F1000Prime REPORTS

Published: 03 February 2014

Increasing the resolution of the adult neurogenesis picture

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F1000Prime Reports 2014, **6**:8 (doi:10.12703/P6-8)

Abstract

The birth of new neurons in the adult mammalian brain—once thought impossible—is now a well-accepted phenomenon that takes place in the subventricular zone of the lateral ventricles and the hippocampus. This review focuses on the recent work that has sharpened our views of how hippocampal newborn neurons are regulated and function. Areas of study include (a) how neurogenesis contributes to behavioral pattern separation, (b) how pattern separation may be influenced by the properties and circuitry of newborn neurons, (c) differences along the dorsal-ventral axis of how neurogenesis is regulated and functions, and (d) adult neurogenesis in primates, including new human data. These current avenues of research reveal new details of adult neurogenesis and foreshadow what we may learn about this exciting phenomenon in the near future.

Introduction

While the first reports of mammalian adult neurogenesis in the 1960s were met with little fanfare, the revival of the field in the 1990s incited both excitement and skepticism; until that time, it was accepted that after birth, the brain could only lose and not gain neurons. However, with the advent of new techniques to label dividing cells and distinguish neuronal from glial populations, evidence for adult neurogenesis accumulated throughout the 1990s and 2000s. It is now well established that the birth of new neurons in the adult brain occurs in two regions: the subventricular zone of the lateral ventricles and the hippocampus. Increasingly sophisticated questions have since been asked, refining our image of how these newborn neurons are regulated and how they function.

In this review, we will cover several themes that have emerged in the last few years in the study of adult hippocampal neurogenesis. These themes share a common goal of defining the unique contributions of adult-born cells, albeit at different levels of study: learning and memory, physiology, hippocampal anatomy, and comparative biology.

(a) **Newborn neurons contribute to dentate gyrus pattern separation function.** Both positive and negative alterations in neurogenesis affect discrimination between memories of recalled events and similar present events, also referred to as behavioral pattern separation.

(b) **Young adult-born hippocampal neurons have unique physiology and circuitry that may contribute to pattern separation.** Although links are largely speculative, current hypotheses have attempted to link pattern separation to the period of hyperexcitability in newborn neurons.

(c) **The position of newborn cells within the dentate gyrus may alter their fate and function.** Differences in proliferation, maturation, and function of newborn neurons have been identified along the longitudinal axis of the dentate gyrus.

(d) **The function of new neurons in humans may be unique when compared with other mammals.** Differences in maturation rates, newborn neuron proportion, and anatomy between humans and animal models are now being recognized and studied.

Newborn neurons contribute to dentate gyrus pattern separation function

Current inquiries into the functional significance of adult-born neurons have heavily emphasized the concept of pattern separation. Pattern separation, a term appropriated from computational models of neural networks, has been loosely used to describe the process by which similar, but not identical, patterns of inputs are classified as distinct [1-3]. At the behavioral level, these inputs reflect both external sensory input and internally generated representations of a previously experienced environment or event. By manipulating the rate of adult neurogenesis, several groups have shown that newborn neurons are critical for making fine discriminations between neighboring spatial locations or highly similar environments in tests of working memory and long-term memory. Ablating adult neurogenesis via irradiation impairs performance on a touchscreen task in which mice must discriminate between two adjacent stimuli presented simultaneously in close proximity [4]. The same irradiation treatment interfered with the recall of nearby arm locations after a brief delay (<30 s) on a radial arm maze task [4]. In contrast, an increase in rates of neurogenesis via running improves the performance on the touchscreen task [5]. Improving the survival of newborn neurons via a genetic strategy similarly enhances the ability to discriminate between two similar contexts during contextual fear conditioning, a distinction that arises over the course of several days of training [6]. Notably, the contribution of adult neurogenesis in each of these cases emerges only on more difficult discriminations. When difficulty is reduced by either increasing the spatial separation or making the contextual conditioning environments more distinct, both impaired and enhanced neurogenesis groups perform comparably to controls. These data support the hypothesis that the advantage provided by adult-born neurons grows as the overlap between two input patterns increases.

Newborn neurons that are 3-4 weeks of age are particularly distinct in function from mature granule cells (see below). Optogenetic silencing of newborn cells at 4 weeks of age, but not at 2 or 8 weeks, impairs the retrieval of both previously learned spatial location on the Morris water maze and of a previously learned fear-conditioned context [7]. From these studies, it remains unclear whether these 4-week-old cells contribute solely to the retrieval of an existing memory or whether they also play a role in encoding. Genetic suppression of mature granule cell activity, while leaving younger granule cells less than 4 weeks of age intact, also improves contextual fear discrimination of two similar contexts [8]. Conversely, this young cell-dominated dentate gyrus impairs performance on a water maze task requiring the opposite process—pattern completion—when navigation must be completed using only a subset of the cues present during training. This study suggests that a dentate gyrus network dominated by young granule cells is biased towards interpreting similar but not identical inputs as distinct, whereas older granule cells are biased towards interpreting similar inputs as equivalent. However, the behaviorally optimal amount of pattern separation versus completion will depend on the relevance of particular stimuli to the demands of the task and motivation of the individual. The extent to which separation and completion are reciprocal processes is also unclear. It is possible that a deficit in pattern separation does not automatically imply an enhancement of pattern completion but rather a global deficit in the detailed recall of a particular context [9].

Young adult-born hippocampal neurons have unique physiology and circuitry that may contribute to pattern separation

The physiological properties of newborn neurons and their effects on dentate gyrus circuitry provide some explanation for their time-limited role in pattern separation as described above. Newborn neurons have a developmental time window during which they exhibit unique intrinsic and circuit-level properties.

Physiology and novel circuit tracing studies in mice have revealed details in newborn neuron development. Days after birth, newly generated cells respond to ambient γ-aminobutyric acid (GABA) with tonic activation due to a high concentration of intracellular chloride that leads to depolarization [10,11]. In 1-2 weeks, newborn neurons begin to receive synaptic GABAergic input [11]. After 2-3 weeks, they start expressing glutamatergic receptors [10,11], and subsequently, the direction of the chloride gradient switches such that GABAergic input hyperpolarizes newborn neurons [10-12]. At around 1 month, new neurons receive synaptic glutamatergic input from the entorhinal cortex, similar to mature cells [13-16]. However, at this time point, new neurons have a lower density of GABA inputs [10,12,17] and inhibitory post-synaptic currents (IPSCs) compared with mature granule neurons [17]. Once fully mature (about 6 weeks after birth), newborn neurons are essentially indistinguishable physiologically from developmentally born granule neurons.

Hence, at 4 weeks after birth, new neurons receive input from the same sources as mature granule cells but,

because of their unique properties, they are hyperexcitable and show broader tuning than surrounding mature granule cells; young neurons are more likely to respond to two separate inputs than mature granule cells [12]. The effect of this developmental time course is a period during which excitation dominates over inhibition. By contrast, inputs to fully mature granule neurons are biased towards inhibition, as they fire very infrequently [12]. Adult neurogenesis therefore serves to make the principal cells of the dentate gyrus physiologically heterogeneous and distinct subpopulations are constantly shifting: as one newborn neuron subpopulation matures, another develops to replace it.

The physiological differences between mature granule cells and 4-week-old newborn neurons suggest at least two mechanisms for how neurogenesis may affect pattern separation and completion. One mechanism involves interpreting the activity of individual granule cells directly in response to two different inputs as being reflective of overall dentate gyrus activity. In this case, mature granule neurons, which require high input specificity and maintain a high activation threshold, potentially serve as good pattern separators. The hyperexcitability and broad tuning properties of newborn neurons would conversely suggest that they could serve as pattern integrators [12]. However, this hypothesis is inconsistent with the behavioral evidence discussed above, in which increases in the newborn neuron population improve pattern separation. An alternative mechanism is to consider how local dentate gyrus interneurons may influence overall dentate gyrus activity [18]. Both young and mature granule cells stimulate local inhibitory interneurons either directly or indirectly via mossy cells in the hilus. Those interneurons in turn also send efferents to granule cells but with a higher density of inhibitory inputs to mature as compared with young neurons (as described above). Thus, by dampening the activity of mature granule cells, newborn cells increase their influence on the network. By this proposed mechanism, increased numbers of hyperexcitable neurons paradoxically make the dentate gyrus sparser, supporting a role for newborn neurons in enhancing pattern separation function [2,18].

The position of newborn cells within the dentate gyrus may alter their fate and function

While the evidence for a role for newborn neurons in pattern separation is accumulating, we are also beginning to appreciate that this function depends on the location of new cells within the dentate gyrus. The dentate gyrus can be anatomically distinguished along the dorsal-ventral (septo-temporal) axis, and it is becoming increasingly recognized that newborn neurons arising from the dentate gyrus may be functionally distinguished along this axis. Differences in the generation and maturation of adult-born neurons appear along the dorsal-ventral axis [19,20]. New neurons in the dorsal dentate gyrus may mature significantly faster than in the ventral dentate gyrus because of higher levels of basal local network activity in the former. These distinctions might arise from the region-specific variation in cortical and subcortical connections to the hippocampus [19]. A newborn neuron's maturation time—and therefore its unique properties—is linked with its position within the dentate gyrus.

An additional distinction of newborn neuron function may be related to the idea that the dorsal hippocampus is involved in spatial learning and memory, whereas the ventral hippocampus has been linked with emotional behavior [21]. With these associations, it has been proposed that a cognitive-specific task or a stimulus with emotional valence would selectively affect neurogenesis in the dorsal and ventral hippocampus, respectively. However, these links are tenuous or overly simplified. When adult rats learned a spatial water maze task, enhanced neurogenesis was observed in the dorsal, but not ventral, hippocampus, as predicted [22]. In probing the activation of granule cells after water maze learning, c-fos expression was higher in the dorsal than ventral hippocampus when considering the overall granule cell population, but among the adult-born subpopulation alone, c-fos expression was higher in the ventral hippocampus [22]. Acute stress or administration of corticosterone in adult rats was predicted to alter neurogenesis in the ventral hippocampus, when, in fact, neurogenesis increases were observed selectively in the dorsal hippocampus [23]. Therefore, although there is evidence for cognition primarily involving the dorsal hippocampus and emotional behavior utilizing mainly the ventral hippocampus, the links with neurogenesis require further refinement.

Collectively, these studies highlight the idea that newborn neurons can be born at the same time yet mature differently, and/or subserve unique functions depending on their position along the long axis of the dentate gyrus. The nature and consequence of having variability within a newborn neuron population along the dorsal-ventral axis are usually not reported and warrant re-evaluation of previous studies and further attention in future studies.

The function of new neurons in humans may be unique when compared with other mammals

While we have known for 15 years that adult neurogenesis takes place in the adult human [24], most of our understanding of mammalian adult neurogenesis comes from studies of rodents. Therefore, it has been tempting to view our knowledge of rodent adult neurogenesis

from an anthropocentric viewpoint. However, recent adult neurogenesis studies in primates and humans are reshaping ideas of how new neurons may function within us.

As suggested from evaluating non-human primates, the developmental timeline of newborn neurons in humans may be much longer than previously estimated. Two-thirds of $BrdU^+$ cells continued to express the immature neuron marker doublecortin (DCX) at 6 months in an adult macaque hippocampus [25], whereas DCX expression in the dentate gyrus neurons in an adult rodent lasts only several weeks [26]. A report by Spalding, Frisen and colleagues confirmed that neurogenesis continues to occur in the adult human hippocampus and to a much greater extent than previously estimated. They showed that hippocampal neurogenesis in adult humans is robust and continues through at least the fifth decade of life [27]. While these data suggest that the age-related decline in adult neurogenesis is significantly slower in humans than in rodents, a direct comparison requires further validation because of the impoverished and sedentary environment of rodents reared under typical laboratory conditions. An emerging idea is that newborn neurons may be playing significantly larger roles in hippocampal function and human cognition than previously thought.

Previous models utilized rodent neurogenesis data for proposing computational roles for newborn neurons in learning and memory [28]. Given that the study by Spalding and colleagues [27] suggests that most human dentate gyrus neurons are subject to turnover [26] compared with 10% of mouse dentate granule neurons [29], new models may be required for predicting the contribution of adult-born neurons in human hippocampal function. The next leap in understanding the role of newborn neurons in human health and disease will require studying hippocampus-dependent behaviors in humans [30]. Development of novel imaging techniques to visualize newborn neuron activity in the dentate gyrus of humans would lead to breakthroughs. One example of a funding initiative that would encourage development of necessary technologies is the recently announced Brain Research through Advancing Innovative Neurotechnologies (BRAIN) funding initiative by the Obama administration, which encourages development of these transformational techniques.

Conclusions

About 20 years ago, the dogma that no new neurons are born in adulthood began to crumble. The advances in the last few years have shown why neurogenesis may be important (theme 1), revealed a mechanism by which it may work (theme 2), suggested that newborn neuron function is heterogeneous along its axes (theme 3), and hinted at how what we know may be modified in the case of humans (theme 4).

Although these themes may at first appear to concern separate aspects of neurogenesis, it could be that the interrelationships between these themes will be critical for understanding the importance of newborn neurons in humans. For example, the longer developmental time window in humans compared with rodents suggests a relatively prolonged state of hyperexcitability in newborn neurons. This extended period may impact the human dentate gyrus circuitry such that pattern separation may function qualitatively or quantitatively differently in humans than in rodents. Humans also have a different hippocampal anatomy than rodents. Does the presence of a different/larger ventral dentate gyrus have implications for whether newborn neurons function differently there? And, as noted, the larger scale of human adult neurogenesis may mean that we need to modify our computational models.

The first reports of adult neurogenesis focused attention on the existence of the phenomenon. Recent work has sharpened our view of the regulation and function of adult hippocampal neurogenesis. New techniques and advancements will—literally and figuratively—present a progressively higher-resolution image of this striking example of neural plasticity.

Abbreviations

BRAIN, Brain Research through Advancing Innovative Neurotechnologies; DCX, doublecortin.

Disclosures

The authors declare that they have no disclosures.

Acknowledgments

The authors wish to thank M.L. Gage for editorial comments. This work is funded by the National Institute of Mental Health (MH-095741) and the James S. McDonnell Foundation.

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