Adult Neurogenesis in the Human Brain: Paradise Lost?

Human Hippocampal Neurogenesis Drops Sharply in Children to Undetectable Levels in Adults.

Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste KI, Chang EF, Gutierrez AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A. *Nature* 2018;555(7696):377–381.

New neurons continue to be generated in the subgranular zone of the dentate gyrus of the adult mammalian hippocampus. This process has been linked to learning and memory, stress and exercise, and is thought to be altered in neurological disease. In humans, some studies have suggested that hundreds of new neurons are added to the adult dentate gyrus every day, whereas other studies find many fewer putative new neurons. Despite these discrepancies, it is generally believed that the adult human hippocampus continues to generate new neurons. Here we show that a defined population of progenitor cells does not coalesce in the subgranular zone during human fetal or postnatal development. We also find that the number of proliferating progenitors and young neurons in the dentate gyrus declines sharply during the first year of life and only a few isolated young neurons are observed by 7 and 13 years of age. In adult patients with epilepsy and healthy adults (18–77 years; n = 17 post-mortem samples from controls; n = 12 surgical resection samples from patients with epilepsy), young neurons were not detected in the dentate gyrus. In the monkey (*Macaca mulatta*) hippocampus, proliferation of neurons in the subgranular zone was found in early postnatal life, but this diminished during juvenile development as neurogenesis decreased. We conclude that recruitment of young neurons to the primate hippocampus decreases rapidly during the first years of life, and that neurogenesis in the dentate gyrus does not continue, or is extremely rare, in adult humans. The early decline in hippocampal neurogenesis raises questions about how the function of the dentate gyrus differs between humans and other species in which adult hippocampal neurogenesis is preserved.

Commentary

The relatively recent discovery of adult neurogenesis in the hippocampal dentate gyrus led to an explosion of research to understand this phenomenon. While adult neurogenesis is well established and accepted in many mammalian species (1), evidence in humans is comparatively sparse (2, 3). Nonetheless, many in the field had accepted that humans are not exempt from adult neurogenesis. Therefore, the recent report by Sorrells and colleagues (2018), concluding that neurogenesis is *absent* from adult humans, is surprising. Further complicating the story, however, a new study of human autopsy material by Boldrini et al. (4) concluded that human neurogenesis does persist into old age.

The mystery of whether neurogenesis occurs in adult humans will not be solved here. New methodologies to definitively distinguish adult-generated from developmentally generated neurons in humans—a key source of controversy—are needed to definitively answer this question. Nonetheless, the controversy raises some interesting questions for the epilepsy field. Rodent models of mesial temporal lobe epilepsy (mTLE) reveal a complex interaction between the disease and adult neurogenesis, suggesting that adult-generated granule cells could play a causal role in epileptogenesis. Impaired neurogenesis could also modulate epilepsy comorbidities. In rodents, for example, adult neurogenesis is dramatically increased in the weeks following an epileptogenic brain injury, while animals with chronic epilepsy often exhibit impaired adult neurogenesis—a change linked to depression (1). Depletion of neural progenitor cells, shifting of newborn cells from neuronal to glial fates, and outright destruction of the neurogenic niche following extensive cell loss all contribute to impaired neurogenesis in epileptic rodents. Whether these findings in animals are relevant to human epilepsy depends entirely on whether adult neurogenesis occurs in humans.

One notable caveat of the Sorrells study is that it included the use of surgically resected tissue from 22 patients with epilepsy. Surgical specimens allow for optimal tissue preservation, providing a clear advantage over postmortem tissue (obtained from the remaining 37 subjects). Studies demonstrating impaired neurogenesis in animals with chronic epilepsy, however, raise particular concerns regarding the use of epileptic tissue from humans. With few exceptions,

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candidates for epilepsy surgery have failed multiple drug trials and suffer from chronic, uncontrolled epilepsy. If these patients are reflective of animal models of chronic epilepsy, rates of granule cell neurogenesis may be well below healthy levels. Notably, in the more recent study by Boldrini et al. (4) in which human adult neurogenesis was found, only tissue from healthy subjects was used, possibly accounting in part for the different findings.

Given the ongoing controversy, it is worth considering the implications for understanding mTLE if in fact human adult neurogenesis does not occur. mTLE is associated with numerous granule cell abnormalities hypothesized to contribute to epileptogenesis. Changes include the sprouting of granule cell mossy fiber axons, misplacement of granule cells to ectopic locations, and the appearance of granule cells with a range of dendritic abnormalities (5). These anatomic observations in the epilepsy field converged with developments in the adult neurogenesis field, leading to the discovery that—at least in rodents—many abnormal granule cells are newly generated. Correlational studies implicating adult-generated granule cells in epilepsy progressed to more direct manipulations, with recent work showing that both antineurogenic agents and targeted ablation of newly generated cells reduce seizure frequency in epileptic rodents (6, 7). These findings support the hypothesis that disruption of adult neurogenesis by epileptogenic brain injury leads to the accumulation of aberrant, miswired granule cells, which in turn promote hyperexcitability and seizures. In human epilepsy, however, this hypothesis is challenged if neurogenesis is absent in adults.

Assuming neurogenesis is absent from adult humans, several key insights can be made based on established literature. Perhaps the most critical finding is that while the occurrence of adult neurogenesis in humans is controversial, the presence of abnormal granule cells in patients with mTLE is not. Mossy fiber sprouting is a hallmark pathology of mTLE, and studies in tissue resected from epilepsy patients have revealed almost all the abnormalities identified in rodents. If these cells are not adult-generated, then where did they come from?

One possibility is that these abnormalities originate from mature granule cells in humans. In the case of mossy fiber sprouting, rodent studies demonstrate that granule cells up to 2 months old can contribute (8), so it is conceivable that much older granule cells (i.e., years) may be able to do so in humans. Rodent studies also demonstrate that granule cell dispersion affects mature cells. Other abnormalities, however, originate almost exclusively from newborn cells in rodents. These include the formation of aberrant dendrites and the mismigration of granule cells to the dentate hilus. This finding makes their presence in human tissue more difficult to explain. Nonetheless, it is possible that distinct mechanisms may be able to produce anatomically similar pathologies.

Second, there is agreement that neurogenesis continues in the dentate gyrus throughout childhood in humans—perhaps into the teenage years. This raises the possibility that abnormal granule cells observed in adults with mTLE may have been generated much earlier in life. In patients with pediatric epilepsy, there could be a relatively tight temporal link between the accumulation of abnormal cells and disease onset. It is also conceivable that abnormal granule cells generated in childhood may lie "dormant" for years, leading to clinical epilepsy only after the occurrence of other age-related changes or in combination with other risk factors. Indeed, many known childhood risk factors for epilepsy, such as complex febrile seizures or status epilepticus, promote aberrant integration of newborn granule cells in rodents.

A third intriguing possibility stems from the observation that maturation of adult-generated granule cells occurs much more slowly in nonhuman primates than in rodents. In rodents, most newborn granule cells have downregulated immature neuron markers and begin expressing mature neuron markers by 1 month. In contrast, less than half of newborn granule cells in nonhuman primates achieve a similar maturational stage by 8 months (9). It is conceivable that cells may persist in these immature states for years. This is important for mTLE, because rodent studies have demonstrated that immature neurons exposed to an epileptogenic brain injury integrate abnormally (10). Therefore, even if adult neurogenesis has ceased in the human brain, residual populations of immature neurons may still be able to mediate epileptogenic rewiring of the dentate gyrus.

Given the difficulty of assessing adult neurogenesis in humans, controversy over the presence or absence of the phenomena is likely to continue for the foreseeable future. Regardless of their origin, however, abnormal granule cells are present in the brains of patients with mTLE. Understanding the functional impact of these cells on the etiology of epilepsy remains an important area of investigation.

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