rats that ablate new neurons at a specific ‘stage’ of their development, manipulate the number, structure or activity of new DG neurons, or couple ‘classic’ new-neuron deletion techniques, such as irradiation, with behavioral investigations that reflect modern understanding of new neuron function[29,51–65]. For example, by using retroviral-mediated gene transfer to express light-sensitive channels in proliferating precursors, researchers are able to control new neuron firing remotely[52]. Recently developed transgenic mouse lines also enable the targeting of new neurons[56] or of mature DG granule neurons[54] with these light-sensitive channels, and they enable inducible

gene expression or deletion selectively in new neurons[53,56,62,63,65] or mature DG granule neurons[54,55,57]. The temporal control that researchers have over the firing of the targeted cell population in these optogenetic studies is ideal for behavioral investigations. As discussed below, most data are available for memory and mood, although studies have also confirmed a role for new DG neurons in pattern separation and reward[29,51–65].

Memory

Neuropsychiatric disorders are accompanied by memory dysfunction[20–22]. Given that recent studies support the idea that manipulation of new neurons can alter memory, it is possible that the activation of new neurons might be useful for normalizing memory dysfunction seen in neuropsychiatric disorders. For example, studies in mice have found that the ablation or inducible silencing of new or mature DG neurons impairs aspects of memory function[9,26,102], with some finding impairments in memory acquisition or the learning of a new memory[52,56], and others finding impaired retrieval, or expression of the memory after it has been formed[52,55]. These studies, all of which manipulate adult or embryonic-generated neurons during or before learning, suggest that enhancing neurogenesis might improve memory.

Notably, understanding the timing of neurogenesis disruption is crucial to understanding the role of new neurons in memory. For example, disruption of neurogenesis after learning has taken place impairs memory retrieval, which suggests that new neurons are needed as well for 'forgetting'[66,67]. Given that certain neuropsychiatric disorders (PTSD, substance-related and other addictive disorders) can be considered as being marked by aberrantly strong memories, it is feasible that postlearning enhancement of neurogenesis might help to drive the forgetting of such memories.

Also relevant to neuropsychiatric disorders is recent work showing that the 'age' or stage of new DG neurons determines whether the cells are involved in functional DG output[52,56]. For example, the stimulation of 4-week-old new DG neurons—but not of 2-week-old immature neurons or 8-week-old fully mature neurons—is required for memory retrieval[52]. This timing fits with that of new-neuron integration into DG-CA3 circuitry (Fig. 1a)[32], and with the concept that there is a 'critical period' during which new neurons are needed for successful memory processing[103].

Mood disorders

With regard to mood disorders, MDD, anxiety and PTSD are strongly linked to abnormal hippocampal structure and function, and impaired mood and greater anxiety are hallmarks of these human disorders[18,26]. Humans diagnosed with MDD often have an exacerbated or prolonged stress response and lack the typical hippocampal inhibition of the stress axis relative to individuals without depression, which again indicates that this mood disorder is linked to a dysfunctional hippocampus[18]. Notably, many correlative studies support the idea that rodents (mice and rats) exposed to chronic stress and humans diagnosed with MDD have decreased or dysfunctional neurogenesis, and that antidepressant treatment drives neurogenesis[47,104]. Techniques used to ablate new neurons led to a depressive-like

phenotype in mice and rats in some studies, but not others[47,105]. These mixed messages as to the role that new neurons have in depression raises concerns that neurogenesis is an epiphenomenon, and thus not a reasonable target for treatment[106].

However, a relatively consistent conclusion from the recent studies in rodents is that new DG neurons are required for antidepressant efficacy[58–61](Table 2; Supplementary Table 1). One clue to a potential underlying mechanism is that new neurons buffer the body's stress axis responsiveness and associated behaviors[62,107]. For example, a loss of new neurons results in a hyperactive stress response in mice[62]. In fact, it is now hypothesized that having a decreased number of DG neurons contributes to the development of depressive-like behaviors particularly under stressful conditions, such as the psychosocial stress experienced during social defeat stress[63]. Indeed, increased DG neurogenesis in mice is sufficient to attenuate anxiety and depressive-like behavior under stress-like conditions in which the rodents are given the stress hormone corticosterone[68]. In further support of the role of new DG neurons in buffering the stress response, the positive effect on stress-induced anxiety of a neurogenic-compound-induced increase in neurogenesis is blunted by the ablation of neurogenesis[108].

Current studies have manipulated new DG neurons or DG activity in the absence of substantial stress to address whether mood regulation is mediated by them. Notably, direct stimulation or inhibition of new DG neurons does not change anxiety behavior under basal, nonstressed conditions[56]. However, direct stimulation of mature DG granule neurons in either the dorsal or ventral DG has an innate anti-anxiety effect[54]. This fits with prior work showing that the dorsal DG is more linked to spatial or contextual functions, whereas the ventral DG is more linked to mood and related emotional functions[72,74,75], and suggests that subregional targeting of DG activity is a potential intervention for mood disorders. This functional neuroanatomical gradient is also evident in studies in which neurogenesis is manipulated. For example, whereas reversible silencing or stimulation of new neurons in the dorsal—but not ventral—DG impairs memory acquisition and retrieval, direct stimulation of ventral DG granule cells—but not of new neurons—decreases anxiety in mice, as compared to controls[54,56]. Thus, acute stimulation of ventral DG granule neurons could be a very useful intervention for relieving anxiety.

Pattern separation

Pattern separation is a computational term often applied to the DG to explain how cortical inputs representing spatial and contextual information converge onto the DG yet diverge into distinct outputs in the downstream CA3, a hippocampal region involved with the complementary function of pattern completion[109]. However, pattern separation is also a very relevant concept in neuropsychiatric disorders because overgeneralization (impaired pattern separation) is a barrier to symptom relief and is seen in many individuals with neuropsychiatric disorders[22]. For example, humans diagnosed with PTSD have diminished pattern separation; they generalize cues associated with a traumatic memory (crime victimization or war, for instance) to nonthreatening contexts, which thus drives fear and anxiety in these nonthreatening contexts[22]. Notably, this deficit is apparent in tests of pattern separation unrelated to the particular trauma: humans diagnosed with PTSD or related

anxiety disorders perform poorly on neuropsychological tests of pattern separation[22]. By contrast, some humans diagnosed with autism spectrum disorder have enhanced pattern separation and note even slight differences in contexts or routines[110]. In PTSD, the severity of symptoms is correlated with a smaller and less active DG, as compared to healthy controls. These connections raise the possibility that the normalization of pattern separation will be accompanied by normalization of DG activity and diminished symptom severity.

Indeed, targeting new neurons in rodents can mimic these findings in humans: inhibition or ablation of new neurons impairs pattern separation, whereas stimulation of mature DG neurons or inducible enhancement of new neurons enhances pattern separation[53,56,57,68,111,112] (Table 2 and Supplementary Table 1). In fact, when computational models of DG pattern separation account for the addition of new DG neurons, there is reduced overlap of activated GCs by previous memories, and thus improved pattern separation as compared to controls[27]. As with learning and memory, the 'stage' of the new neurons matters in regard to pattern separation. For example, pattern separation is reliant on young new neurons (just integrated into DG circuitry) but not on older mature new neurons or embyronic-generated DG neurons[113]. These aspects will be useful for guiding and fine-tuning potential future new-neuron-based therapies for pattern separation.

Reward

With regard to reward, the ablation of new DG neurons in rats increases cocaine drug-taking and drug-seeking, as compared to controls, which suggests that decreased adult neurogenesis is a vulnerability factor in a rat model of cocaine addiction[64] (Table 2 and see also Supplementary Table 1). Given work showing that environmental-enrichment- or running-induced increase in adult neurogenesis correlates with a reduction of addictive-like behaviors in rats and mice[114,115], it would be interesting to selectively and inducibly increase the number of new DG neurons or stimulate existing new DG neurons to test whether this would diminish drug-taking or drug-seeking in animal models of addiction. However, the only other study that has inducibly manipulated new neurons and examined reward-based hedonic behavior found the opposite result: the deletion of new DG neurons decreases a mouse's preference for a rewarding substance, in this case, sucrose[62]. Given that it is challenging to compare an animal model of cocaine addiction with oral sucrose intake, more studies are warranted to see how the manipulation of new neurons influences reward processing.

Harnessing the DG to treat neuropsychiatric disorders

Given the above studies, it is intriguing to consider targeting new neurons to recalibrate dysfunctional DG activity to treat neuropsychiatric disorders. For example, in contrast to the healthy DG wherein Ent projections to the DG and its new neurons drive memory processes, mood regulation, pattern separation and processing of rewarding stimuli (Fig. 2a)[9–16], this functional output is disrupted in neuropsychiatric disorders, which perhaps leads to or exacerbates symptoms (Fig. 2b). Regardless of whether the dysfunctional DG is due to changes in Ent input, the number of new DG neurons, regulation of DG activity, or some

other parallel process, we propose two putative approaches for targeting new DG neurons as a way to normalize DG activity and functional output (Fig. 2c).

The first approach—increasing Ent input to DG and thus increasing the activity of DG neurons—might be useful for disorders that have common traits of impaired learning and memory induced by hippocampal or DG dysfunction and Ent afferent dysfunction, such as MDD, PTSD and schizophrenia. In such cases, recalibration of DG functional output is feasible via the stimulation of upstream DG regions, such as deep-brain stimulation of Ent (Fig. 2d). Indeed, it has already been shown that Ent stimulation enhances neurogenesis in mice and improves memory in both humans and mice[29,116]. More recently, Ent stimulation is also able to activate a DG memory in a mouse model of Alzheimer's disease[117], although the role of new neurons is not assessed in that study. It remains to be tested, however, whether this upstream stimulation and the subsequent putative enhanced new neuron number or activity will have beneficial effects on mood, pattern separation or reward (Fig. 2d). However, given that lesioning of Ent impairs pattern separation in mice[84], it is reasonable to hypothesize that Ent stimulation would improve pattern separation, and in turn, improve PTSD symptoms. Notably, whereas Ent-stimulation-induced memory improvement in mice acts via increased neurogenesis[29], it remains unclear whether Ent-stimulation-induced improvement in DG function is always reliant on intact neurogenesis.

The second approach—increasing new DG neuron number or activity—builds off the unique physiology and positioning of new DG neurons and the many neuropsychiatric disorders that are linked with dysfunctional DG activity (Fig. 2e). Many studies support the idea that the ablation or silencing of new neurons impairs aspects of memory, mood, pattern separation and the response to rewarding stimuli (Table 2 and Supplementary Table 1). By contrast, inducible increase in the number of new DG neurons formed, or inducible modulation of their spines, improves pattern separation and cognitive flexibility, respectively, in mice[57,118], and stimulation or induction of new or mature DG neurons decreases anxiety in mice[54,68]. These studies suggest that a therapy based on the induction of new neurons has the potential to boost pattern separation and normalize learning and memory deficits (Fig. 2e). However, the stimulation of new neurons or mature DG neurons can also inhibit DG function[54,56]. Although the discrepancies between studies that stimulate new neurons might be due to technical issues, this urges caution when developing and employing such new-neuron-based therapies.

Because new neurons are highly sensitive to activity-dependent regulation, a related approach would be to stimulate DG activity to subsequently stimulate new neurons. Intriguingly, 'neurogenic' compounds exist that drive neurogenesis and/or improve some aspect of DG functional output in an activity-dependent manner[108,119]. However, so far, no neurogenic compounds act directly and solely on new DG neurons. A major challenge is identifying specific receptors or proteins on new DG neurons that could be exploited for treatment purposes. This is a particularly problematic obstacle in that new DG neurons move through so many developmental stages (Fig. 1a,b). However, the fact that new neurons develop much more slowly in primates than in rodents[76], yet a larger proportion of hippocampal neurons turn over in humans than in rodents[31,120], raises the possibility that identifying a new-neuron target might be more feasible in humans.

One final way to target new neurons would be to regulate their microcircuitry to normalize dysfunctional DG activity. For example, the activation of certain DG interneurons in rodents drives sparse encoding by feedback inhibition onto mature GCs[81], which might improve pattern separation, as has been studied indirectly[121]. In addition, the stimulation of other DG interneurons in mice promotes progenitor survival and thus adult neurogenesis[122], which might also enhance sparse encoding and pattern separation. Indeed, the regulation of any local mechanism that drives sparse encoding and the accompanying improvement in temporal precision of activation might be a candidate for this approach[123]. Such studies are not currently feasible in humans because of the limited knowledge of new-neuron microcircuitry in humans and the invasive nature of such approaches.

Conclusions and future directions

A dysfunctional DG is considered to be an endophenotype or biological correlate of most neuropsychiatric disorders[22,24,59,61,124,125]. The normalization or recalibration of aberrant DG function holds potential for treatment of these disorders. New DG neurons have unique connections and physiological properties that enable them to both sense and influence DG activity. Thus, we propose that targeting new DG neurons is one way of normalizing or recalibrating a dysfunctional DG (Fig. 2e). Another way of recalibrating a dysfunctional DG is upstream stimulation of the Ent (Fig. 2d). We think that both of these approaches merit consideration for therapeutic normalization of DG functional output, and we predict that—in animal models at least—this normalization occurs in part via the stimulation of new DG neurons.

There are numerous knowledge gaps that remain. First, specific DG output circuits in mice and rats need to be thoroughly defined, as has been done in regard to the ventral hippocampus–nucleus accumbens circuits for mood regulation[126], because incorrect neuroanatomical or functional targeting of a circuit might impair an already disrupted network[127]. This is feasible, given the next generation of functional neuroanatomical techniques, which employ genetic promoter enhancers with cell-specific genetic- and viral-mediated, gene-transfer-induced labeling and lineage-specific transgenic lines[128,129]. Second, a broader scope of behaviors should be tested in mice and rats, particularly as new functions of the DG are recognized[130]. It is notable how few studies cross the ‘memory–mood’ divide, or even consider other DG functions, such as reward. Here we have highlighted papers that examine both memory and mood[53,54,65], mood and reward[62], or memory, mood and pattern separation[56,57]. Given that neuropsychiatric disorders are marked by a dysfunctional DG, and that the DG has a range of functional output, we encourage researchers to more frequently and pointedly cross the memory–mood divide and to explore more work with animal models of neuropsychiatric disorders. Third, additional human and postmortem work is warranted, particularly with regard to development, regulation, and most ambitiously, *in vivo* imaging[31,131]. Finally, although neurogenesis does exist in the postnatal primate and specifically human DG[31,131], the process is presumed to take much longer than in the mouse or rat, and it is more challenging to detect cells in select stages of neurogenesis, given the limitations of current markers and the modes of assessment of new neurons in the adult human. This is relevant because postmortem human neurogenesis studies most commonly measure proliferating cells, not immature or specifically new

neurons, because of technical obstacles. Should any future therapies emerge that, for example, normalize the proliferating cells that are reduced in humans diagnosed with either schizophrenia or MDD[97,132], a post-treatment waiting period would be warranted to assess whether indeed the therapy has any influence on DG function. Therefore, although the common model of neurogenesis and its timeline (Fig. 1a) is a simplified representation of our current knowledge, it should continue to be rigorously tested and refined, particularly in regard to human neurogenesis.

We hope that this current view of new DG neurons and neuropsychiatric disorders will drive interest in testing the postulates put forth here. These recent studies underscore that the regulation of adult-generated DG neurogenesis merits continued and focused attention in the ongoing effort to develop novel treatments and to enable expansion of the toolkit available to treat neuropsychiatric disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants to A.J.E. from the US National Institutes of Health (DA023701, DA023555, MH107945) and the US National Aeronautics and Space Administration (NNX15AE09G). S.Y. was funded by a postdoctoral institutional training grant (NIMH T32-MH076690, Basic Science Training Program in the Neurobiology of Mental Illness, PI, C. Tamminga).

References

1. Murray CJ, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380:2197–2223. [PubMed: 23245608]
2. Bystritsky A. Treatment-resistant anxiety disorders. Mol Psychiatry. 2006; 11:805–814. [PubMed: 16847460]
3. Mouchlianitis E, McCutcheon R, Howes OD. Brain-imaging studies of treatment-resistant schizophrenia: a systematic review. Lancet Psychiatry. 2016; 3:451–463. [PubMed: 26948188]
4. Culpepper L, et al. Suicidality as a possible side effect of antidepressant treatment. J Clin Psychiatry. 2004; 65:742–749. [PubMed: 15291649]
5. Player MJ, et al. Neuroplasticity in depressed individuals compared with healthy controls. Neuropsychopharmacology. 2013; 38:2101–2108. [PubMed: 23676792]
6. Narayan VA, Manji HK. Moving from ‘diagnose and treat’ to ‘predict and pre-empt’ in neuropsychiatric disorders. Nat Rev Drug Discov. 2016; 15:71–72. [PubMed: 26612665]
7. Fattore L, Diana M. Drug addiction: An affective-cognitive disorder in need of a cure. Neurosci Biobehav Rev. 2016; 65:341–361. [PubMed: 27095547]
8. Ahmed AIA, et al. Neuropsychiatric adverse events of varenicline: a systematic review of published reports. J Clin Psychopharmacol. 2013; 33:55–62. [PubMed: 23277249]
9. Jonas, P., Lisman, J. Structure, Function, and Plasticity of Hippocampal Dentate Gyrus Microcircuits. Frontiers Media SA; 2015.
10. Kesner, RP. The Dentate Gyrus: A Comprehensive Guide to Structure, Function, and Clinical Implications. Vol. 163. Elsevier; 2007. p. 567-576.
11. Scharfman, HE. The Dentate Gyrus: A Comprehensive Guide to Structure, Function, and Clinical Implications. Elsevier; 2011.

12. Lopez-Rojas J, Kreutz MR. Mature granule cells of the dentate gyrus–Passive bystanders or principal performers in hippocampal function? Neurosci Biobehav Rev. 2016; 64:167–174. [PubMed: 26949226]
13. Gilpin, NW., Martin-Fardon, R. Brain Reward & Stress Systems in Addiction. Frontiers Media SA; 2015.
14. Koob, GF., Le Moal, M. Neurobiology of Addiction. Academic Press; 2005.
15. Wosiski-Kuhn M, Stranahan AM. From pattern separation to mood regulation: multiple roles for developmental signals in the adult dentate gyrus. Front Cell Neurosci. 2013; 7:96. [PubMed: 23805072]
16. Amaral, DG., Scharfman, HE., Lavenex, P. The Dentate Gyrus: A Comprehensive Guide to Structure, Function, and Clinical Implications. Vol. 163. Elsevier; 2007. p. 3-790.
17. Eisch AJ, Petrik D. Depression and hippocampal neurogenesis: a road to remission? Science. 2012; 338:72–75. [PubMed: 23042885]
18. Schoenfeld TJ, Cameron HA. Adult neurogenesis and mental illness. Neuropsychopharmacology. 2015; 40:113–128. [PubMed: 25178407]
19. Lucassen PJ, et al. Stressing new neurons into depression? Mol Psychiatry. 2013; 18:396–397. [PubMed: 22547116]
20. Marvel CL, Paradiso S. Cognitive and neurological impairment in mood disorders. Psychiatr Clin North Am. 2004; 27:19–36. [PubMed: 15062628]
21. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophr Bull. 2009; 35:383–402. [PubMed: 19011234]
22. Kheirbek MA, Klemenhagen KC, Sahay A, Hen R. Neurogenesis and generalization: a new approach to stratify and treat anxiety disorders. Nat Neurosci. 2012; 15:1613–1620. [PubMed: 23187693]
23. Liberzon, I., Ressler, K. Neurobiology of PTSD: From Brain to Mind. Oxford University Press; 2016.
24. Das T, Ivleva EI, Wagner AD, Stark CEL, Tamminga CA. Loss of pattern separation performance in schizophrenia suggests dentate gyrus dysfunction. Schizophr Res. 2014; 159:193–197. [PubMed: 25176349]
25. Dichter GS, Damiano CA, Allen JA. Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: animal models and clinical findings. J Neurodev Disord. 2012; 4:19. [PubMed: 22958744]
26. Kang E, Wen Z, Song H, Christian KM, Ming GL. Adult neurogenesis and psychiatric disorders. Cold Spring Harb Perspect Biol. 2016; 8:a019026. [PubMed: 26801682]
27. Aimone JB, et al. Regulation and function of adult neurogenesis: from genes to cognition. Physiol Rev. 2014; 94:991–1026. [PubMed: 25287858]
28. Morishita T, Fayad SM, Higuchi MA, Nestor KA, Foote KD. Deep brain stimulation for treatment-resistant depression: systematic review of clinical outcomes. Neurotherapeutics. 2014; 11:475–484. [PubMed: 24867326]
29. Stone SSD, et al. Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J Neurosci. 2011; 31:13469–13484. [PubMed: 21940440]
30. Suthana N, Fried I. Deep brain stimulation for enhancement of learning and memory. Neuroimage. 2014; 85:996–1002. [PubMed: 23921099]
31. Bergmann O, Spalding KL, Frisén J. Adult neurogenesis in humans. Cold Spring Harb Perspect Biol. 2015; 7:a018994. [PubMed: 26134318]
32. Ge S, Sailor KA, Ming GL, Song H. Synaptic integration and plasticity of new neurons in the adult hippocampus. J Physiol (Lond). 2008; 586:3759–3765. [PubMed: 18499723]
33. Vivar C, van Praag H. Functional circuits of new neurons in the dentate gyrus. Front Neural Circuits. 2013; 7:15. [PubMed: 23443839]
34. Toni N, Sultan S. Synapse formation on adult-born hippocampal neurons. Eur J Neurosci. 2011; 33:1062–1068. [PubMed: 21395849]

35. Song J, Olsen RHJ, Sun J, Ming GL, Song H. Neuronal circuitry mechanisms regulating adult mammalian neurogenesis. Cold Spring Harb Perspect Biol. 2016; 8:a018937. [PubMed: 27143698]
36. Vivar C, Potter MC, van Praag H. All about running: synaptic plasticity, growth factors and adult hippocampal neurogenesis. Curr Top Behav Neurosci. 2013; 15:189–210. [PubMed: 22847651]
37. Bekinschtein P, Oomen CA, Saksida LM, Bussey TJ. Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable? Semin Cell Dev Biol. 2011; 22:536–542. [PubMed: 21767656]
38. Kempermann G. Seven principles in the regulation of adult neurogenesis. Eur J Neurosci. 2011; 33:1018–1024. [PubMed: 21395844]
39. Cameron, HA. Handbook of Contemporary Neuropharmacology. John Wiley & Sons, Inc; 2007.
40. Kempermann, G. Neurogenesis in the Adult Brain I. Seki, T.Sawamoto, K.Parent, MD.J, M., Alvarez-Buylla, A., editors. Springer; Japan: 2011. p. 271-284.
41. Noonan MA, Choi KH, Self DW, Eisch AJ. Withdrawal from cocaine self-administration normalizes deficits in proliferation and enhances maturity of adult-generated hippocampal neurons. J Neurosci. 2008; 28:2516–2526. [PubMed: 18322096]
42. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci. 2000; 20:9104–9110. [PubMed: 11124987]
43. Brown ES, Rush AJ, McEwen BS. Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. Neuropsychopharmacology. 1999; 21:474–484. [PubMed: 10481830]
44. Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry. 1999; 46:1181–1191. [PubMed: 10560024]
45. Canales JJ. Comparative neuroscience of stimulant-induced memory dysfunction: role for neurogenesis in the adult hippocampus. Behav Pharmacol. 2010; 21:379–393. [PubMed: 20700045]
46. Mandyam CD, Koob GF. The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. Trends Neurosci. 2012; 35:250–260. [PubMed: 22265158]
47. Petrik D, Lagace DC, Eisch AJ. The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building? Neuropharmacology. 2012; 62:21–34. [PubMed: 21945290]
48. Levone BR, Cryan JF, O'Leary OF. Role of adult hippocampal neurogenesis in stress resilience. Neurobiol Stress. 2014; 1:147–155. [PubMed: 27589664]
49. Castilla-Ortega E, et al. A place for the hippocampus in the cocaine addiction circuit: Potential roles for adult hippocampal neurogenesis. Neurosci Biobehav Rev. 2016; 66:15–32. [PubMed: 27118134]
50. Solinas M, Thiriet N, Chauvet C, Jaber M. Prevention and treatment of drug addiction by environmental enrichment. Prog Neurobiol. 2010; 92:572–592. [PubMed: 20713127]
51. Drew MR, Denny CA, Hen R. Arrest of adult hippocampal neurogenesis in mice impairs single- but not multiple-trial contextual fear conditioning. Behav Neurosci. 2010; 124:446–454. [PubMed: 20695644]
52. Gu Y, et al. Optical controlling reveals time-dependent roles for adult-born dentate granule cells. Nat Neurosci. 2012; 15:1700–1706. [PubMed: 23143513]
53. Kheirbek MA, Tannenholz L, Hen R. NR2B-dependent plasticity of adult-born granule cells is necessary for context discrimination. J Neurosci. 2012; 32:8696–8702. [PubMed: 22723709]
54. Kheirbek MA, et al. Differential control of learning and anxiety along the dorsoventral axis of the dentate gyrus. Neuron. 2013; 77:955–968. [PubMed: 23473324]
55. Denny CA, et al. Hippocampal memory traces are differentially modulated by experience, time, and adult neurogenesis. Neuron. 2014; 83:189–201. [PubMed: 24991962]
56. Danielson NB, et al. Distinct contribution of adult-born hippocampal granule cells to context encoding. Neuron. 2016; 90:101–112. [PubMed: 26971949]
57. McAvoy KM, et al. Modulating neuronal competition dynamics in the dentate gyrus to rejuvenate aging memory circuits. Neuron. 2016; 91:1356–1373. [PubMed: 27593178]

58. Santarelli L, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science. 2003; 301:805–809. [PubMed: 12907793]
59. Airan RD, et al. High-speed imaging reveals neurophysiological links to behavior in an animal model of depression. Science. 2007; 317:819–823. [PubMed: 17615305]
60. Surget A, et al. Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biol Psychiatry. 2008; 64:293–301. [PubMed: 18406399]
61. Surget A, et al. Antidepressants recruit new neurons to improve stress response regulation. Mol Psychiatry. 2011; 16:1177–1188. [PubMed: 21537331]
62. Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature. 2011; 476:458–461. [PubMed: 21814201]
63. Lehmann ML, Brachman RA, Martinowich K, Schloesser RJ, Herkenham M. Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. J Neurosci. 2013; 33:2961–2972. [PubMed: 23407954]
64. Noonan MA, Bulin SE, Fuller DC, Eisch AJ. Reduction of adult hippocampal neurogenesis confers vulnerability in an animal model of cocaine addiction. J Neurosci. 2010; 30:304–315. [PubMed: 20053911]
65. Seo DO, Carillo MA, Chih-Hsiung Lim S, Tanaka KF, Drew MR. Adult hippocampal neurogenesis modulates fear learning through associative and nonassociative mechanisms. J Neurosci. 2015; 35:11330–11345. [PubMed: 26269640]
66. Arruda-Carvalho M, Sakaguchi M, Akers KG, Josselyn SA, Frankland PW. Posttraining ablation of adult-generated neurons degrades previously acquired memories. J Neurosci. 2011; 31:15113–15127. [PubMed: 22016545]
67. Akers KG, et al. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. Science. 2014; 344:598–602. [PubMed: 24812394]
68. Hill AS, Sahay A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors. Neuropsychopharmacology. 2015; 40:2368–2378. [PubMed: 25833129]
69. van Dijk RM, Huang SH, Slomianka L, Amrein I. Taxonomic separation of hippocampal networks: principal cell populations and adult neurogenesis. Front Neuroanat. 2016; 10:22. [PubMed: 27013984]
70. Bédard, A., Bernier, PJ., Parent, A. Neurogenesis in the Adult Brain II. Seki, T.Sawamoto, K.Parent, JM., Alvarez-Buylla, A., editors. Springer; Japan: 2011. p. 1-21.
71. Kempermann, G. Adult Neurogenesis: Stem Cells and Neuronal Development in the Adult Brain. Oxford University Press; 2006.
72. O'Leary OF, Cryan JF. A ventral view on antidepressant action: roles for adult hippocampal neurogenesis along the dorsoventral axis. Trends Pharmacol Sci. 2014; 35:675–687. [PubMed: 25455365]
73. Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci. 2007; 10:1110–1115. [PubMed: 17726477]
74. Fanselow MS, Dong HW. Arethe dorsal and ventral hippocampus functionally distinct structures? Neuron. 2010; 65:7–19. [PubMed: 20152109]
75. Lacar B, Parylak SL, Vadodaria KC, Sarkar A, Gage FH. Increasing the resolution of the adult neurogenesis picture. F1000Prime Rep. 2014; 6:8. [PubMed: 24592320]
76. Kohler SJ, Williams NI, Stanton GB, Cameron JL, Greenough WT. Maturation time of new granule cells in the dentate gyrus of adult macaque monkeys exceeds six months. Proc Natl Acad Sci USA. 2011; 108:10326–10331. [PubMed: 21646517]
77. Bayer SA, Yackel JW, Puri PS. Neurons in the rat dentate gyrus granular layer substantially increase during juvenile and adult life. Science. 1982; 216:890–892. [PubMed: 7079742]
78. Altman, J., Bayer, S. The Hippocampus. Isaacson, RL., Pribram, KH., editors. Springer; US: 1975. p. 95-122.
79. Amrein I, Slomianka L, Lipp HP. Granule cell number, cell death and cell proliferation in the dentate gyrus of wild-living rodents. Eur J Neurosci. 2004; 20:3342–3350. [PubMed: 15610166]

80. West MJ, Coleman PD, Flood DG. Estimating the number of granule cells in the dentate gyrus with the disector. Brain Res. 1988; 448:167–172. [PubMed: 3292009]
81. Temprana SG, et al. Delayed coupling to feedback inhibition during a critical period for the integration of adult-born granule cells. Neuron. 2015; 85:116–130. [PubMed: 25533485]
82. Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron. 2011; 70:687–702. [PubMed: 21609825]
83. Lepousez G, Nissant A, Lledo PM. Adult neurogenesis and the future of the rejuvenating brain circuits. Neuron. 2015; 86:387–401. [PubMed: 25905812]
84. Vivar C, et al. Monosynaptic inputs to new neurons in the dentate gyrus. Nat Commun. 2012; 3:1107. [PubMed: 23033083]
85. Platel JC, Kelsch W. Role of NMDA receptors in adult neurogenesis: an ontogenetic (re)view on activity-dependent development. Cell Mol Life Sci. 2013; 70:3591–3601. [PubMed: 23397131]
86. Ma DK, Kim WR, Ming GL, Song H. Activity-dependent extrinsic regulation of adult olfactory bulb and hippocampal neurogenesis. Ann NY Acad Sci. 2009; 1170:664–673. [PubMed: 19686209]
87. Mongiat LA, Schinder AF. Adult neurogenesis and the plasticity of the dentate gyrus network. Eur J Neurosci. 2011; 33:1055–1061. [PubMed: 21395848]
88. Doetsch F, Hen R. Young and excitable: the function of new neurons in the adult mammalian brain. Curr Opin Neurobiol. 2005; 15:121–128. [PubMed: 15721754]
89. Wadiche JI, Overstreet-Wadiche L. New neurons don't talk back. Neuron. 2015; 85:3–5. [PubMed: 25569342]
90. Lemaire V, et al. Long-lasting plasticity of hippocampal adult-born neurons. J Neurosci. 2012; 32:3101–3108. [PubMed: 22378883]
91. Vaidya VA, Vadodaria KC, Jha S. Neurotransmitter regulation of adult neurogenesis: putative therapeutic targets. CNS Neurol Disord Drug Targets. 2007; 6:358–374. [PubMed: 18045164]
92. Yamasaki N, et al. Alpha-CaMKII deficiency causes immature dentate gyrus, a novel candidate endophenotype of psychiatric disorders. Mol Brain. 2008; 1:6. [PubMed: 18803808]
93. Takao K, et al. Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia. Neuropsychopharmacology. 2013; 38:1409–1425. [PubMed: 23389689]
94. Hayes JP, et al. Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. J Psychiatr Res. 2011; 45:660–669. [PubMed: 21047644]
95. Zhai TY, et al. Altered intrinsic hippocmapus declarative memory network and its association with impulsivity in abstinent heroin dependent subjects. Behav Brain Res. 2014; 272:209–217. [PubMed: 25008351]
96. Alia-Klein N, Parvaz MA, Woicik PA. Gene × disease interaction on orbitofrontal gray matter in cocaine addiction. Arch Gen Psychiatry. 2011; 68:283–294. [PubMed: 21383264]
97. Boldrini M, et al. Hippocampal angiogenesis and progenitor cell proliferation are increased with antidepressant use in major depression. Biol Psychiatry. 2012; 72:562–571. [PubMed: 22652019]
98. Han K, et al. SHANK3 overexpression causes manic-like behaviour with unique pharmacogenetic properties. Nature. 2013; 503:72–77. [PubMed: 24153177]
99. Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. J Neurochem. 2000; 75:1729–1734. [PubMed: 10987856]
100. Peng Z, et al. Ziprasidone ameliorates anxiety-like behaviors in a rat model of PTSD and up-regulates neurogenesis in the hippocampus and hippocampus-derived neural stem cells. Behav Brain Res. 2013; 244:1–8. [PubMed: 23384713]
101. Keilhoff G, Fusar-Poli P, Becker A. Effects of antipsychotics on dentate gyrus stem cell proliferation and survival in animal models: a critical update. Neural Plast. 2012; 2012:832757. [PubMed: 23150836]
102. Tannenholz L, Jimenez JC, Kheirbek MA. Local and regional heterogeneity underlying hippocampal modulation of cognition and mood. Front Behav Neurosci. 2014; 8:147. [PubMed: 24834033]

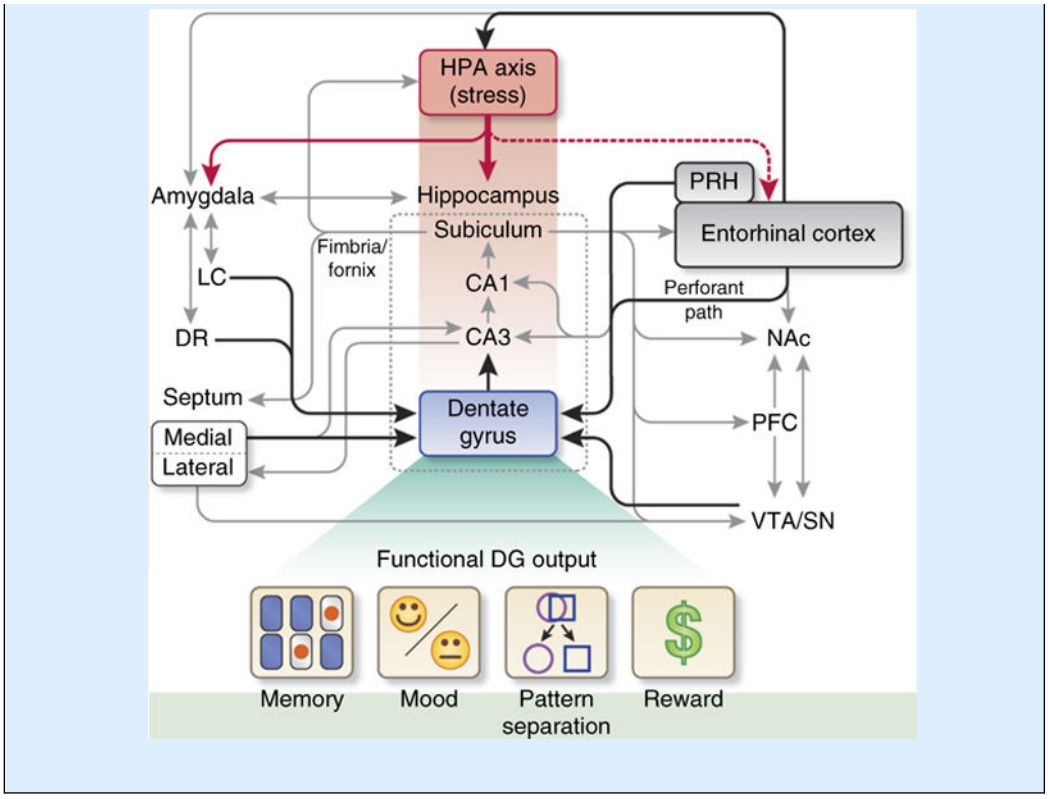
103. Kropff E, Yang SM, Schinder AF. Dynamic role of adult-born dentate granule cells in memory processing. Curr Opin Neurobiol. 2015; 35:21–26. [PubMed: 26100379]
104. Boldrini M, et al. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. Neuropsychopharmacology. 2013; 38:1068–1077. [PubMed: 23303074]
105. Miller BR, Hen R. The current state of the neurogenic theory of depression and anxiety. Curr Opin Neurobiol. 2015; 30:51–58. [PubMed: 25240202]
106. Henn FA, Vollmayr B. Neurogenesis and depression: etiology or epiphenomenon? Biol Psychiatry. 2004; 56:146–150. [PubMed: 15271582]
107. Tsai CY, Tsai CY, Arnold SJ, Huang G-J. Ablationof hippocampal neurogenesis in mice impairs the response to stress during the dark cycle. Nat Commun. 2015; 6:8373. [PubMed: 26415720]
108. Walker AK, et al. The P7C3 class of neuroprotective compounds exerts antidepressant efficacy in mice by increasing hippocampal neurogenesis. Mol Psychiatry. 2015; 20:500–508. [PubMed: 24751964]
109. Johnston ST, Shtrahman M, Parylak S, Gonçalves JT, Gage FH. Paradox of pattern separation and adult neurogenesis: A dual role for new neurons balancing memory resolution and robustness. Neurobiol Learn Mem. 2016; 129:60–68. [PubMed: 26549627]
110. Liu KY, Gould RL, Coulson MC, Ward EV, Howard RJ. Tests of pattern separation and pattern completion in humans-A systematic review. Hippocampus. 2016; 26:705–717. [PubMed: 26663362]
111. Clelland CD, et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science. 2009; 325:210–213. [PubMed: 19590004]
112. Niibori Y, et al. Suppression of adult neurogenesis impairs population coding of similar contexts in hippocampal CA3 region. Nat Commun. 2012; 3:1253. [PubMed: 23212382]
113. Nakashiba T, et al. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell. 2012; 149:188–201. [PubMed: 22365813]
114. Chauvet C, Lardeux V, Goldberg SR, Jaber M, Solinas M. Environmental enrichment reduces cocaine seeking and reinstatement induced by cues and stress but not by cocaine. Neuropsychopharmacology. 2009; 34:2767–2778. [PubMed: 19741591]
115. Mustroph ML, Stobaugh DJ, Miller DS, DeYoung EK, Rhodes JS. Wheel running can accelerate or delay extinction of conditioned place preference for cocaine in male C57BL/6J mice, depending on timing of wheel access. Eur J Neurosci. 2011; 34:1161–1169. [PubMed: 21864322]
116. Suthana N, et al. Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med. 2012; 366:502–510. [PubMed: 22316444]
117. Roy DS, et al. Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. Nature. 2016; 531:508–512. [PubMed: 26982728]
118. Sahay A, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature. 2011; 472:466–470. [PubMed: 21460835]
119. Petrik D, et al. Functional and mechanistic exploration of an adult neurogenesis-promoting small molecule. FASEB J. 2012; 26:3148–3162. [PubMed: 22542682]
120. Lagace DC, et al. Dynamic contribution of nestin-expressing stem cells to adult neurogenesis. J Neurosci. 2007; 27:12623–12629. [PubMed: 18003841]
121. Ikrar T, et al. Adult neurogenesis modifies excitability of the dentate gyrus. Front Neural Circuits. 2013; 7:204. [PubMed: 24421758]
122. Song J, et al. Parvalbumin interneurons mediate neuronal circuitry-neurogenesis coupling in the adult hippocampus. Nat Neurosci. 2013; 16:1728–1730. [PubMed: 24212671]
123. Yu EP, et al. Protracted postnatal development of sparse, specific dentate granule cell activation in the mouse hippocampus. J Neurosci. 2013; 33:2947–2960. [PubMed: 23407953]
124. Hagihara H, Takao K, Walton NM, Matsumoto M, Miyakawa T. Immature dentate gyrus: an endophenotype of neuropsychiatric disorders. Neural Plast. 2013; 2013:318596. [PubMed: 23840971]

125. Walton NM, et al. Detection of an immature dentate gyrus feature in human schizophrenia/bipolar patients. Transl Psychiatry. 2012; 2:e135. [PubMed: 22781168]
126. Bagot RC, et al. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. Nat Commun. 2015; 6:7062. [PubMed: 25952660]
127. Cho KO, et al. Aberrant hippocampal neurogenesis contributes to epilepsy and associated cognitive decline. Nat Commun. 2015; 6:6606. [PubMed: 25808087]
128. Yang SM, Alvarez DD, Schinder AF. Reliable genetic labeling of adult-born dentate granule cells using Ascl1 CreERT2 and Glast CreERT2 murine Lines. J Neurosci. 2015; 35:15379–15390. [PubMed: 26586824]
129. Lerner TN, Ye L, Deisseroth K. Communication in neural circuits: tools, opportunities, and challenges. Cell. 2016; 164:1136–1150. [PubMed: 26967281]
130. Sweeney P, Yang Y. An excitatory ventral hippocampus to lateral septum circuit that suppresses feeding. Nat Commun. 2015; 6:10188. [PubMed: 26666960]
131. Manganas LN, et al. Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science. 2007; 318:980–985. [PubMed: 17991865]
132. Allen KM, Fung SJ, Weickert CS. Cell proliferation is reduced in the hippocampus in schizophrenia. Aust N Z J Psychiatry. 2016; 50:473–480. [PubMed: 26113745]
133. Lucassen PJ, Stumpel MW, Wang Q, Aronica E. Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. Neuropharmacology. 2010; 58:940–949. [PubMed: 20138063]
134. Boldrini M, et al. Antidepressants increase neural progenitor cells in the human hippocampus. Neuropsychopharmacology. 2009; 34:2376–2389. [PubMed: 19606083]
135. Reif A, et al. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry. 2006; 11:514–522. [PubMed: 16415915]
136. Geuze E, Vermetten E, Bremner JD. MR-based *in vivo* hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Mol Psychiatry. 2005; 10:160–184. [PubMed: 15356639]
137. Elvsåshagen T, et al. Evidence for reduced dentate gyrus and fimbria volume in bipolar II disorder. Bipolar Disord. 2013; 15:167–176. [PubMed: 23317454]
138. Frey BN, et al. The role of hippocampus in the pathophysiology of bipolar disorder. Behav Pharmacol. 2007; 18:419–430. [PubMed: 17762510]
139. Otten M, Meeter M. Hippocampal structure and function in individuals with bipolar disorder: a systematic review. J Affect Disord. 2015; 174:113–125. [PubMed: 25496759]
140. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. Lancet. 2000; 356:1241–1242. [PubMed: 11072948]
141. Manji HK, et al. The underlying neurobiology of bipolar disorder. World Psychiatry. 2003; 2:136–146. [PubMed: 16946919]
142. Barbeau D, Liang JJ, Robitalille Y, Quirion R, Srivastava LK. Decreased expression of the embryonic form of the neural cell adhesion molecule in schizophrenic brains. Proc Natl Acad Sci USA. 1995; 92:2785–2789. [PubMed: 7708724]
143. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry. 2006; 188:510–518. [PubMed: 16738340]
144. Heckers S. Neuroimaging studies of the hippocampus in schizophrenia. Hippocampus. 2001; 11:520–528. [PubMed: 11732705]
145. Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. Neuroimaging Clin N Am. 2007; 17:523–538. [PubMed: 17983968]
146. Bayer R, et al. Alterations of neuronal precursor cells in stages of human adult neurogenesis in heroin addicts. Drug Alcohol Depend. 2015; 156:139–149. [PubMed: 26416695]
147. Mackey S, Paulus M. Are there volumetric brain differences associated with the use of cocaine and amphetamine-type stimulants? Neurosci Biobehav Rev. 2013; 37:300–316. [PubMed: 23253945]
148. Thompson PM, et al. Structural abnormalities in the brains of human subjects who use methamphetamine. J Neurosci. 2004; 24:6028–6036. [PubMed: 15229250]

Box 1

The circuits and functional output of the hippocampal DG

The healthy hippocampal DG receives input (black lines) from the limbic system (Entorhinal cortex (Ent) via perforant path (PP), perirhinal cortex (PRH), medial septum and (not shown) contralateral DG and recurrent collaterals from hippocampal CA3) and midbrain and hindbrain modulatory regions (VTA/SN, LC, DR)[16]. Many other non-DG connections that might affect the DG indirectly are also indicated (gray lines). The DG and hippocampus are highly sensitive to stress (for example, physiological, environmental) owing to direct inputs from the hypothalamic–pituitary–adrenal axis (HPA, red lines, red shading) and putative, indirect effects from the HPA to Ent (red dotted line)[17–19]. In turn, the HPA axis is influenced by the DG in part through hippocampal, subicular and Ent projections to the HPA axis. Working in concert, these and other brain circuits contribute to functional DG output, which are shown in schematic form to represent memory, mood, pattern separation and reward. As discussed in the main text, neuropsychiatric disorders are marked by dysregulated memory, mood, pattern separation and reward processing, symptoms that are correlated with impaired DG function and/or impaired generation or function of new DG neurons which may be affected by stress (Table 1). CA1, cornu ammon 1; CA3, cornu ammon 3; DG, dentate gyrus; DR, dorsal raphe; Ent, entorhinal cortex; HPA, hypothalamic–pituitary–adrenal; LC, locus coeruleus; NAc, nucleus accumbens septi; PFC, prefrontal cortex; PP, perforant path; PRH, perirhinal cortex; SN, substantia nigra; VTA, ventral tegmental area.



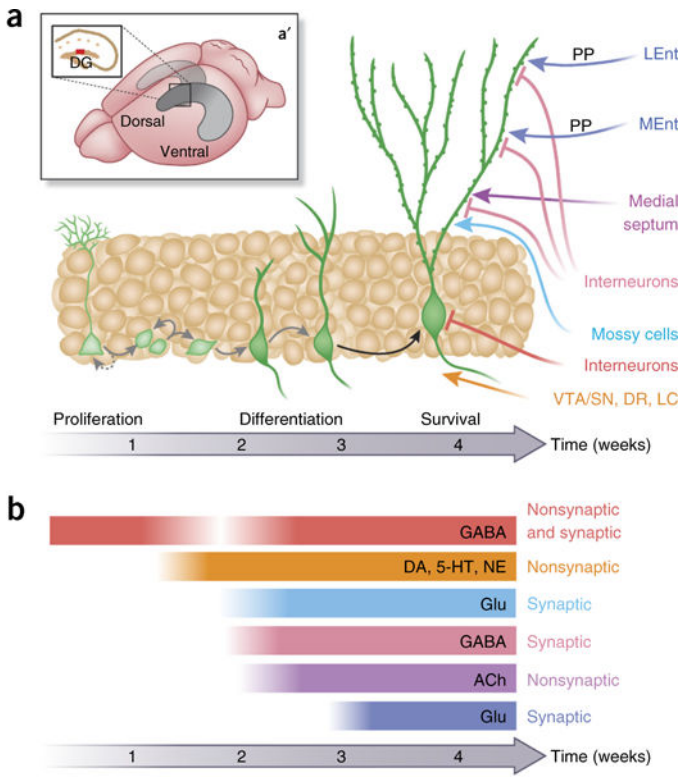


Figure 1.

Neurogenesis in the DG and its sensitivity to neurotransmitter systems with relevance to common therapies. (**a**) In the adult mouse DG (**a**′ hippocampus in gray, dorsal DG in tan, main schematic in **a** is expanded view of red bar in the inset), new neurons are generated over time, depicted as green cells maturing through developmental 'stages' of proliferation, differentiation and survival, a process that takes ~4 weeks. Mature DG granule neurons (right, green cells) receive diverse input from other DG cells (Mossy Cells, blue; interneurons, red and pink) and other limbic (lateral and medial entorhinal cortex (LEnt, MEnt) in dark blue; medial septum in purple) and midbrain and hindbrain regions (ventral tegmental area/substantia nigra (VTA/SN), dorsal raphe (DR), locus coeruleus (LC) in orange). The main somatic input to new DG granule neurons is from inhibitory interneurons (red flathead lines; for example, DG basket cells). Late-stage differentiation and surviving cells are darker green, whereas proliferating cells are lighter green. (**b**) As new DG neurons develop, they are regulated by an increasingly diverse set of neurotransmitters. The first input is nonsynaptic (ambient) GABA (red bar) from DG interneurons (red input, **a**), which eventually transitions to include synaptic GABA as well (white gradient in red bar). The last being synaptic glutamate (bottom dark blue bar, **b**) from Ent neurons (dark blue arrows (**a**)). Treatments for neuropsychiatric disorders act on many of the neurotransmitter systems that regulate new neurons (**b**). Ach, acetylcholine; DA, dopamine; DG, dentate gyrus; DR, dorsal raphe; Ent, entorhinal cortex (LEnt, lateral Ent; MEnt, medial Ent); GABA, gamma-aminobutyric acid; Glu, glutamate; LC, locus coeruleus; NE, norepinephrine/noradrenergic; SN, substantia nigra; VTA, ventral tegmental area.

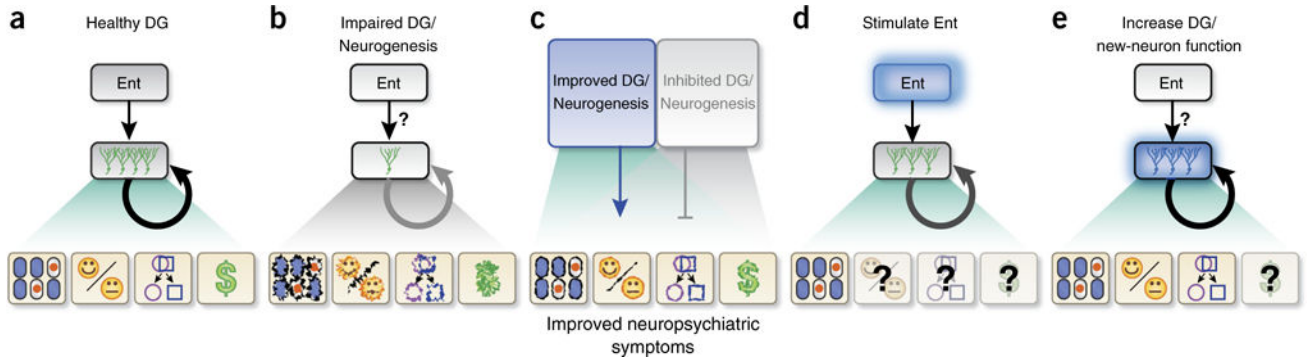


Figure 2.

Proven and proposed approaches to targeting new DG neurons to recalibrate DG functional output in neuropsychiatric disorders. (**a**) In the healthy DG, input from the Ent into the DG drives new neurons and ultimately results in functional DG output, such as memory, mood, pattern separation and reward (green shaded triangle). When DG activity or function is aberrant, as is the case in many neuropsychiatric disorders (**b**, gray shaded triangle), new neurons are often decreased in number or function, perhaps in part owing to a dysfunctional upstream input from the Ent (indicated by a question mark (?)). (**c**) We propose that inducible increase in new neuron number, activity or DG activity can improve neuropsychiatric symptoms (blue box, arrow, green shaded triangle), whereas inhibition of new neuron number, activity or DG activity can block such improvement (gray box, flat head line, gray shaded triangle). Thus, targeting new neuron number, activity or DG activity might be a novel treatment for neuropsychiatric disorders. Recalibration of DG functional output is feasible via the stimulation of upstream DG regions (e.g., Ent, **d**) or increased number of new neurons or increased activity of new neurons or DG (**e**). For (**d**), it has already been shown in mice that Ent stimulation (blue box, bold font) enhances neurogenesis and improves learning and memory in both humans and mice (green shaded triangle, **d**). It remains to be tested whether this upstream stimulation and enhanced new neuron number or activity will affect mood, pattern separation or reward (indicated by question mark (?)). For (**e**), it has been shown in mice that direct stimulation or induction of adult neurogenesis (blue box) can improve memory, mood and pattern separation, although most of the work in this regard has shown the opposite (e.g., direct inhibition or suppression of adult neurogenesis impairs memory, mood and pattern separation). Although it has not been tested whether direct stimulation or induction of adult neurogenesis can improve reward, the converse has been shown: the suppression of adult neurogenesis enhances vulnerability in animal models of aberrant reward (e.g., addiction). DG, dentate gyrus; Ent, entorhinal cortex.

Table 1

Overview of studies correlating neurogenesis in the DG and neuropsychiatric disorders. Given that more than 2,000 publications have contributed to the correlative findings summarized here, review publications are primarily cited in Table 1 to direct the reader to comprehensive and referenced tables in the literature

Correlated with neuropsychiatric disorders	Stage of neurogenesis (human postmortem)			Hippocampal		Normalize/improve with treatment? (human/ rodents)
	Proliferation	Differentiation	Survival	Volume (human)	Network activity (human/rodents)	
Major depressive disorder	Decreased/nc[133–135]	–	Decreased*[104]	Decreased[136]	Decreased[59,61]	✓/nc[42,97,104,133,134]
Bipolar disorder	nc[135]	Increased[125]	Decreased (trend)[125]	Decreased/nc[137,138]	Decreased/Increased/nc[139]	✓[99,140,141]
Schizophrenia	Decreased[132,135]	Decreased[142]	–	Decreased[143]	Increased/Decreased[92,93,144]	✓[101]
Post-traumatic stress disorder	–	–	–	Decreased[145]	Decreased[94]	✓[100]
Substance-related and addictive disorder	Decreased[146]	Decreased#[146]	–	Decreased/nc[147,148]	Increased^[95]	✓[41]

Asterisk (*), fewer DG granule neurons in MDD versus MDD with medication and controls;

#decreased dendritic arborization of immature neurons in heroin addicts;

carat (^), increased connectivity between hippocampus and reward-related brain regions. nc, not changed;

dash (–), not studied.

Table 2

Overview of studies linking DG neurogenesis and features of psychiatric disorders in a causative manner

Approach to manipulate new neurons or DG					
Disrupt or inhibit	**Enhance or stimulate**	**Animal model**	**Behavioral assessment of DG function**	**Reference**	**Influence of manipulation on DG function**
MEMORY					
Disrupt	–	–	Acquisition	51	Impaired
Disrupt	–	–	Retrieval	66	Impaired
–	Enhance	–	Acquisition/retrieval	118	nc
Disrupt	–	–	Acquisition/retrieval+	29	Impaired
Inhibit	–	–	Acquisition/retrieval	52	Impaired
Disrupt	–	–	Acquisition	53	Impaired
Inhibit	Stimulate	–	Acquisition/retrieval+	54	Impaired (inhib or stim)
Disrupt	Enhance	–	Retrieval*	67	Enhanced or impaired
Inhibit, Disrupt	–	–	Retrieval	55	Impaired
Disrupt	–	–	Acquisition/retrieval^	65	Impaired
Inhibit	Stimulate	–	Acquisition/retrieval	56	Impaired (inhib or stim)
–	Enhance	–	Acquisition/retrieval+	57	Enhanced
MOOD					
Disrupt	–	Stress (chronic)	Anxiety, stress-induced despair	58	Increased
Disrupt	–	–	Despair	59	Increased
Disrupt	–	Stress (chronic)	Stress-induced despair	60	Increased
Disrupt	–	–	Anxiety, stress-induced despair	66	nc
–	Enhance	–	Anxiety, stress-induced despair	118	Decreased or nc
Disrupt	–	Stress (acute)	Anxiety, despair	62	Increased
Disrupt	–	Stress (chronic)	Anxiety	61	Increased
Disrupt	–	–	Anxiety, despair	53	nc
Inhibit	Stimulate	–	Anxiety	54	Decreased (stim)
Disrupt	–	Stress (chronic)	Stress-induced anxiety, despair#	63	Increased
–	Enhance	Stress hormone	Anxiety, stress-induced despair	68	Decreased

Approach to manipulate new neurons or DG					
Disrupt or inhibit	**Enhance or stimulate**	**Animal model**	**Behavioral assessment of DG function**	**Reference**	**Influence of manipulation on DG function**
Disrupt	–	–	Anxiety§	65	Increased
Disrupt	–	Stress (chronic)	Stress-induced anxiety	108	Increased
Inhibit	Stimulate	–	Anxiety	56	nc
–	Enhance	–	Anxiety, stress-induced despair	57	nc
PATTERN SEPARATION					
–	Enhance	–	Pattern separation	118	Enhanced
Disrupt	–	–	Pattern separation	53	Impaired
Inhibit	–	–	Pattern separation	56	Impaired
–	Stimulate	–	Pattern separation	57	Enhanced
REWARD					
Disrupt	–	Cocaine self-admin	Rat model of addiction	64	Increased
Disrupt	–	Stress (acute)	Natural reward	62	Decreased

References cited target and manipulate new DG neurons or DG activity and assess a DG function (memory, mood, pattern separation, reward) relevant to neuropsychiatric disorders. Influence on DG function for memory and pattern-separation outcomes are given as enhanced, impaired or nc. Influence on DG function for mood- and reward-related are given as increased, decreased or nc. For study inclusion criteria, detailed list of results and specific figure panels that led to our conclusions in Table 2, see Supplementary Table 1.

Asterisk (*), altered neurogenesis post-learning;

carat (ˆ), dependent on type of conditioning (trace or delay);

cross (+), cognitive flexibility;

pound sign (#), only after adrenalectomy;

dollar sign (§), only after, not before, memory testing;

nc, not changed; self-admin, self-administration; —, not examined.