Please cite this article in press as: Kempermann et al., Human Adult Neurogenesis: Evidence and Remaining Questions, Cell Stem Cell (2018), https://doi.org/10.1016/j.stem.2018.04.004

Cell Stem Cell
Minireview

Human Adult Neurogenesis: Evidence and Remaining Questions

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https://doi.org/10.1016/j.stem.2018.04.004

Renewed discussion about whether or not adult neurogenesis exists in the human hippocampus, and the nature and strength of the supporting evidence, has been reignited by two prominently published reports with opposite conclusions. Here, we summarize the state of the field and argue that there is currently no reason to abandon the idea that adult-generated neurons make important functional contributions to neural plasticity and cognition across the human lifespan.

Adult hippocampal neurogenesis, the lifelong generation of new neurons in a brain region that is central to learning and memory (Altman and Das, 1965), exerts a strong fascination for scientists and the public alike. Knowledge about this process has fundamentally changed our ideas about how the hippocampus works and, by extension, our ideas about the structural substrates that underlie human cognition, cognitive aging, and the loss of hippocampal functions in, for example, Alzheimer's disease or stress-related disorders and depression.

Two prominently published studies have now reignited the scientific debate about adult neurogenesis in humans. A report by Sorrells et al. (2018) concluded that neurogenesis in the human hippocampal dentate gyrus drops to undetectable amounts during childhood, and that the human hippocampus must function differently from that in other species, in which adult neurogenesis is conserved (Sorrells et al., 2018). In another study, Boldrini et al. (2018) came to the opposite conclusion and reported lifelong neurogenesis in humans. Thus, in the space of only a few weeks, two reports have been published that could not be more different. Herein, we discuss how the current state of knowledge about adult hippocampal neurogenesis applies to the human situation (Figure 1).

The Evidence for Adult Neurogenesis in the Human Brain

In 1998, Eriksson and colleagues applied the current "gold standard" adult hippocampal neurogenesis method, which was previously established in animal studies, on the human hippocampus (Eriksson et al., 1998). They identified patients who had received infusions of the thymidine analog bromodeoxyuridine (BrdU) for tumor-staging purposes, but did not receive any treatment that is thought to affect cell generation, and they analyzed the brains postmortem. Their conclusion from five brains was that adult neurogenesis could be detected in the human hippocampus in the same location and numbers as expected based on work in rats. BrdU and other halogenated thymidine analogs, such as IdU or CldU, are incorporated into the DNA of dividing precursor cells and can be detected immunohistochemically. Detecting a BrdU-positive neuron thus indicates that the neuron has originated from a cell that underwent division at exactly the time at which BrdU was applied, since BrdU has a short biological half-life. Incorporation of thymidine analogues or ^{14}C into DNA could theoretically be caused by processes other than duplication of DNA during mitosis, such as DNA repair or methylation. However, BrdU does not appear to be significantly incorporated during DNA

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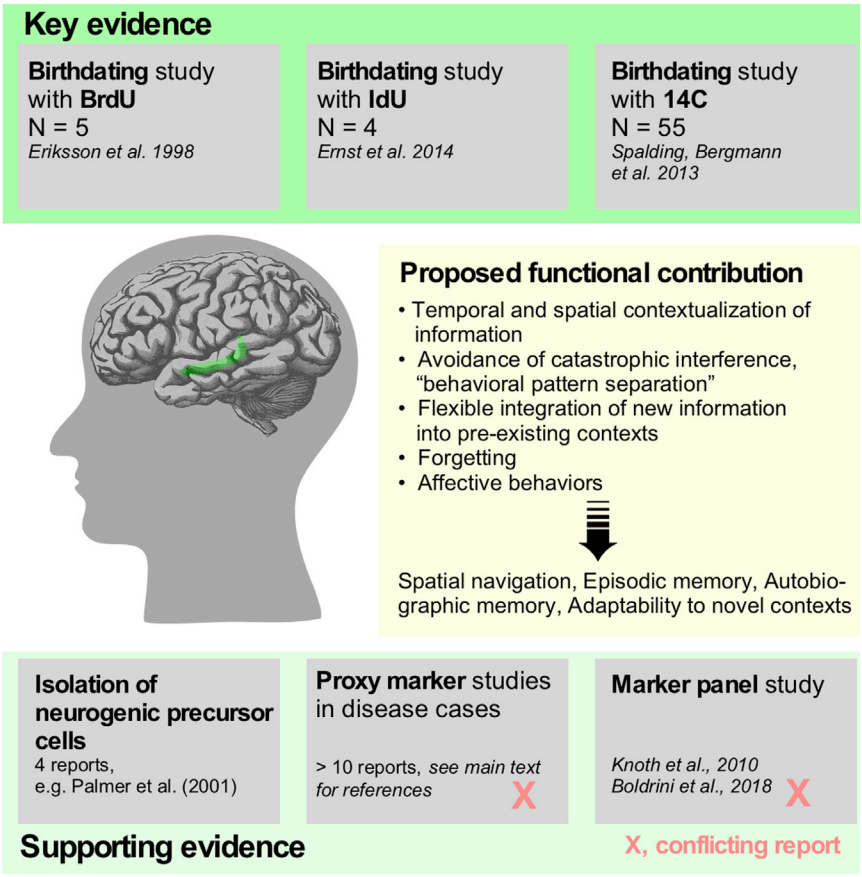

Figure 1. Multiple Lines of Evidence in Support of Adult Hippocampal Neurogenesis in Humans

Data from rodents suggest a particular and specific function for adult-generated neurons of the dentate gyrus, which would be of great relevance to human cognition in health and disease (green box). Three birthdating studies confirm the idea that adult hippocampal neurogenesis exists in humans (dark green box, top), and a much larger set of studies based on *ex vivo* analyses of precursor cells and marker expression provide supportive evidence (light green box, bottom). Sorrells et al. (2018) have questioned the validity of marker studies (red X), and we discuss evidence for and against human hippocampal adult neurogenesis in this Minireview.

repair and is not taken up by dying neurons (Bauer and Patterson, 2005), and ^{14}C incorporation during extensive DNA repair in cortical neurons after stroke was below the level detected by carbon dating (Huttner et al., 2014). For the ^{14}C levels in the DNA of adult human hippocampal neurons to be explained by DNA repair or methylation, the entire genome would have had to be exchanged in 35% of the neurons by these processes (Spalding et al., 2013), which is by a very large margin beyond any type of DNA modification described.

While such birthdating methods are cornerstones of demonstrating adult neurogenesis, especially in undescribed regions of the brain or in new species, they alone are not sufficient as proof but require support by methodologically independent lines of evidence.

Providing such supporting evidence, stem cells with neurogenic potential were isolated from the adult human hippocampus (e.g., Palmer et al., 2001). In addition, several studies have used immunocytochemistry to detect cells expressing cell proliferation markers in human postmortem brains (e.g., Boekhoorn et al., 2006; Curtis et al., 2003; Dennis et al., 2016; Liu et al., 2008; Mathews et al., 2017).

Both Sorrells et al. and Boldrini et al. primarily base their main conclusions on the individual or combined expression of key marker proteins such as doublecortin (DCX) or PSA-NCAM as markers for intermediate progenitor cells and early immature neurons (often dubbed "neuroblasts"). In rodents, DCX (and PSA-NCAM) characterizes an intermediate phase of adult neurogenesis between the precursor cell stage and immature neurons, and it is widely used as a proxy marker for adult neurogenesis, although it is also expressed in other contexts (Kuhn et al., 2016). Several earlier studies have used DCX to assess adult neurogenesis in humans (Dennis et al., 2016; Galán et al., 2017; Knoth et al., 2010; Liu et al., 2008; Mathews et al., 2017).

Sorrells et al. and Boldrini et al. use the approach first reported by Knoth et al. (2010), who assessed 54 samples across the lifespan of 0 to 100 years using combinations of 14 markers (Knoth et al., 2010). In contrast to Sorrells et al. (2018), Knoth et al. and now Boldrini et al. found DCX-positive cells co-expressing other neurogenesis markers. But while Sorrells et al. and several other studies pointed out an age-related decrease in marker overlap and a sharp decline in proliferating cells (Dennis et al., 2016; Knoth et al., 2010; Mathews et al., 2017), Boldrini et al. employed additional validation methods that did not find an association between labeled cells and increasing age. In contrast to previous studies, they applied stereology, a method for unbiased quantification within a tissue volume. The conclusion still stands in contrast to quantitative estimates, based on carbon 14 (^{14}C) birthdating of neuronal DNA (Spalding et al., 2013). That study by Spalding, Bergmann, and colleagues notably assessed ^{14}C data from 55 individuals, and this broad range of samples and alternative method of quantitation serves as independent validation for adult neurogenesis in the human hippocampus. Another study by the same group, though focused on striatal neurogenesis, also contained a replication of Eriksson's findings using the thymidine analog IdU in four more subjects (Figure S2 of Ernst et al., 2014).

The studies by Eriksson et al., Ernst et al., and Spalding et al. used a form of lineage tracing in which the DNA of dividing precursor cells was labeled (by ^{14}C, BrdU, or IdU) and their progeny was analyzed for the expression of neuronal markers. Thus, these studies focus on identifying the presence of newly formed neurons. In contrast, Sorrells et al. and other studies base their conclusions about neurogenesis on histological analysis of markers for precursor cells and their proliferative status, as well as early immature stages.

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Technical Issues

The Limitations of Marker Studies

Sorrells et al. essentially based their conclusion about the rareness or even absence of neurogenesis on the absence of morphological features and the lack of detection of two marker proteins, DCX and PSA-NCAM. In contrast, Boldrini et al. detected a large number of cells displaying the very same markers and saw that as evidence of neurogenesis. A crucial factor in accurate detection of marker proteins is the postmortem delay (PMD), i.e., the time between the death of a person and fixation of the brain. DCX rapidly breaks down after death: a controlled time course study of PMD in rats has shown that DCX staining becomes weak within a few hours of PMD (Boekhoorn et al., 2006). In the Sorrells paper, many subjects had very long PMDs of "less than 48 hr" (that is, up to 2 full days before fixation), whereas in Boldrini et al. (2018) the PMD was up to 26 hr. Some samples in Sorrells et al., however, also had only short postmortem intervals of below 5 hours. It thus would be valuable to know whether the inter-individual variation in neuroblast numbers in Boldrini et al. correlated to the PMD. In addition, it would be interesting to learn how well the different marker combinations (and, hence, cell types) correlated. Type and duration of fixation are other relevant methodological factors. Human samples might be stored in the fixative for years. Based on their long fixation period in 10% formalin, masking of the PSA-NCAM antigen has likely occurred, possibly explaining the relative absence of this marker in Sorrells et al.'s tissues. Other samples in that study, however, were fixed in 4% paraformaldehyde, so this problem might not extend to all cases. The key point is that these technical issues need to be taken into consideration for a full evaluation of the evidence.

As what could be considered a control for the issue of postmortem interval, Sorrells et al. also examined tissue from epilepsy surgery. While this is rare tissue, it is challenging to investigate and its use is potentially confounded by the fact that epilepsy results in a massive reorganization of the hippocampal circuitry and damage to the neurogenic niche (Jessberger and Parent, 2015). On the other hand, others have reported evidence of neurogenesis in epilepsy patient samples (Coras et al., 2010; Liu et al., 2008). Nevertheless, the caveats of studying epileptic tissue and these clear discrepancies between the different studies make it difficult to confidently interpret these results. The disease phase preceding the study subjects' deaths also generally needs to be considered. Moreover, in humans, the act of dying itself massively elevates stress hormones (Bao and Swaab, 2018), and since DCX staining dropped dramatically as soon as 30 minutes after capture in bats, stress hormones may have reduced DCX levels in the human brain as well (Chawana et al., 2014).

Variability can also be explained by the many genetic and environmental factors that regulate neurogenesis in rodents such as exercise, hormonal status, diet, epilepsy, anxiety, addiction, inflammation, and stress (Lucassen et al., 2015). The study by Boldrini et al. differs from previous studies in that it attempts to correlate adult neurogenesis with angiogenesis and tissue volume as additional tissue parameters, which are influenced by activity. Moreover, they included only subjects without neurological or psychiatric disease.

Given these methodological issues and the impact of lifestyle factors for the human tissues that were studied at an end stage, it seems likely that the Sorrells et al.'s study was at least not optimized for the detection of neurogenesis.

An important consequence of the renewed discussion will therefore be a raised awareness of the challenges that these approaches pose when studying human brains (Bao and Swaab, 2018).

Quantitative Aspects

Several groups have previously reported quantitative estimates of the presence of DCX- or PSA-NCAM-positive cells in adult humans (Dennis et al., 2016; Galán et al., 2017; Knoth et al., 2010), and Boldrini et al. (2018) have been among the first to make a serious attempt to apply proper stereological principles to the analysis. This approach is urgently needed, but the implementation is challenging in the kind of tissue samples usually available from humans. Irrespective of the approach used, all of these studies reported only sparse DCX-positive cells in the adult dentate gyrus, and the rough quantitative estimates actually seem comparable between the studies.

Carbon dating indicates that about 700 new neurons are added per day in each dentate gyrus and it seems that, even if one allows a large margin of error, the available numbers for DCX-expressing cells fall into the same order of magnitude. The decline in the number of DCX-positive cells during adulthood and into old age, reported in most studies, is closely paralleled by a decreased generation of new neurons measured by carbon dating (Figure 5A in Spalding et al., 2013). This decline is also found in rodents, where not only proliferation decreases but also the subsequent neurogenesis phase slows down with increasing age. If the numbers from Boldrini et al. are confirmed, the extent of adult human neurogenesis would previously have been under-estimated rather than over-estimated.

For the number of DCX-positive cells found by Knoth et al. to give rise to the number of new neurons estimated by carbon dating, the phase of DCX expression could last for approximately 3 weeks if half of them gave rise to mature neurons. This duration of the DCX-positive stage is comparable to what is seen in rodents, in which approximately half of the DCX-positive intermediate cells give rise to a mature neuron. Thus, it is conceivable that the reported very sparse numbers of DCX-positive cells in the adult human dentate gyrus can still give rise to the number of new neurons quantified by the BrdU method and carbon dating. However, there is a large inter-individual variation in the number of neuroblasts reported by Boldrini et al., with very low numbers in some subjects. Such inter-individual variation has been suggested by a previous marker study (Dennis et al., 2016), as well as by carbon dating (Spalding et al., 2013). It does not seem likely, but it is still conceivable that the individuals in the sample of the Sorrells et al. study all happened to have minimal or no neurogenesis.

Conceptual Contexts

Potential Species Differences

The use of DCX and PSA-NCAM expression as sole indicators of neurogenesis is also problematic as, in humans, we might find a relative temporal "decoupling" of precursor cell proliferation, which builds the potential for neurogenesis, from the actual recruitment or differentiation into new neurons. One study suggested, for example, that the decrease in DCX in the aging

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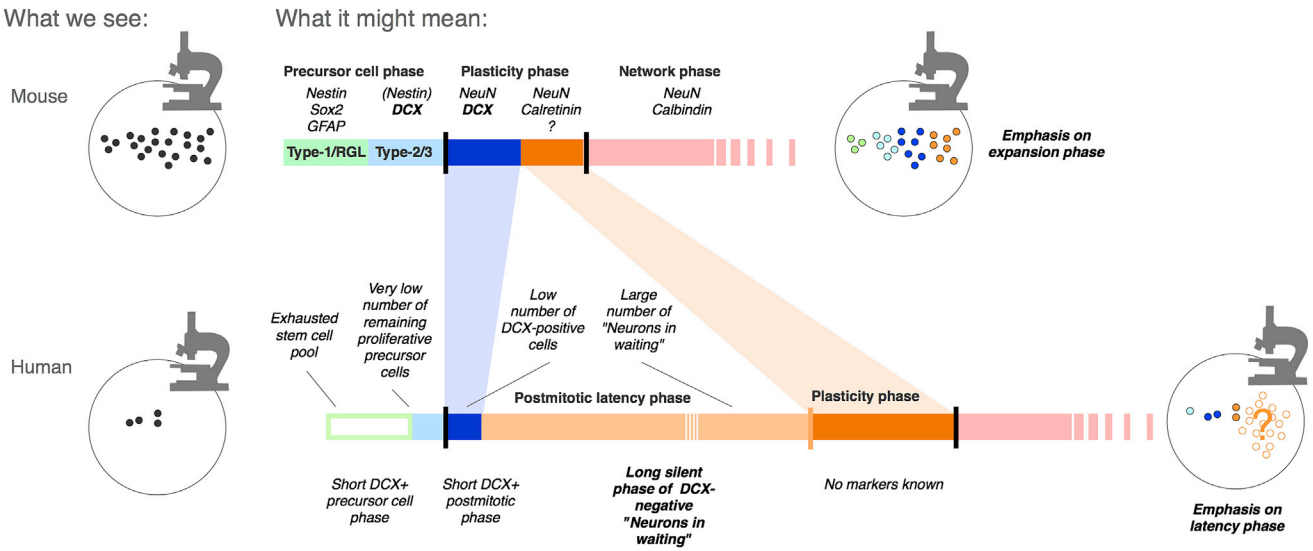

Figure 2. Consequences of Species Differences in the Course of Neurogenesis

Besides methodological considerations, a hypothetical concept of a temporal decoupling of the stages of adult neurogenesis and species differences in marker expression, although largely speculative at this time, might explain part of the discrepancies between rodent and human data. The point is that alternative hypotheses that are consistent with the available data are possible.

human hippocampus is not paralleled by similar decreases in proliferation marker Ki67, putative stem cell marker GFAPδ, or neurogenic transcription factor Tbr2/EOMES (Mathews et al., 2017). The learning-induced recruitment of newborn neurons (at least in rodents) is dependent on a reservoir of recruitable postmitotic cells and not on precursor cell proliferation per se. DCX is often used as a proxy for this population of ''immature'' neurons. However, there is no simple relationship between cell proliferation, the number of DCX-positive cells, and net neurogenesis. In fact, DCX expression is not required for adult neurogenesis or synaptic plasticity during that period (Germain et al., 2013). DCX expression alone is thus likely not sufficient to fully predict the functional potential of neurogenesis.

In addition, new neurons in mice are not DCX-positive throughout their entire postmitotic maturation period, and rats have many fewer DCX-positive cells than mice, despite having higher rates of neurogenesis, because their neurons mature faster (Snyder et al., 2009). In mice, Calretinin (CR) appears to be a better proxy marker for this period. Ironically, CR does not seem to be similarly expressed even in rats, but it has been used in at least one human study (Galán et al., 2017). It is clearly speculation at this time, but if DCX does not cover the entire period of increased plasticity in mice, we should be open to the possibility that species (as well as inter-individual) differences also apply to the dynamics of marker expression and the lengths of critical phases (Figure 2).

Functional Aspects

Research across many laboratories has painted an increasingly complete picture of how new neurons contribute to hippocampal function (Abrous and Wojtowicz, 2015; Christian et al., 2014). These studies support the view that adult neurogenesis is not needed for learning per se but rather for an advanced level of functionality. The new neurons allow the spatiotemporal contextualization of information and they help avoid catastrophic interference in the hippocampal network, promoting ''behavioral pattern separation.'' They facilitate the integration of new information into pre-existing contexts and help to clear the dentate gyrus at the circuit level and, at least in this sense, support forgetting. In addition, as the hippocampus is part of the limbic system, new neurons are involved in affective behaviors.

The new neurons contribute synaptic plasticity to the dentate gyrus, measured as increased long-term potentiation (LTP; Ge et al., 2007; Marín-Burgin et al., 2012; Schmidt-Hieber et al., 2004). All other neurons are massively inhibited by the local interneurons. At a given time, synaptic plasticity in the dentate gyrus is thus concentrated in a defined, functionally naive subset of (new) neurons. This unique mechanism of focusing plasticity sets this neuronal network apart from all others studied to date. In this context, the number of new cells required for a functional benefit is actually very low.

As an important and influential discussion point, Pasko Rakic has famously argued that adult hippocampal neurogenesis would not be possible in humans because the adult human brain has to favor stability over plasticity in order to accomplish its computational tasks (Rakic, 1985). Current theories usually argue the other way around: it is exactly its amazing plasticity that has made the human brain so flexible and successful. The question is: what is the contribution of new neurons to this success? As adult neurogenesis is spatially limited, this contribution cannot be general, as most brain regions, including the neocortex, work without it, but its effects might still be strategic. Simple brains are highly effective but in their ''hard-wiredness,'' they are hardly adaptable. Adult hippocampal neurogenesis is a prime tool for adaptability and seems to be a solution to the specific computational challenge in the dentate gyrus. Without it, yet another solution to the plasticity-stability dilemma as seen in rodents would need to have evolved in humans. Whether such a parallel solution is likely or not remains to be discussed, but the functional contribution that new neurons would make to human cognition is not negligible.

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Evolutionary Considerations

The mammalian dentate gyrus as we see it in rodents and primates, including humans, is an "add-on" structure that evolved late phylogenetically and developed late ontogenetically. Signs of adult hippocampal neurogenesis have been detected across essentially all land-born mammalian species; that is, except for the aquatic and possibly some flying mammals (Kempermann, 2012). Dolphins, despite their ascribed "intelligence," have a habitat that is profoundly different from humans, and they have an exceptionally small hippocampus and a cortical architecture that differs massively from terrestrial mammals. By all standards, humans are more like mice in this respect.

Adult hippocampal neurogenesis evolved with the dentate gyrus; it shows little resemblance to the more diffuse neurogenesis found in the non-mammalian equivalents. Additional comparative studies are still needed, but the hypothesis is that adult hippocampal neurogenesis is an advanced solution to a particular network situation that delivers added specialized functionality to the hippocampus—including that of humans. Sorrells et al. argue that there is no condensed subgranular zone stem cell niche or neurogenesis in humans and thus that such continuity in function might not exist, but this cannot be concluded from the presence or absence of marker proteins alone. The described functional relevance of adult neurogenesis is dependent on the availability of "immature" neurons with reduced inhibition and high synaptic plasticity, not on precursor cell proliferation or intermediate progenitor cells per se.

Neocortical development is an example of where, in the human brain, a common developmental principle has evolved to greater complexity: a precursor cell population that is only transient in mice and rats became the foundation of the massive expansion and gyrification of the neocortex in primates (Fietz et al., 2010). However, the basal progenitor cell that allowed this step at least transiently also exists in mice. With respect to adult neurogenesis, a key difference between rodents and humans might therefore lie in the specific qualitative and quantitative relationship between precursor cell proliferation, a hypothesized non-proliferative waiting state, a period of high synaptic plasticity, and the lasting integration of the new neurons.

The contribution of such highly plastic "neurons in waiting" not only depends on the number of cells but also on the duration of this critical time window of enhanced plasticity (Kempermann, 2012). The period of DCX expression appears to be about a month long in humans, as it is in mice, but species might still differ in that respect. In any case, full maturation of newborn neurons might take several months in primates (Kohler et al., 2011), resulting in a heterogeneity of the granule cell population with a relatively large subpopulation of early neurons in waiting with delayed final maturation.

Different mammalian species might have developed different solutions to the problem of how to provide a critical population of highly plastic cells to the network. For example, the red fox (*Vulpes vulpes*) has very high numbers of DCX-positive cells but very low levels of proliferation, which is quite different from mice (Amrein and Slomianka, 2010).

The balance between retained neurogenic potential from proliferating progenitor cells or from a reservoir of pre-generated, highly excitable cells might also vary between human individuals (see discussion above and within Spalding et al., 2013). In addition, this balance is likely to change across the lifespan. If the duration of the window of plasticity lengthens with age, extremely low numbers of proliferating cells could still contribute to a reservoir of plastic cells that sustain the required functionality. To some extent, this functionality also seems to be additive, in that past neurogenic events also lastingly change the networks (because the new neurons survive for long durations with presumably normal levels of synaptic plasticity), so that aged individuals might actually require lower numbers of new neurons.

The process of adult neurogenesis may somewhat parallel what occurs in the female reproductive system of mammals, where all stem cell proliferation that generates the population of egg cells occurs very early in life and further development is delayed. The case of adult neurogenesis might not be as extreme, depending on whether the study by Sorrells et al. or Boldrini et al. best reflects the situation, but there is no fundamental need for substantial stem cell proliferation in adult neurogenesis to extend throughout the ever-expanding lifespan of humans. There might also be a "neurogenic menopause," in which the potential is used up, and this might indeed contribute to age-related cognitive decline.

Conclusion

Regarding adult hippocampal neurogenesis in humans, many questions remain unanswered. Species differences are interesting and important, and the report by Sorrells et al. reminds us that simple 1:1 translations from animal studies to humans are problematic. But the coincident publication by Boldrini et al., which in our view is more in line with the other current body of knowledge briefly summarized in the present article, not only further questions the interpretation that there is minimal or undetectable adult neurogenesis in the human hippocampus, but also points out the direction in which this kind of research will develop: toward a more quantitative analysis that aims at relating neurogenesis parameters to other features of plasticity and to behavior in health and disease. There is a clear need for additional ways to study the generation of new neurons in adult humans. A more complete analysis of cell phenotypes and potential differentiation trajectories, by for example single-cell RNA-sequencing, is likely to provide valuable information. Methods for following the process of adult neurogenesis *in vivo* would be extremely valuable, particularly for assessing changes under different conditions and in pathology.

Since the serendipitous discovery of adult neurogenesis by Joseph Altman (Altman and Das, 1965) and the heated discussion about "Limits of neurogenesis in primates" (Rakic, 1985) after Fernando Nottebohm's description of adult neurogenesis in songbirds in the 1980s, the field has come a long way and amassed a more than critical and multifaceted body of evidence supporting the existence of adult neurogenesis in human brains. Human evolution might have found very efficient ways to balance proliferation and the duration of the critical maturation period in order to provide the level of hippocampal plasticity that the individual requires.

ACKNOWLEDGMENTS

This research was in part supported by the Intramural Research Program of the NIMH (ZIAMH002784 to H.A.C.).

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