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(Radio)active Neurogenesis in the Human Hippocampus

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Abstract

Fifteen years ago, the generation of new neurons in adulthood was documented in the human hippocampus, but lingering questions have remained about the extent of this process. In this issue of Cell, Spalding et al. provide elegant evidence for continued neurogenesis into adulthood at rates that suggest it may play a significant role in human behavior.

For most of the 20th century, neuroscientists thought that the adult mammalian brain did not generate new neurons. Evidence that this wasn't the case was reported (Altman and Das, 1965), but only in the 1990s did sufficient data accumulate for the field to accept that adult neurogenesis did occur in mammals. Now, it is well established that, in rodents, the olfactory bulb and the dentate gyrus (DG) region of the hippocampus incorporate new neurons in adulthood. However, in nonhuman primates, lower levels of adult neurogenesis were observed. These data, despite evidence that neurogenesis does occur in the adult human DG (Eriksson et al., 1998), caused considerable anxiety in the field. When it comes to the relevance of adult neurogenesis in humans, two questions have remained: to what extent does this process occur in our species and can a small number of cells generated in the adult hippocampus impact human behavior? In this issue of *Cell*, Spalding et al. (2013) have answered the first question by providing powerful evidence for extensive neurogenesis in humans throughout adulthood with numbers comparable to those seen in rodents.

In 2005, Spalding and Frisén took the concepts underlying radiocarbon-dating techniques used in archaeology and developed an ingenious strategy for birth-dating cells from postmortem tissue (Spalding et al., 2005). The technique is based on the pronounced spike in global levels of ^{14}C that resulted from extensive above-ground nuclear weapon testing during the Cold War and the fact that there has been a steady decline in atmospheric ^{14}C since such testing was banned. Because plants absorb ^{14}C via CO_2 during photosynthesis, animals that eat them also take in radioactive carbon; therefore, the ^{14}C level in our bodies reflects that of the atmosphere. Consequently, when a cell divides, newly synthesized DNA integrates a trace amount of ^{14}C that is proportional to the environmental level at the time of

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mitosis; hence, the radioactivity of a cell nucleus can be used as a time stamp of the cell's genesis.

Using this technique, this group had previously found that the human olfactory bulb did not contain neurons born in adulthood (Bergmann et al., 2012), a result that is strikingly different than the one observed in rodents, where olfactory bulb neurogenesis continues throughout life. But, in the hippocampus, they found that neurogenesis occurs at significant levels through adulthood and until old age.

The first surprise from this study was that, unlike the stark age-related decline seen in rodents, the human hippocampus appears to generate new neurons at a fairly steady rate well into old age (Figure1). Their computational modeling studies indicated that their data was best fit by a scenario in which there was one population of hippocampal neurons that did not turn over, whereas 35% of the neurons did. Given that DG neurons correspond to roughly 35% of the total hippocampal population, this suggests that a majority of DG cells are subject to exchange. This is in dramatic contrast to rodents, where it has been estimated that neurons generated in adulthood correspond to only 10% of DG granule cells (Imayoshi et al., 2008). About 700 neurons are added daily in the adult human DG, corresponding to an annual turnover rate of 1.75%, which is similar to the levels found in middle-aged rodents.

This study is of profound importance, given that it will further invigorate the field for the study of the contribution of adult hippocampal neurogenesis to human behavior and mental health. Previous concerns about low levels of neurogenesis in humans and its potentially limited importance in aged individuals can now be tempered. For instance, these findings support the importance of investigating the therapeutic potential of harnessing adult neurogenesis for the treatment of age-related cognitive disorders. In rodents, adult neurogenesis is involved in modulating pattern separation, a cognitive process that declines with age (Sahay et al., 2011). In addition, neurogenesis has been implicated in the behavioral effects of antidepressants (Santarelli et al., 2003) and memory generalization in anxiety disorders (Kheirbek et al., 2012), links that can now be investigated in humans with renewed confidence. Interestingly, the individuals used in Spalding et al. (2013) showed significant variability in levels of incorporated ^{14}C, which could serve as an opportunity to retrospectively compare levels of hippocampal neurogenesis with each individual's medical history in order to probe for a relationship between psychiatric conditions and rates of cell turnover.

Yet, this remains only the beginning, because much of our knowledge about the contribution of hippocampal neurogenesis to behavior is derived from rodent studies, and the significant differences between rodents and humans in the neurogenic process remains to be fleshed out. For example, a recent report indicated that the maturation process in nonhuman primates extended up to 6 months, significantly longer than the month or so it takes in rodents (Kohler et al., 2011). In addition, in humans, it has been reported that there exists regional differences in the neurogenic effects of antidepressants (Boldrini et al., 2009). Specifically, the ability of antidepressants to increase neurogenesis in humans appears to be most pronounced in the anterior pole of the hippocampus. Future studies comparing the temporal and regional rates of neurogenesis between humans and rodents will provide

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essential clues about the contribution of adult-generated granule cells to DG physiology and behavior in humans.

The study from Spalding et al. (2013) also underscores the necessity for developing methods for imaging human hippocampal neurogenesis in vivo. Such methods are still in their infancy but are a necessary step for understanding how neurogenesis may change under disease and treatment conditions.

This landmark study by Spalding et al. (2013) legitimizes the explosion of research into the process of adult neurogenesis in recent years. The discovery that the human hippocampus can generate new cells at a significant rate until old age puts to rest concerns about whether or not this process occurs at significant rates in people. Moreover, it will energize efforts to answer the second question of how this small number of cells impact human behavior and will fuel efforts to target this process for the development of new therapies for the treatment of disorders of cognition and mood.

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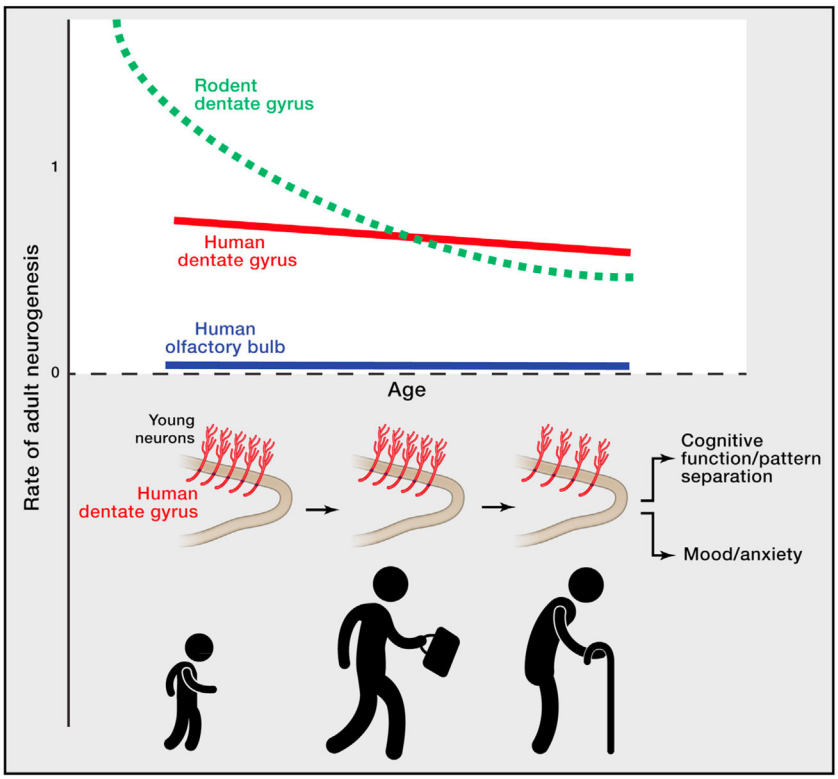

Figure 1. Comparative Rates of Adult Neurogenesis in Mice and Men

In contrast to the very low levels of adult neurogenesis reported in the human olfactory bulb (blue line), the human hippocampus continues to generate neurons at a steady rate well into old age with only a modest decline throughout adulthood (red line). The rate of neurogenesis in adult humans is comparable to levels seen in middle-aged rodents (9 months old; intersection of green line and red line). These results suggest that studies in rodents revealing the role of adult hippocampal neurogenesis in cognitive function (pattern separation) and emotional behavior (mood/anxiety) may also hold true in adult humans.