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Evidence for adult neurogenesis in humans

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[Abstract]

Two prominently published reports with opposite conclusions about whether or not adult neurogenesis exists in the human hippocampus have spurred discussion about the nature and the strength of the current evidence. 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 life span.

[Main text]

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 adult hippocampal neurogenesis has fundamentally changed our ideas about how the hippocampus works and, by extension, 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 re-ignited the scientific debate about adult neurogenesis in humans. A report by Sorrells et al. (2018)concluded that neurogenesis in the human hippocampal dentate gyrus would drop to negligible amounts during childhood and that the human hippocampus must function differently from other species, in which adult neurogenesis is conserved (Sorrells et al., 2018). In contrast, in another study, Boldrini et al. (2018) came to the opposite conclusion and reported lifelong neurogenesis in humans (Boldrini et al., 2018). Thus, in the space of only a few weeks, two reports have been published that could not be more different: one that used the inability to confirm histological findings to question the functional relevance of adult neurogenesis for humans and one that not only confirmed the literature that argues against such a view but also took important, albeit still descriptive, steps towards placing adult hippocampal neurogenesis into its functional context in humans. We here discuss how the current

state of knowledge about adult hippocampal neurogenesis applies to the human situation (Fig. 1).

The evidence for adult neurogenesis in the human brain

In 1998, Eriksson and colleagues applied to the human hippocampus the 'gold standard' method established in animal studies on adult hippocampal neurogenesis at the time (Eriksson et al., 1998). They identified patients who had received infusions of the thymidine analog bromodeoxyuridine (BrdU) for tumor staging purposes, but only surgical therapy, and they analyzed the brains post mortem. 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 is not significantly incorporated during DNA repair and is not taken up by dying neurons (Kuhn et al., 2016). While such birthdating methods are cornerstones of demonstrating adult neurogenesis, especially in undescribed regions of the brain or new species, they alone are not sufficient for a 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 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).

In Knoth et al. (2010), in a first example of the approach now taken by Sorrells et al. and Boldrini et al., 54 samples across the life span from 0 to 100 years were assessed 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. state that these numbers would hardly change across adulthood. In contrast to previous studies, they applied stereological tools for quantification, so their argument carries more weight. 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, including ^{14}C data from 55 individuals, is widely seen as the long-awaited independent proof that adult neurogenesis does indeed exist 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 (Fig. 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 (either by ^{14}C, BrdU or IdU) and their progeny analyzed for the expression of neuronal markers. While histological marker studies like Sorrells et al. based their conclusion about neurogenesis on the starting point of adult neurogenesis, i.e., the precursor cells, their proliferation and early immature stages, these other studies focussed on the end product, i.e., the actual demonstration of the presence of newly formed neurons.

Technical issues

The limitations of marker studies

Sorrells et al. essentially based their conclusion about the absence of neurogenesis on the absence of morphological features and the lack of detection of two marker proteins, DCX and PSA-NCAM. Boldrini et al. used the same markers 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 hrs' (that is, up to 2 full days before fixation). Type and duration of fixation are other relevant methodological factors. Human samples might be stored in the fixative for years. With the long fixation in 10% formalin used by Sorrells et al., masking of the PSA-NCAM antigen has likely occurred, possibly explaining the relative absence of this marker in their tissues.

The disease phase preceding the death of the subjects studied also needs to be considered. Moreover, in humans, the act of dying itself massively elevates stress hormones (Bao and Swaab, 2018) and, since DCX staining was shown to drop dramatically as soon as 30 min after capture in bats, stress hormones may have reduced DCX levels in 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.'

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. 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 and colleagues (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 this, 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 (Fig 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 three 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 the 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 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 into new neurons. One study suggested, for example, that the decrease in DCX in the aging 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 understand the functional potential of neurogenesis.

In addition, in mice the new neurons 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 has been used in at least one human study (Galán et al., 2017). It is clearly a 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 (Fig. 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, they are involved in affective behaviors.

The new neurons contribute synaptic plasticity to the dentate gyrus, as 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 sub-set 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.

Pasko Rakic has famously argued that adult hippocampal neurogenesis would not be possible in humans because the adult human brain had to favor stability over plasticity in order to accomplish its computational tasks (Rakic, 1985). Modern theories usually argue the other way around: it is exactly its amazing plasticity that makes the human brain special. Simple brains are highly effective but, in their "hard-wiredness," they are hardly adaptable. Adult hippocampal neurogenesis is a prime tool for adaptability; without it yet another solution to the plasticity-stability dilemma as seen in rodents would have 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.

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 develops 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, however, 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 in humans. Sorrells et al. argue 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), which has very high numbers of DCX-positive cells but very low levels of proliferation, quite different from mice (Amrein and Slomianka, 2010).

The balance between a 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 Spalding et al., 2013). In addition, this balance is likely to change across the life span. 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 times 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, but there is no fundamental need for substantial stem cell proliferation in adult neurogenesis to extend throughout the ever-expanding life span 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 is more in line with the current body of knowledge briefly summarized in the present article, not only further questions the categorical claim that there is no adult neurogenesis in the human hippocampus but also points out the direction in which this kind of research will develop: towards a more quantitative analysis that aims at relating neurogenesis parameters to other features of plasticity and to behavior in health and disease. Interestingly, Sorrells et al. might not be fully convinced of their conclusion themselves: even after submission of their report, they contributed to a study on the negative consequences on adult hippocampal neurogenesis in patients with amyotrophic lateral sclerosis (Galán et al., 2017).

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.

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Figure legends

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), but there is little general support for that claim. The other lines of evidence are untouched by their argumentation.

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 are possible that are consistent with the available data.

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