Opinion

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Adult neurogenesis: bridging the gap between mice and humans

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Neural stem/progenitor cells (NSPCs) generate new neurons in the mammalian brain throughout life. Over the past two decades, substantial progress has been made in deciphering the cellular and molecular mechanisms underlying adult neurogenesis and in understanding the role played by new neurons in brain function in animal models of health and disease. By contrast, knowledge regarding the extent and relevance of neurogenesis in the adult human brain remains scant. Here we review new concepts about how new neurons shape adult brain circuits, discuss fundamental, unanswered questions about stem cell-associated neural plasticity, and illustrate how the gap between the animal-based basic research and current efforts to analyze life-long neuronal development of the human brain may be overcome by using novel experimental strategies.

From thymidine analogs to nuclear bomb testing: discovery of adult neurogenesis in humans

After the days of the pioneering neuroscience research of Ramon y Cajal, scientists assumed that the birth of neurons in the mammalian brain was restricted to embryonic and early postnatal development. Given the complexity of neural networks, it was assumed to be impossible for any newborn cells to integrate into the adult brain in a meaningful way; if they were to do so, they would destabilize existing information and acquired skills by disrupting preexisting circuits. Given this prevalent thinking, the publication in the mid-1960s of the first data suggesting that the postnatal mammalian brain continued to harbor sites of active neurogenesis was met with skepticism and largely rejected by the neuroscience community [1]. However, in the 30 years thereafter, several key findings – such as the discovery that songbirds remodel substantial parts of their vocal center every year through newborn neurons, and the isolation and cell-culture propagation of cells with stem cell properties (i.e., self-renewal and multipotency) from the adult mammalian brain – softened this resistance [2–4]. The breakthrough for the field came with the use of thymidine analogs such as bromodeoxyuridine (BrdU) to label dividing cells and their progeny, allowing the combined use of antibodies detecting BrdU-labeled nuclei with neuronal markers such as NeuN (Fox3) to unambiguously identify adult-born cells within the neuronal lineage [5]. Thus, it was not until the late 1990s that adult neurogenesis was broadly accepted as an integral part of adult brain plasticity, first in rodents and then in nonhuman primates; finally, the existence of human brain neural stem/progenitor cells (NSPCs) that retain the capacity to generate new neurons was discovered [6,7]. However, neurogenesis in the adult mammalian brain is not widespread; rather, it is restricted to distinct areas, with the main sites of postnatal neurogenesis in rodents being the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) lining the lateral ventricles, with newborn cells migrating toward the olfactory bulb (OB) where they differentiate into olfactory neurons [8,9]. There is now clear evidence that new neurons in rodents are of pivotal importance for several behavioral tasks that depend on the DG and OB [9–11]. Furthermore, failing or altered neurogenesis has been characterized in numerous rodent models of neuropsychiatric disease, such as major depression and epilepsy [9]. However, recent data revealed significant differences between the brains of laboratory rodents and humans with regard to the extent and magnitude of neurogenesis: whereas neurogenesis is substantial in the human DG, it may be absent in the human SVZ/OB [12,13]. However, the human brain also appears to retain its neurogenic potential outside the hippocampal formation, because new striatal interneurons that become depleted in disease states, such as Huntington's disease (HD), are generated throughout life, most likely by local astrocytic cells [14,15]. Nevertheless, there is a gap between current knowledge regarding the regulation, function, and molecular mechanisms that govern the neurogenic process in the rodent brain and the human brain. Here we discuss current key questions and illustrate novel approaches striving to extend the field's focus on laboratory rodents to more clinically relevant studies by characterizing the role of adult neurogenesis in human health and disease.

Analyzing neurogenesis in rodents and humans

Measuring the extent of neurogenesis in rodents is largely based on histological techniques using thymidine analogs, transgenic marker expression in NSPCs and immature neurons, transgenesis-based lineage tracing, and retroviral vectors that selectively label dividing cells and their progeny [16]. Using these approaches, the developmental

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steps that take the dividing NSPC toward the integrating neuron were extensively characterized, showing that in the DG glutamatergic granule cells are generated whereas in the SVZ a set of heterogeneous NSPCs generates diverse subtypes of olfactory neuron that integrate into the OB after migration through the rostral migrator stream (RMS) [17–19]. In addition, numerous studies revealed that neurogenesis is a highly dynamic process, influenced by positive and negative regulators such as physical exercise and environmental enrichment but also stress and age [9,20,21]. The first evidence that neurogenesis occurs within the human hippocampus was based on analyses of tissue obtained from deceased cancer patients that had received BrdU injections before tumor-removing surgery and using markers such as doublecortin that are transiently expressed in immature neurons [6,22]. However, similar studies conducted in the SVZ/OB led to controversial conclusions, with some groups reporting neurogenesis whereas others found no evidence for sustained neurogenesis in the human OB [23,24].

A novel approach was developed by the Frisen group, who introduced the use of carbon dating (based on elevated ^{14}C levels following terrestrial nuclear bomb testing) to birth date neurons and glial cells in human tissue samples [25]. Strikingly, this innovative strategy confirmed the existence of substantial amounts of neurogenesis in the human DG whereas no evidence of ongoing neurogenesis was detected in the human OB [12,13]. However, it appears that NSPCs in the human SVZ retain their neurogenic potential by generating a subset of striatal interneurons, a neurogenic route that is absent in the rodent brain [15]. The use of carbon dating to birth date neural cells marks a major advance for the field and is expected to substantially increase our knowledge regarding the turnover of neurons (and glial cells) in the human brain (Figure 1). However, this technique has its limitations, given the highly specialized and expensive infrastructure required to perform this type of birth-dating analysis (e.g., accelerators) and the fact that ^{14}C levels in the atmosphere and biomass have declined substantially over past decades, resulting in a natural date of expiration for this technique [25]. An alternative approach to measure levels of neurogenesis in humans may be the use of noninvasive imaging strategies based on magnetic resonance imaging (MRI) and positron emission tomography (PET). Several studies have described associations between MRI-measured hippocampal blood volume and specific lipid peaks, as measured by magnetic resonance spectroscopy, with levels of neurogenesis [26–28]. However, the specificity and sensitivity of these approaches remain controversial. Nonetheless, noninvasive imaging strategies raise the possibility of performing longitudinal studies of individuals (for example, before and after manipulations that may affect levels of neurogenesis such as physical activity) and of testing the effects of potential proneurogenic treatments in the context of neuropsychiatric disease. Undoubtedly, the ^{14}C-based data confirming the relevance of neurogenesis in the human brain will spur additional efforts to validate existing imaging approaches and to develop novel tools required to measure levels of neurogenesis noninvasively in the human brain.

Mechanisms regulating NSPC activity, neuronal differentiation, and integration

Besides confirming the existence of neurogenesis in the adult mammalian brain, substantial progress has been made in elucidating the mechanisms regulating NSPC activity and subsequent neuronal differentiation and integration (Box 1). Key mechanisms include transcriptional programs mediated through, for example, SOX2, NeuroD1, PAX6, GSX2, and Prox1, as well as epigenetic mechanisms acting through, for example, histone modifications (e.g., MeCp2 and MDB1), in addition to noncoding RNAs (e.g., miR-124) [29–31]. Furthermore, niche-derived morphogens, neurotransmitters, growth factors, and cytokines are important in controlling NSPC activity and neuronal differentiation [examples include gamma aminobutyric acid (GABA), glutamate, brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), fibroblast growth factor (FGF)-2, Wnt ligands, Shh, bone morphogenetic protein (BMP), interleukin (IL)-6, and tumor necrosis factor alpha (TNFα)] [9]. Furthermore, there is now compelling evidence showing how network activity directly affects the neurogenic process in the DG and SVZ [32–35]; however, these findings are exclusively based on rodent data. How can this knowledge be transferred or tested for its relevance to human neural development and how can we study the mechanisms of neurogenesis using human tissue?

The use of human pluripotent embryonic stem cells (hESCs) has revolutionized our understanding of the molecular mechanisms underlying fate-choice decisions and the differentiation of human neural cells (Figure 1). It is now possible to study in the culture dish which genes/pathways are involved in the developmental steps from multipotent NSPCs toward region-specific neuronal differentiation [36]. Moreover, the use of patient-derived induced pluripotent stem cells (iPSCs) allows the study of mechanisms of stem cell activity and neuronal differentiation within defined patient populations, thus allowing testing of the relationships between clinical, genetic, and molecular regulators directly within human tissue [37]. Currently, substantial efforts are underway to develop techniques and culturing methods that yield neuronal subtypes generated in the adult brain and approaches that will allow us to study complex structures such as the whole hippocampal circuitry in the dish [36,38]. One spectacular example of how we may study human development is the recent finding of how to generate cerebral organoids derived from human cells [39]. Once we are able to reconstruct whole circuitries such as the hippocampus (or parts of it) with human-derived cells in the dish, we will be able to study how NSPC-derived human cells may integrate into these preexisting circuitries. However, developing true models that resemble the structural organization of human neurogenic regions will remain a major challenge in the near future [40]. Complementing these cell culture-based strategies will be the approach to transplant human-derived cells (genome-edited ESC derived or iPSC derived) into the developing or adult rodent brain. This will allow the study of the behavior and functionality of human cells (healthy and diseased) within neurogenic niches. These experiments will need close ethical monitoring and may be technically challenging; however, this approach holds

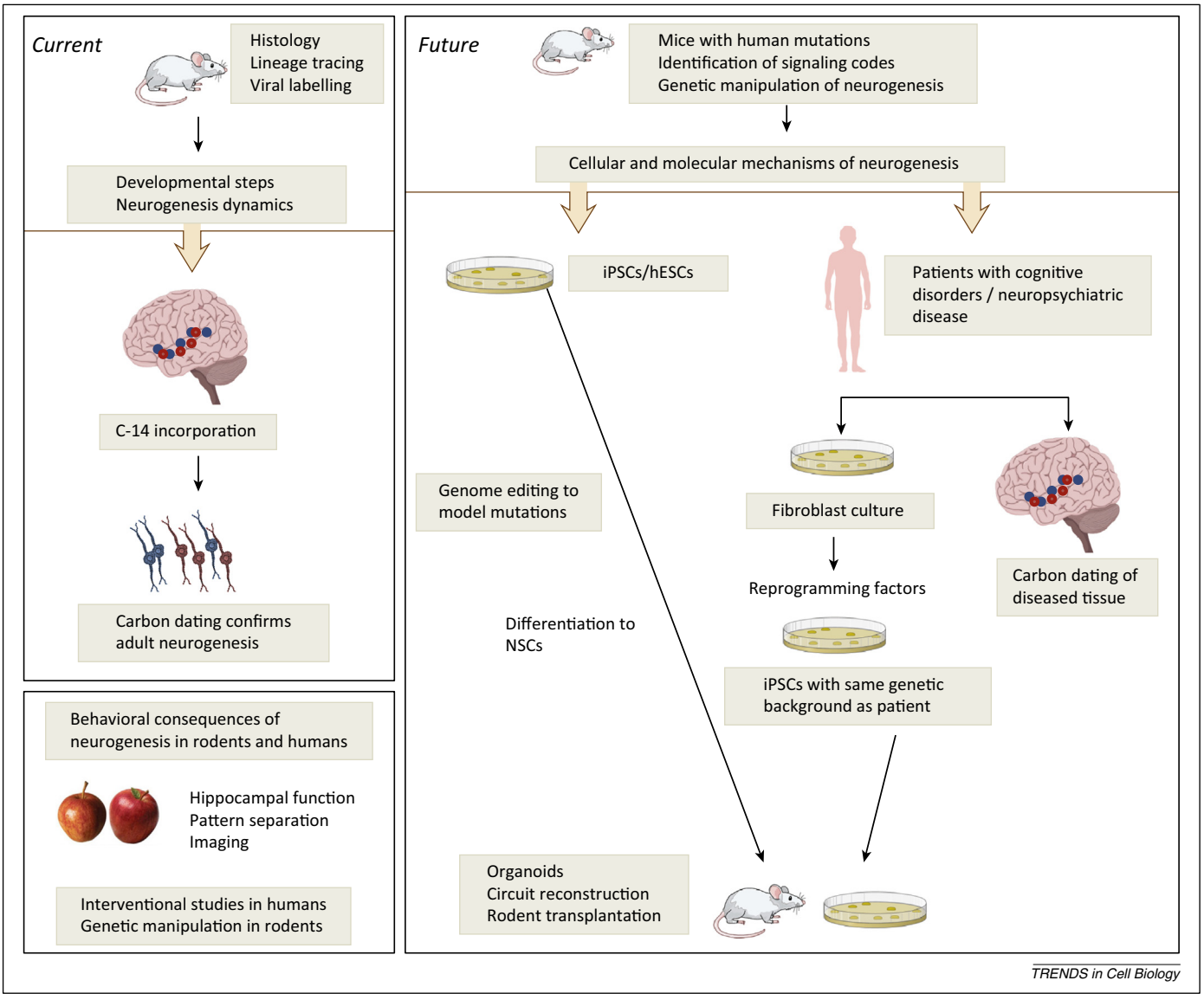

Figure 1. Future perspectives of understanding adult neurogenesis in rodents and humans. Shown here is a potential approach for how basic research findings obtained mostly in laboratory animals may be translated into the analysis and eventual therapeutic targeting of neurogenesis in the adult human brain. Currently, substantial progress is being made in understanding the molecular mechanisms of neurogenesis in rodents and detecting neurogenesis in the human brain; for example, by using ^{14}C birth dating [6,12,15]. In the near future, the aim will be to associate region-specific behavioral tasks (such as dentate gyrus-dependent behavioral pattern separation [54]) with imaging tools. In addition, future experiments will aim to model human development and disease in cell-based assays; for example, using induced pluripotent stem cell (iPSC) and human pluripotent embryonic stem cell (hESC) approaches in healthy controls or patients with neuropsychiatric disease [36]. The relevance and extent of disease-associated changes in the neurogenic process will be characterized using cell-based models or imaging and postmortem analyses of the diseased human brain [15,55].

promise to allow us to study the integration and functional contribution of human cells in live neural networks. The cellular and molecular mechanisms identified in rodents will be essential to guide these experiments. In addition, knowledge acquired by studying differentiation and integration processes in the neurogenic niches of the adult brain will be fundamental to improve current approaches to reprogram endogenous cells for cell replacement and to enhance the fidelity and usefulness of exogenous transplants. These experiments will identify the factors needed for directed fate conversion and what it takes for a newborn cell, neuronal or glial, to integrate successfully into mature neural circuits.

Linking adult neurogenesis with cognition

Why does the adult brain exert all this effort to maintain neurogenic niches throughout life? What are newborn cells good for? After revealing correlative evidence of increased (or reduced) levels of neurogenesis with hippocampus- or OB-dependent forms of learning and memory, the field has moved toward defining more causative relationships between newborn neurons and adult brain behavior. Using genetic gain- and loss-of-function strategies to manipulate levels of neurogenesis, strong associations between newborn neurons and region-specific cognitive tasks have been identified [10,11]. Specifically, accumulating data suggest that new neurons in the DG (and potentially the OB) are required for behavioral pattern separation, which describes a process that transforms similar inputs or experiences into distinct and non-overlapping representations [41–43]. In addition, it has been recently proposed that the addition of new neurons into the DG circuit is associated with the forgetting of previously acquired memory [44]. How can new neurons fulfill this task? Is it reasonable to speculate that the few

Box 1. Cellular and molecular mechanisms regulating neurogenesis

The number of newborn and fully integrated neurons is the readout that determines the levels and efficiency of the neurogenic process in the adult brain. However, it is now becoming obvious that this process is tightly controlled by numerous extrinsic and intrinsic molecular mechanisms that regulate each developmental step from activated NSPCs toward highly proliferative progenitor cells and, finally, maturing and integrating newborn neurons [66]. For simplification, the examples provided here are largely derived from experiments aiming to understand the cellular and molecular control of hippocampal neurogenesis, but similar principles also apply to neurogenesis in the rodent SVZ/OB. Initially, quiescence (and subsequent activation) of NSPCs is tightly controlled to prevent premature exhaustion of the stem-cell pool. This is, for example, mediated through intrinsic mechanisms such as control of metabolic activity, BMP- and Notch-mediated signaling, and niche-derived mechanisms such as extrasynaptic GABA-signaling [33,67–69]. Presumably, committed progenitors then pass through a stage of high proliferative activity before the cells exit the cell cycle and start to differentiate into neuronal cells, an event that depends on several transcriptional regulators, including Prox1 and NeuroD1 [70,71]. Newborn neurons start a few days after their birth to extend dendrites into the molecular layer of the DG and grow axonal processes toward area cornu ammonis (CA) 3 – processes that depend on local network activity, transcription factors such as phosphorylated cAMP response element-binding protein (pCREB), and, for example, the proper activity of small Rho GTPases such as Cdc42 [72–74]. Notably, newborn cells undergo an activity-dependent selection process before they become stably integrated into the DG circuitry [48,75]. Known extrinsic positive (such as physical activity) and negative (such as stress) regulators can affect distinct steps during this process (e.g., [76]). Interestingly, new neurons mature through a stage of heightened excitability that may mediate their requirement for certain forms of hippocampus- (or OB-) dependent learning and memory [66]. Although the details of synaptic integration and the resulting connectivity are not fully understood, it appears that newborn cells become largely indistinguishable from granule cells born during embryonic or early postnatal development approximately 8 weeks after they are born [77–79]. The mechanisms underlying this functional switch remain poorly understood but current hypotheses suggest that it will depend on both intrinsic signaling pathways and extrinsic regulators and local network activity.

hundreds of neurons born every day in the human DG can truly make a difference?

Newborn neurons differentiate through a critical period of heightened excitability and plasticity until they are approximately 6–8 weeks of age [45–47]. This period is important for their successful survival and integration [48]. This critical period of heightened excitability may also hold the key to understanding how new neurons exert their functional impact on the mature brain. New neurons are not a mere replacement for embryonically generated granule cells or OB neurons: they display unique features given their cellular properties and connectivity during the critical period. Simplified, newborn neurons are much more excitable than granule cells born during embryonic development, such that a smaller stimulus (e.g., exciting current) is required to elicit plasticity-associated responses in newborn cells, such as long-term potentiation [49]. Current hypotheses predict that the low thresholds of stimulation required to elicit a response in 4–6-week-old neurons is critical for the ability of the DG (and the OB) to distinguish highly similar inputs and then, over time, to transform this information into highly specific representations [50,51]. Large-scale models of the hippocampal circuitry support this hypothesis [52]. Furthermore, new neurons may not only be critical for input representations but might also be the cellular correlate of how associations are formed between temporally related but content-unrelated experiences (as, for example, occurs during flashback memories) [53]. Will similar functions for new neurons hold true in the human brain? One approach will be to correlate DG-dependent behavioral pattern separation with imaging surrogates of neurogenesis [54] (Figure 1). Most excitingly, it is now possible to design studies using interventions (e.g., presumably enhancing neurogenesis through controlled physical activity) or stratifying populations depending on previous experiences or disease states [55]. At this time the required techniques and concepts to design human behavioral tasks that challenge, for example, the DG, as well as the tools to image neurogenesis and to evaluate region-specific activity, are now becoming available; however, these methods and approaches have not been brought together effectively.

In addition, future studies will aim to link genetic disorders and diseases affecting (selectively) the neurogenic regions of the adult brain by using iPSC-based technologies or genome editing of hESCs to model these conditions in the dish. With this approach, it will be possible to associate region-specific alterations in the neurogenic process with the clinical and genetic data of individuals. This approach has been used for some genes associated with neuropsychiatric disease (such as DISC-1 in schizophrenia), where mouse models were used to analyze what the effects of defined genetic defects might be in the context of adult neurogenesis [56]. However, many more studies using mouse-based transgenic approaches but also iPSC- and hESC-based models are required to analyze the effects of human mutations or genetic compositions that are, for example, associated with cognitive impairment (Figure 1). These experiments have now become feasible on an even larger scale, given the dramatic improvements made over past years in generating patient-specific human pluripotent cells and editing the human genome.

Neurogenesis in neuropsychiatric disease

Neurogenesis is important for more than physiological brain function: failing or altered neurogenesis has been associated in rodent models with several neuropsychiatric diseases. Reduced neurogenesis is a prominent feature in rodent models of stress and depression and certain antidepressants that enhance the number of neurons born require neurogenesis to be effective [57]. Similarly, it has been shown that age-associated cognitive decline is associated with reduced numbers of newborn granule cells in the DG [9]. Other neurological diseases lead to substantial alterations in the integration pattern of newborn cells in the DG that may be causally linked to the development of epilepsy and cognitive impairments observed in some patients suffering from seizures or traumatic brain injury [58–60].

Nonetheless, altered neurogenesis may not only be a cause of neuropsychiatric disease; the discovery of the

existence of NSPCs within the neurogenic regions has spurred hopes of activating and specifically targeting this portion of the brain for endogenous repair in the context of acute and chronic neurodegeneration. To reach this challenging goal, we must first understand the molecular details of NSPC activation and the subsequent steps of neuronal differentiation and integration [29]. Such an understanding may allow us eventually to recruit cells for brain repair in non-neurogenic areas that display stem cell properties when isolated and propagated in the dish. Ideally, the identification of codes that govern the neurogenic process under normal conditions can be translated to generate cells to replace lost neurons in, for example, Alzheimer's disease (AD) and Parkinson's disease (PD) or to enhance proper glial responses (e.g., in the context of chronic demyelinating diseases such as multiple sclerosis) [61,62].

What is the evidence that neurogenesis is altered in human disease? Given the difficulties of quantifying the neurogenic process in humans, the current situation is blurry. However, several studies have reported alterations in the DG in surgical specimens and/or postmortem tissue samples from patients with temporal lobe epilepsy, AD, or major depression [9,57,63,64]. Another striking example of how neurogenesis may be involved in human disease is a recent study that used ^{14}C birth dating and found that levels of striatal neurogenesis were substantially reduced in patients with HD [15]. These findings clearly point to the sustained ability of neurogenic cells to generate neurons in the human brain. However, it seems that the source for newborn striatal interneurons is a local astrocytic cell population and that cells in the human SVZ are not responsible for the generation of new striatal neurons [14]. Applying *in vitro* models of postnatal neurogenesis using human cells and shuttling between rodent data and observations in the human brain may lead to the identification of approaches to target NSPCs or local neurogenic cells for future therapeutic interventions (Figure 1). This approach may also prove to be valuable in disease conditions that, at least in humans, fail to illicit a neurogenic response, such as ischemic stroke [65].

Concluding remarks

It took 30 years before the neuroscience community accepted that the mammalian brain harbors NSPCs that generate new neurons throughout life. Another 25 years later, the field is on the verge of transferring basic research findings obtained largely through the use of laboratory animals to human health and disease. New detection methods for neurogenesis in humans and the development of techniques allowing the analysis of patient-specific cellular development in the culture dish will be key to achieving this aim. Currently, the cellular and molecular machinery that controls neurogenesis and the functional mechanisms behind how new neurons shape adult brain circuits are far from being fully understood. Even in the rodent, fundamental questions such as the stemness and self-renewing capacity of single NSPCs remain unclear. Furthermore, the details of how newborn neurons shape the connectivity and activity of preexisting circuits remain largely unknown. New *in vivo* imaging and electrophysiological recording approaches, combined with genetic techniques allowing manipulation of newborn neurons with high tissue selectivity and temporal control, will make substantial contributions over the next few years. In addition, future studies will aim to identify the mechanisms by which the plethora of previously identified molecular regulators may converge on a few key hubs that control NSPC activity and subsequent steps of neuronal differentiation and integration. Most importantly, several new studies will work to link human disease conditions with alterations in the neurogenic process. One approach is likely to use iPSC- and hESC-based disease modeling. In addition, noninvasive imaging approaches combined with interventions to manipulate levels of neurogenesis will bring us closer to understanding the relevance of adult neurogenesis for human physiology and disease and eventually to target NSPCs or their progeny to treat patients.

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