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Human Adult Olfactory Bulb Neurogenesis? Novelty is the Best Policy

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There is ongoing controversy as to whether the understanding of adult mammalian neurogenesis gained from rodent studies is applicable to humans. In this issue of *Neuron*, Bergmann et al. propose that adult human olfactory bulb neurogenesis with long-term neuronal survival is extremely limited.

At the core of much classic and modern philosophy, and key in controversies about human evolution, both broadly genetic-biological and with special focus on cognition and other brain functions, is the question “are we really special as humans?” Is there something really exceptional and unique about the human brain that sets it apart from what we discover in mice, or are we, rather, just more complex in most ways? Does our ability to discuss that very philosophy, or interact with other humans, or to appreciate flavorful food and wine and freshly roasted coffee, simply reflect the same biological processes as in mice, amplified or refined – or are there core differences? In this issue of *Neuron*, Bergmann et al. report analyses of human brains that address one informative corner of that immense question via investigation of whether adult olfactory bulb (OB) neurogenesis – the birth of new neurons – occurs in humans.

Adult Mammalian Neurogenesis over the Past 50 Years

Over the past 50 or so years, since early work by Altman and Das (1965), the fields of developmental and regenerative neuroscience have been slowly pulled and convinced, sometimes dragged kicking and screaming, away from the prior ~100 years of dogma that there is no new neuronal birth – neurogenesis – in the mammalian central nervous system (and other advanced vertebrates, for that matter) after developmental neurogenesis is completed. Though controversies have come and gone, with some early data largely unconvincing to, and largely not accepted by, the field due to inherent technical limitations at the time, the tide has slowly-but-surely changed since the early 1980s. This turnaround started especially once newer work in songbirds (e.g. Goldman and Nottebohm, 1983) and rodents (e.g. Lois et al., 1996) reinitiated the now fully accepted and large body of work that there is ongoing adult neurogenesis of at least a few subtypes of evolutionarily old neurons in the mammalian olfactory bulb and dentate gyrus sub-region of the hippocampus. The field has identified that adult neurogenesis occurs in at least these two regions in rodents through non-human primates (e.g. Imayoshi, 2008; Kornack, 2001), and in human dentate gyrus as assessed directly using BrdU in cancer patients (Eriksson, 1998).

Adult neurogenesis in the OB and dentate gyrus has been increasingly implicated in, and demonstrated to function in, olfactory and spatial learning and memory, respectively. Connections to learning and memory make these processes especially interesting, for at least two distinct sets of reasons. First, because of the core puzzle of how does brain circuitry modify itself with learning – at the levels of molecular changes, synaptic spine changes, connectivity changes, and even via insertion of new neurons by adult neurogenesis. The second is that adult neurogenesis, and reductions thereof, have been implicated in many human disease states (with varying levels of supporting data and plausibility), from major affective psychiatric disease, to neurodegenerative diseases like Alzheimer's and Parkinson's diseases, to drug abuse and addiction. Thus, adult neurogenesis, and by its central place in that field, adult OB neurogenesis, have assumed positions that are seen to touch upon much broader issues of learning, memory, cognition, plasticity, disease, regeneration, and – yes – even the question of our uniqueness as humans with regard to mental complexity and function.

How Similar and Conserved is Adult Neurogenesis in Rodents and Humans?

There has been a relatively recent controversy about whether all the deeply interesting results in the field regarding OB neurogenesis in rodents are even relevant in humans. Does the rostral migratory stream (RMS) through which newborn OB neurons migrate in rodents through non-human primates even exist in humans? Is there evidence of continued neuroblast migration through an RMS in postmortem human brains? Does that reduce to a trickle or less in adult humans? There is compelling evidence that this system is smaller, different in form, and substantially reduced after infancy (Sanai, 2004; Sanai, 2011), but work by others indicates that, though its anatomy is altered by brain expansion, a functional RMS exists (Curtis, 2007; Wang, 2011). Other work identifies some progenitors directly within the OB itself, perhaps an additional local source for human adult OB neurogenesis (Pagano, 2000). Taken together, the system in humans appears different to some or great extent, but is it unique? Does it function at all?

In this issue of *Neuron*, Bergmann et al. report that adult human OB neurogenesis with long-term neuronal survival is extremely limited... at least in a limited cohort of Swedes, many of whom with neuropsychiatric disease and substance abuse. The authors apply state-of-the-art approaches of ^{14}C cell birth dating that their labs developed several years ago (Spalding et al., 2005), taking advantage of cold war era above-ground nuclear weapons testing that resulted in a peak in atmospheric ^{14}C from the mid 1950s to early 1960s. This results in ^{14}C incorporation in all newborn cells with a “time stamp” assessed by known decreasing atmospheric ^{14}C concentration since that time. Though they find clear evidence of ongoing cell birth in the OBs of these select adult humans, this is found to be almost all non-neuronal, using broad neuronal vs. non-neuronal marker combinations for sorting of nuclei for ^{14}C analysis.

These results are rigorously based, and the experiments solidly performed. But is the question put to rest? Though very intriguing, and these data certainly weigh in on how generally dependent adult humans are on olfactory bulb neurogenesis in affluent, western cultural settings (seemingly not much at all), there are caveats and limitations to consider before making strong conclusions about the existence of adult neurogenesis in the human olfactory bulb.

One main caveat concerns the approach itself, which is not able to identify new neuron birth in which the adult-born neurons go on to die. Results in mice (Magavi, 2005; Lazarini, 2011) have shown that adult-born neurons not activated by novel odorants while they are forming synaptic circuitry in the OB go on to die. Further, results in rodents have found that adult-born neurons do not serve as simple “replacement parts” for developmentally born neurons, but, rather, serve as part of a unique function of novel odorant learning. Thus, some of the basic assumptions used in the current work about the relative percentages of ^{14}C -labeled OB neurons might be incorrect; there might be a higher percentage turnover in a smaller subset of adult-born neurons – but only if novel odors are often encountered.

What these data might actually confirm is that average humans in some affluent and western societies are not nearly as olfaction-dependent as our hunter-gatherer ancestors, or as modern humans in cultures with more novel odors day-to-day (smellier environments, frankly), or as those among us who are chefs, sommeliers, perfumers, vintners, “foodies”, nomads, back-country hunters, or multi-cultural travelers or migrants. The question remains. The detailed lists of human subjects from whom the postmortem tissue samples derived raise the question of whether these Swedish adults, many with neuropsychiatric and addiction disorders (both of which are known to substantially reduce adult neurogenesis, as discussed by the authors), some institutionalized (neurogenesis is reduced in “deprived” conditions), and without any reason to think that they have lived adult lives with rich and diverse novel odorant stimulation, would be anywhere close to the limits of human OB adult-born neuron survival and incorporation into OB circuitry. Though more difficult, finding those rare human brains of the novel odor-encountering groups noted above, especially those who might unfortunately die accidentally in the midst of life while still active in those pursuits, would be needed to test this question most rigorously.

In the future, it will be critical to use the ^{14}C approach to assess neurogenesis in the human dentate gyrus. This would seem to be the perfect system in which to directly test the method using human tissue (and even potentially non-human primate tissue), allowing direct comparison with results obtained using BrdU in humans (Erikson, 1998) and non-human primates (e.g. Kornack, 2002). Such data could serve as direct calibration and control for the issues of cellular resolution and long-term survival of adult born neurons. Analysis of dentate gyrus neurogenesis

would provide more direct support of the approach with relatively small neuronal subpopulations in relatively large central nervous system tissue samples, or might raise issues regarding ultimate interpretability about lifetime neuronal birth, death, and turnover.

Conclusions

The work by Bergmann et al. (2012) adds an intriguing and powerful set of data to the continuing discussion of whether there is ongoing olfactory bulb neurogenesis in humans, and, by extension, whether studies in rodents can be correctly generalized to human brain function and disease. Had there been considerable neurogenesis found, that would have been definitive. However, the finding of extremely limited OB neurogenesis in the currently analyzed brains and analyses cannot weigh in definitively on whether some chefs, sommeliers, nomads, hunter-gatherers, among others – not those undergoing forensic autopsy in Sweden largely with neuropsychiatric disease and substance abuse – have ongoing adult OB neurogenesis. While these data add to the debate, how similar we are to mice remains unsettled.

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