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Adult neurogenesis, human after all (again): Classic, optimized, and future approaches

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A B S T R A C T

In this perspective article, we reflect on the recent debate about the existence of human neurogenesis and discuss direct, and also indirect, support for the ongoing formation, and functional relevance, of new neurons in the adult and aged human hippocampus.

To explain the discrepancies between several prominently published human studies, we discuss critical methodological aspects and highlight the importance of optimal tissue preservation and processing for histological examination.

We further discuss novel approaches, like single-cell/nucleus sequencing and magnetic resonance spectroscopy, that will help advance the study of human neurogenesis to its fullest potential – understanding its contribution to human hippocampal functions and related disorders like depression and dementia.

1. Introduction

For most of us, the question of whether adult neurogenesis exists in the human brain was a no-brainer. After all, over the past two decades, its presence had been reported by several landmark studies that applied independent approaches and had demonstrated the generation of new neurons in the postnatal/adult human brain ('adult' from now on, for brevity) in at least two regions, *i.e.* the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) [1–5]. Using immunocytochemistry, neurogenic markers have also been observed in other species and other brain regions, such as the entorhinal and neocortex, olfactory bulb, amygdala, striatum, spinal cord [6–17,247]. Also in the hypothalamus of mouse, sheep and human brains, neurogenic changes occur [18–23], while the C14 approach (see below) has further identified neurogenesis also in the human striatum. For many of these regions, this awaits further confirmation in human brain, and we therefore focus this perspective on human hippocampal neurogenesis only.

Historically, the first evidence of human adult neurogenesis was based on bromodeoxyuridine (BrdU) pulse-chase experiments, traditionally used to label dividing cells in live tissue and to trace their (surviving) progeny using subsequent immunofluorescent labeling of fixed tissue. Using this BrdU approach, neurogenesis was demonstrated in a small series of postmortem hippocampal samples of cancer patients where BrdU had been injected for diagnostic purposes [1].

Another way to detect adult neurogenesis was carbon 14 (^{14}C) birth–dating. This approach takes advantage of the nuclear-bomb-tests-derived rise in atmospheric ^{14}C and its incorporation into genomic DNA, which allows to measure cellular age and demonstrate cell renewal of pre-sorted neuronal NeuN + nuclei. Although ingenious, ^{14}C-dating uses complex methodology and requires unique equipment [24,5]. Perhaps for these reasons, the ^{14}C approach has so far not been replicated by other groups.

In yet another approach, neurogenesis is studied in *in vitro* cell-based models [25] and stem cells and/or neuroblasts are isolated from human postmortem hippocampi to demonstrate their capacity to form neurons *in vitro* [2,4,26]. More conventional immunocytochemical methods furthermore, using markers such as Ki-67, proliferating-cell-nuclear antigen (PCNA) and doublecortin (DCX), have also identified ongoing proliferation and young, migratory neurons in human postmortem samples (for references see below).

To the scientific community focused on adult hippocampal neurogenesis, it was therefore at least surprising that all this evidence was apparently overlooked when a single paper reporting a negative finding, *i.e.* a failure to detect neurogenesis in the adult human hippocampus, was published in *Nature* in 2018 [27]. In this paper, a unique age series of hippocampal control samples was investigated, together with monkey samples and neurosurgical specimens from epilepsy patients. The authors reported that the number of proliferating progenitors and young neurons in the dentate gyrus declined sharply during the first years of life to negligible amounts by 7 and 13 years of age. Also, in epilepsy patients and in adult monkeys, young hippocampal neurons

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were not detected. This led the authors to conclude that "neurogenesis in the dentate gyrus does not continue, or is extremely rare, in adult humans" and raise questions about its functional relevance in humans.

Due to its high public exposure, [27] and related papers [28,29] triggered considerable debate and often significant doubt, both in a part of the scientific community (see [30] for example) and in popular laymen media, regarding the existence of neurogenesis in adult humans. Shortly after Sorrells et al. was published however, another study, using very similar immunocytochemical methods, reported the exact opposite, *i.e.* an abundant presence of neural precursor markers throughout the human lifespan [31]. Similar findings have since then been published by two other, independent groups [32,33], altogether calling for a reflection on what might explain these discrepancies, what can be learned for future studies, and what still remains unknown.

After a brief historical overview, we here reflect on this dynamic period and discuss direct and indirect support for the existence of human neurogenesis and its possible involvement in disease. We close by highlighting future approaches and listing outstanding questions that will help advance the field of human neurogenesis and improve our understanding of its role in health and disease.

2. A short overview of the evidence for adult human neurogenesis

Throughout its development, the field of adult neurogenesis has been very lively and seen many challenges and controversies [34]. Major steps forward were often driven by the introduction of new technologies in combination with access to unique tissue samples. The first descriptions of new cell birth were observed in the 1960s and 1980s and based on tritiated (^{3}H) thymidine incorporation into dividing DNA in the brains of adult rodents and birds ([35,36]; see also [37] and [38] for reviews). Due to concerns about the then new methodology to label the dividing cells with ^{3}H-thymidine, the initial reports were received with skepticism and the topic did not receive much follow-up for nearly 2 decades [39]. Moreover, the attempts to detect newborn cells in the hippocampus of non-human primates after puberty were not fruitful [40–42], and hence it was generally assumed that adult neurogenesis was likely also irrelevant for humans.

Another reason for the slow progress was due to methodological limitations: the pulse-chase labeling with ^{3}H-thymidine was cumbersome and hard to work with, and more importantly, conclusions about the phenotype of the newborn cells could not easily be drawn. When non-radioactive thymidine analogues such as BrdU, CldU, and IdU became available, together with the development of confocal microscopy and of antibodies directed against these analogues, and against specific cell cycle and cell type markers, this new experimental 'toolkit' opened up possibilities for many laboratories to detect neurogenesis in rodents. [1] were the first to use such an approach on a unique set of hippocampi obtained from five cancer patients and could identify new cell formation and neuronal differentiation, confirming the overall location and extent of neurogenesis as seen in rodents (reviewed in Ernst and Frisen, 2015).

This landmark paper was followed by more conventional immunocytochemical studies on postmortem samples, confirming the presence of dividing, proliferating and/or neuronal precursor cells (NPCs) in the human hippocampus [43–55,245–246]. Studying the actual phase of adult neurogenesis, however, proved to be more challenging in postmortem human brain tissues. For example, the morphology and numbers of DCX-expressing cells reported in various papers on human brain [43,29,56–59] differ considerably from those reported in rodent brain (see for example [60–62]) and even astrocyte-like morphologies of DCX-positive cells were observed in human cortex [63]. In particular the dendritic extent of DCX-positive cells in the hippocampus appeared sensitive to postmortem delay induced breakdown, as was observed in a postmortem series of rat hippocampi ([43], Dr Schmitt-Bohrer, University of Wurzburg, personal communication). As the morphology of DCX-positive cells in human brain, for obvious reasons almost always immersion-fixed in formalin after a given postmortem interval, also lacks the extensive dendritic staining pattern that is so prominent in rodent brains that are generally perfusion-fixed with 4% paraformaldehyde in PBS, this indicates fixation may be critical in explaining differences between findings in rodents or humans. In their extensive methodological optimization studies, [32] now demonstrated that (prolonged) fixation in formalin indeed reduced DCX-immunoreactivity. Since this is generally prolonged for most human brains, also fixation time is a critical variable to consider when detecting these neurogenic markers.

A third line of evidence in support of human neurogenesis made use of the nuclear bomb tests that occurred during the cold war period around the 1950s and 60s. Few labs can perform these types of analyses, but the ^{14}C technique to birthdate DNA has demonstrated the presence of adult-generated cells in the human hippocampus [5] and also the birth of new oligodendrocytes in the cortex [64]. Due to its radioactive nature, C14 can be detected in a more reliable and quantitative manner than other techniques used to estimate neurogenesis, such as immunocytochemistry. The C14 approach can detect a low but stable level of human hippocampal neurogenesis, that remained present throughout life, comparable to levels observed in a middle-aged mouse ([5]; Ernst and Frisen, 2015). In contrast to rodents, neurogenesis could not be detected in the human olfactory bulb with this approach [65]. Surprisingly, and unlike the rodent brain, large numbers of newborn cells were found in the human striatum using the C14 approach, pointing to distinct species-specific differences [9,24,14].

In contrast to the evidence above, the papers by [27,29] and [28] have been interpreted as evidence for an absence of neurogenesis in the adult human brain. However, these particular papers report the *absence of evidence*, *i.e.* a failure to detect neurogenesis. Although the putative positive and negative controls included in their studies may support this interpretation as a possible conclusion, this can, in light of findings by others that were positive, and the limitations stemming from their samples and methodologies, not be considered as conclusive *evidence of absence,* as discussed below.

3. Is there adult neurogenesis in the human hippocampus or not?

Following 2 related papers [28,29], [27] examined various immunofluorescent markers in a unique series of hippocampal samples from 37 cases, that were considered controls and had died at different ages (ranging from 14 weeks of gestation to 77 years old), in an age series of monkey samples, and in 22 neurosurgical specimens from medically-resistant intractable epilepsy patients. The study had clear assets: i) rare embryonic and adult cases were studied in parallel; ii) rare surgical samples were obtained from epilepsy patients, serving as controls for the postmortem interval (*i.e.* absence of it); iii) multiple immunocytochemical markers, like Ki-67 and MCM2 as mitotic markers, SOX2 and BLBP as markers for radial glia-like stem cells (Type-1 cells) and DCX or PSA-NCAM as markers for early immature neurons (a.k.a. 'neuroblasts') and iv) electron microscopy were employed to identify specific stages of neurogenesis, and results were demonstrated in impeccable confocal images from infant brains, a.o..

The authors observed evidence of ongoing neurogenesis, largely based on DCX and PSA-NCAM immunocytochemistry, at early ages and reported that the number of proliferating progenitors and young neurons in the dentate gyrus declined sharply during the first years of life, and only few young neurons were observed by 7 and 13 years of age. In adult patients with epilepsy and in healthy human and monkey adults, young hippocampal neurons were not detected. Based on this standard immunocytochemical approach on conventionally fixed material, the authors concluded that "neurogenesis in the dentate gyrus does not continue, or is extremely rare, in adult humans". Based on this, and given the continued presence of adult neurogenesis in other species, the authors raised questions about the functional relevance of neurogenesis in adult humans [27].

Amidst the debate that emerged following [27], only weeks later [31], published a study using very similar methodology, but instead reported a presence of human neuronal precursors throughout life, while acknowledging the decline in markers of stem cells and angiogenesis. Although the two studies used very similar approaches on comparable tissues, nearly opposite conclusions were reached, triggering considerable discussion in several follow-up papers [66–70].

This discussion appears to be settled now by the publication of [32], who addressed specifically many of the methodological concerns that were raised before in response to [27], regarding for instance the influence of fixation time and postmortem delay, among others [66,68]. They confirmed in a cohort of 58 subjects (13 neurologically healthy subjects and 45 patients with Alzheimer´s disease) an extensive presence of DCX-positive, immature neurons, presumably at distinct maturation stages, from young ages onward up into the 10th decade. Similar findings of ongoing neurogenesis were reported by [33] in old individuals.

Although the rates of decline differed between studies, methods and antibodies used and the decrease was not always gradual, several earlier papers had generally shown a decrease in proliferation and neurogenic markers with increasing age [5,28,29,31,53,57]. The three recent studies now indicate that considerable numbers of neurogenic and DCX-positive cells remain present throughout life and can still be detected even in oldest old, healthy subjects and even suggest a link to cognition [32]; showed consistent and early reductions in neurogenesis in Alzheimer's disease (AD) patients, while [33] reported reductions in the numbers of DCX-positive (DCX+) cells double-labeled for PCNA in patients with mild cognitive impairment (MCI), a stage generally preceding dementia, with higher number of neuroblasts being associated with a better ante-mortem cognitive status [33].

4. Possible explanations for the discrepancy between histological studies

Studying changes in neurogenesis with age or in disease cases can in general only be meaningful when they are compared to a carefully matched cohort of *true control, i.e. healthy, subjects*. Ideally, a thorough clinical documentation is available for each subject, including ethical approval, permission to use brain tissue for research purposes, and a systematic neuropathological investigation to confirm control or disease status [71]. Very little patient information was available in the cohort of [27], and based on what is available, many individuals may have died from a serious illness. Each of those - severe inflammatory disease, medications known to inhibit neurogenesis, chronic systemic toxic conditions - could have inhibited neurogenesis. Besides the direct biological effects of the underlying illnesses, many of the patients studied in Sorrells et al. must have suffered the conditions for a long time. This causes an additional caveat to the findings: disease or the prolonged, chronic stress that is often associated with it, or may precede the death process, is well established to reduce neurogenesis in preclinical models [72,62,73–75]. In contrast, both [31] and [32] took rigorous measures to ensure that their control subjects were indeed physically and psychologically healthy, and provided ample information on their subjects.

A second critical variable in human brain studies is the *postmortem interval*. Protein breakdown that occurs with increasing postmortem interval can affect immunocytochemical results [76] and good quality tissue is therefore critical with, ideally, postmortem intervals and fixation times that are kept as short as possible, and at least matched between groups. Sorrells et al. [27] gave no specific information on the time that lapsed between death and sample collection for their individual subjects, and stated that the postmortem interval was minimal 48 h, whereas the intervals in [32] and [33] were considerably shorter. A precise postmortem interval for each individual sample matters, however, because target antigens may decay at different rates following death and many of the neurogenesis markers studied could therefore have been affected by protein breakdown [76,43,32].

Next to postmortem interval, *agonal state* must be taken into account. Agonal state refers to the type and duration of the death process and is another important readout to match brain tissues for, as it is different between subjects. When the agonal state is prolonged, such as after a chronic disease and long death process, the brain pH becomes more acidic, whereas in subjects who die acutely, for instance because of a heart attack or traffic accident, brain pH remains more physiological [77,78]. Brain pH is known to affect post-translational modifications of proteins and RNA, and matching for agonal state is thus ideally included when comparing patients and controls. This is particularly relevant for patients who, for instance, died of broncho-pneumonia, that results in hypoxia and in a pronounced lactic acidosis of the brain, which can affect PSA-NCAM immunocytochemistry (see also [68]).

Moreover, also *fixation* of the brain tissue brings forward well-known effects. Prolonged fixation in formalin can mask specific antigens and prevent their detection with antibodies, as [32] have now clearly demonstrated for DCX. When fixation was short and tissue well preserved by avoiding freezing and paraffin embedding, and by avoiding any type of mechanical alteration, as was the case in their unique cohort, then many clear DCX-positive cells could still be observed up until old age, although some of these cells lacked the extensive dendritic staining pattern typical of the rodent hippocampus. In their extensive series of tests and parametrical validation in the methods section of their paper, they report that postmortem intervals up to 38 h did not affect the detection of DCX or PSA-NCAM in the human DG (see Figure 1 in the Extended data of [32]), neither in the number of cells, nor in the quality of DCX immunostaining, and thousands of DCX-expressing neurons could be identified in brains that were optimally preserved.

Prolonged fixation and masking effects of antigens are especially relevant when brain samples are fixed conventionally, as done in most medical/neuropathological centers, *i.e.* generally for one month or more in formalin followed by embedding in paraffin. This might imply that the standard fixation conditions in most brain bank collections could be suboptimal for neurogenesis studies. However, some of the deleterious masking effects of prolonged fixation on antigenicity can be rescued by antigen retrieval protocols, using for instance microwave or pressure-cooking with buffers at different pH values, or by aldehyde and autofluorescence elimination procedures. [31] and [33] have for instance shown that neurogenic signal can still be detected even in standard fixed tissues of the oldest old.

Taken together, different aspects of tissue processing, tissue block size, postmortem delay, fixation duration, agonal state, *etc*, that differ considerably between patients and laboratories, can all contribute to the variation observed in DCX signal and morphology in earlier human brain studies. In future studies, it will therefore be very important to extensively test and optimize pre-treatment protocols especially for conventionally formalin-fixed, paraffin-embedded tissues of postmortem human brain; such efforts pay off as they can allow access to tissue collections in human brain biobanks worldwide and thereby enable researchers to compare larger groups of patients to matched control subjects.

Regarding the use and selection of *methodological controls,* [27] used resected human hippocampal tissues, which are indeed unique given the absence of a postmortem interval. Yet, since they were taken from epilepsy patients, such rare samples bring about additional sets of challenges. Only in extreme conditions of chronic and severe epilepsy, patients undergo such an invasive operation to remove the affected tissue, *i.e.* hippocampus. In rodent models, epilepsy strongly reorganizes the hippocampal network, promotes astrogliosis and/or depletes proliferating precursors [79]. Indeed, in a recent paper on surgically removed hippocampal human tissues of epilepsy patients, low levels of proliferating but also considerable numbers of immature neurons were observed [251], parallel to structural hippocampal abnormalities. The differences with [27] and related studies may be explained by different (timing and duration of) disease conditions and

tissue processing. Either way, it is very unlikely that after a prolonged disease duration, neurogenesis, as detected in resected epileptic tissue, still reflects the typical situation in control human brain.

Aside from the many different drug treatments these patients received, which may all affect neurogenesis, epilepsy and the operation itself are also expected to induce plasticity-related changes in the hippocampus, as reported ([80]; see also references in [68]). It is also possible for inflammation, extensively reported in epilepsy in both human and rodent models [81], to have altered neurogenesis per se [82], the antigen expression and/or their post-translational modification [83] in these medically-ill patients. Finally, as mentioned above, even patients with medically-resistant epilepsy requiring surgery may have different amounts of hippocampal neural stem cells (NSCs) [2]. It is thus difficult to rely on such tissue as "controls" for postmortem interval. Ideally, a proper control would be tissue resected from healthy subjects, which, for obvious reasons, cannot be obtained.

A main asset of [31–33] is further their use of *stereology*, considered essential for an unbiased quantification in histological analyses. Especially for relatively 'rare' events, measuring them in only a few thin tissue sections, taken at only a few anatomical levels, will likely miss many cells. The standard for publication of immunocytochemical data from the mouse hippocampus, much smaller than the human hippocampus, requires at least six series of equally spaced 30–50 μm sections systematically sampled over the whole dentate gyrus [84]. Although stereological results are influenced by specific settings, such as the number of counting frames, regions of interests and sampling frequencies [85,86], it is considered important to take into account the entire anatomical structure when quantifying neurogenesis in the hippocampus, given the clear differences in (regulation and function of) neurogenesis between rostral and caudal parts [87–90].

Even though different tissue treatment and antibody protocols were used [31–33], they all used stereology and, in contrast to [16], came to the same conclusion, confirming ongoing neurogenesis up into the 8th and 9th decade of life. Hence, taken all the above together, the main lesson we learned from the human postmortem studies is that methodology and standardization matters, maybe even more so than for rodent work, as they are especially critical in detecting neurogenesis in postmortem human brain tissue.

5. Indirect evidence also supports human adult hippocampal neurogenesis

In addition to direct (histological) observations in human brain, there is also considerable indirect evidence supporting (a functional role for) human neurogenesis. This comes on the one hand from a variety of studies that have demonstrated hippocampal changes associated with neurogenesis in relation to functional changes in animal models. For instance, newly-generated neurons in the murine dentate gyrus contribute to spatial and fear learning and memory (processing) and to pattern separation [91–100], mood and anxiety and affect regulation [101], forgetting [102] and cognitive flexibility [103]. Neurogenesis and these processes can further be affected by environment, mood, drugs and stress [104–106,72,87,107–110], and modulate pattern separation, forgetting and/or spatiotemporal-emotional regulation [91,92,97,111,112].

Certain behavioral tasks, such as *pattern separation*, can be assessed in both mice and men, thus serving as indirect evidence or proxy also for functional human neurogenesis. Pattern separation depends on hippocampal adult neurogenesis and refers to the ability to discriminate and store similar, but not identical, inputs of sensory information into distinct representations [97]. Specific tasks, such as those developed by Kirwan and Stark [248] allow for specific measurements of pattern separation in humans. The so-called Stark test is a mnemonic similarity task that involves discriminating the visual similarities of two different, but similar, images. An increased performance on pattern separation while completing this task was associated with increased blood oxygen level-dependent (BOLD) fMRI signal, selectively in the dentate gyrus [113–116], indirectly linking it to neurogenesis.

Decreased performance on pattern separation is furthermore a well-described phenomenon associated with hippocampal damage and cognitive impairment, both known to decrease neurogenesis and/or dentate gyrus size [115–119]. Moreover, Déry et al. found that anaerobic exercise was prospectively associated with improved performance on the mnemonic similarity task (Stark test) [120]. Interestingly, deficits in pattern separation are a common and early feature in dementia, whereas patients with depression did not perform well on Stark test compared to healthy matched controls. With anaerobic exercise, they not only improved their performance, but their depressive symptoms also declined [120].

To provide additional evidence that adult human hippocampal (NSCs) are present and functional, other groups isolated them from human hippocampal samples to study their potential for proliferation and *neuronal differentiation in vitro* [2,4,25,26]. [2], for example, assessed the neurogenic potential of human NSCs from the dentate gyrus obtained after surgical resections. Interestingly, the isolated adult human NSCs showed either a high or very low proliferative capacity *in vitro*, and surprisingly, patients who had stem cells with high proliferation capacity, had preserved memory performance prior to epilepsy surgery, while patients who had stem cells with a low proliferative capacity, suffered from severe learning and memory impairments.

Changes in neurogenesis may also be indirectly related to changes in *hippocampal volume* that often occur in close correlation with altered stress regulation. For example, prolonged stress-related conditions, such as depression, Cushing's disease, or post-traumatic stress disorder (PTSD), are associated with reductions in hippocampal volume. This reduction could notably be reversed upon successful treatment in some conditions [121,122], indicating that a dynamic substrate such as neurogenesis might be involved [51,105,44,56,123,45,87], at least under stress-related conditions [109,123]. Moreover, prolonged physical exercise in humans, known to boost neurogenesis in rodents [104,124], increased the volume and functional connectivity of the hippocampus specifically, but did not affect other brain regions such as the striatum [125,126].

While earlier studies examined hippocampal volume as a whole, [127] subfractionated it and recently reported on specific subregional changes in depressed patients who were treated with electroconvulsive therapy (ECT), an effective treatment for patients with medically-resistant depression. In rodents, ECS (electroconvulsive shock) strongly increases the extent of neurogenesis [128,129] while high levels of proliferation had been observed in a postmortem study in one patient who had received ECT [51]. [127] used 7 T magnetic resonance imaging with detailed subfield segmentation to detect specific volume changes in subfields of the hippocampus and found a selective, and substantial increase in volume, specifically of the dentate gyrus after ECT treatment. Notably, this increase correlated well with the improvements in depressive symptoms in the same patients.

Although this study did not actually *measure neurogenesis in vivo*, the selective increase of the dentate gyrus after ECT, and not in other hippocampal subregions, suggests that neurogenesis may be involved as an underlying substrate that could be responsible for the hippocampal plasticity and growth after ECT [130], consistent with related proxies of neurogenesis in this context [131,132] or data showing that increasing other measures of plasticity in the dentate is sufficient to improve depressive-like symptoms [133]. Also other structural, metabolic and diffusivity changes, like angiogenesis, altered connectivity or expansions in glia, may possibly contribute to the observed effects, as discussed before [123,134,135], but this awaits further research. Furthermore, it is not known whether the ECT effect may depend on parallel rises in brain serotonin levels [136] and leaves cognitive flexibility [137] untouched or not. Neither is it known what the role of stress *per se* is regarding the hippocampal volume in depression [138],

but the association of a selective dentate gyrus volume increase with mood improvement in these patients is intriguing.

Thus, assessing ECT responsivity based on the measurements of hippocampal subfield volumes could be an interesting future clinical approach, particularly for stratifying patients before treatment onset [139]. Related MRI modalities such as magnetic resonance spectroscopy [140] (see below) might also be of interest in this respect, as first studies indicate that the increase in the spectroscopic neurogenic signal might be predictive of ECT effects in depressed patients [141].

6. Neurogenesis: relevance for hippocampal function and disease

Over the past decades, our understanding of brain plasticity and functions like spatiotemporal and fear-related encoding of memories, has strongly improved due to the discovery that these processes can be modified and/or stabilized by adult neurogenesis, both in the olfactory bulb and within the hippocampal circuitry [8,88,94,99,142]. Aside from the specific molecular regulation of adult neurogenesis [143–147], important for future brain repair approaches, also the regulation of neurogenesis by environmental factors like stress, exercise, inflammatory mediators and microglia, enrichment and learning [66,72,124,148,149] have triggered great interest. The same applies to the possible role of NSCs and neurogenesis in age-related cognitive decline, dementia, epilepsy, and depression [103]; 2018; [150–156, 32,105,109].

Although evidence linking adult hippocampal neurogenesis to *cognitive function* and *brain disease* in humans has been so far still limited and often indirect, [33] is one of the first who found reductions in Alzheimer's disease and also correlated cognitive status with changes in neurogenesis ante-mortem. Of the 18 subjects studied, 6 patients had an AD diagnosis, the other 12 were controls (6) or MCI cases (6), but surprisingly, all the subjects in the three groups show AD neuropathological hallmarks and there are no subjects with a Braak-Tau 0 stage. Although no correlation was present with the extent of Alzheimer neuropathology in the same patients, [33] do report that the number of DCX + PCNA + cells correlated well with functional changes ante-mortem and interestingly, with presynaptic SNARE proteins.

In addition, Moreno-Jiménez et al., found a sharp decrease in the number of DCX + immature neurons at early stages of AD (Braak-Tau stage I), far before the deposition of senile plaques or neurofibrillary tangles in the dentate gyrus and found a marked correlation between the number of DCX + cells and the amount of Amyloid beta plaques and Tau tangles in the granule cell layer in their cohort of 45 patients, and these authors indicate that the maturation of immature DCX + neurons is blocked at multiple time points in AD patients.

In the human studies, Moreno-Jiménez et al. studied patients at all 6 Braak-Tau stages and found a prominent decrease in the number of DCX + cells in all AD cases already at Braak-Tau stage I, indicating that this decrease may precede alterations in other hippocampal regions. In Tobin et al., the Braak-Tau stages (and, consequently, the advance of the neuropathological features) were not taken into consideration. As end-stage human tissues were studied, it remains so far unknown whether patients with lower Braak stages would have developed into higher stages had the patients lived longer. Also, a temporal order of events is hard to assume with certainty and future studies, using *in vivo* imaging of neurogenesis may for instance help to answer (see below) whether in the Moreno-Jiménez et al. and Tobin et al. studies, neurogenesis was already reduced from an early age onwards and before AD pathology developed, or whether the reduction was a consequence of the emerging amyloid deposition and/or other neuropathological changes in AD, like CA1 cell loss. While the positive correlations in [33], were found in several other brain regions as well and the dentate gyrus specificity and the issue of correlation/causation thus remains unresolved, these papers are the first to suggest a preliminary link between changes in neuroblast and precursor numbers and synaptic plasticity/cognition in human.

Interestingly, the prominent and (early) reduction in neurogenesis observed in Alzheimer brains is consistent with similar correlations in *earlier animal studies* [157–159]. Also, many circuit deficits seen in the early stages of dementia and *cognitive decline* resemble those seen in animals whose neurogenesis has been inhibited using viral or transgenic approaches [100,154,159]. Along the same lines, induced pluripotent stem cells (iPSCs) derived from patients with familial AD exhibit early neurogenic aberrations compared to non-demented controls [160]. Together, these studies suggest that aspects of aging and age-related disease can be modeled in a dish [161], and that, in addition to the physiological decrease in neurogenesis caused by physiological aging, independent mechanisms might drive its additional reduction in AD [162].

In this regard, the inability to distinguish between two similar events in space and time could explain why patients with AD have difficulties remembering specific events or their context correctly, or why patients with PTSD can relive the same traumatic experiences for instance, even though their circumstances have changed. Corroborating these hypotheses, individuals with mild cognitive impairment (being at increased risk of developing AD) and genetically predisposed AD patients exhibit poor performance when tested in pattern separation tasks [115,163–165].

When considering *stimuli for neurogenesis*, exercise has been correlated with cognitive benefits, parallel to an increase in neurogenesis and an elevation of brain-derived neurotrophic factor (BDNF), both in old wildtype mice [166] and in the 5xFAD transgenic mouse model of AD [152,153]. The beneficial effects of exercise on cognition in AD mice could even be mimicked by genetically and pharmacologically inducing neurogenesis, notably together with elevation of BDNF levels and despite the persistence of amyloid pathology [152,153]. A similar rescue of cognition by modulating (aspects of) neurogenesis was observed before in another study on AD mice [154,167]. Based on such preclinical data, increasing neurogenesis, together with BDNF or other neurotrophic factors may represent an interesting strategy to maintain and/or improve cognition in AD.

Epilepsy is another disease with a clear link to adult neurogenesis. Newborn neurons are thought to be activated in response to initial cell loss, which may depend on the severity of the initial status epilepticus [168–170]. Likely dependent on seizure severity, the adult-generated cells can develop aberrant morphologies and get miss-wired, thereby disrupting brain circuits and leading to subsequent seizures and potential memory loss [151,171,172]. Also in human epilepsy, changes in neurogenesis markers have been observed postmortem in association with structural abnormalities [248]. In rodent models, preventing or normalizing aberrant neurogenesis was found to modify excitability or cognition in kindling and stroke models [151,173–175]. As epilepsy has been implicated as one of the risk factors for AD [176] as well as for depression and anxiety, it points to a general role for neurogenesis and/or dentate gyrus changes in these disorders.

Finally, neurogenesis is inhibited by *stress*, that forms an important risk factor for psychopathology and also for AD [105,177,109, 62,72,178–180]. Neurogenesis plays for instance an important role in turning off the *stress response* [87,181], while increasing neurogenesis, for instance by exercise, can promote resilience to stress [182,183]. The same applies to antidepressant drugs that can reverse symptoms of stress and depression for which in at least some conditions, neurogenesis is required [106,184]. In fact, if neurogenesis is depleted in rodents, antidepressant drugs do not rescue performance on specific anxiety and depression tests anymore [185,186,108].

In general, many stress-related disorders, including depression and anxiety disorders, and to some extent also aging, have been linked to changes in neurogenesis [89,105,123] and even dentate gyrus volume [127]. Also, the recent studies on neurogenesis in the amygdala and in relation to stress and fear responses are of interest in this respect [6,12,15,16,187,188,249]. Interestingly, in mice, hippocampal NSC populations change not only with age, but also in their responsivity to

stress hormones, such as glucocorticoid hormones [146], indicating a possible link to alterations in the stress axis during aging ([189]; Martin-Suarez et al., 2019).

Other studies in rodents have further shown that neurogenesis as well as dentate gyrus structure and function in rodents can be 'programmed' by stressful experiences, particularly if they occur *early in life* [190–197]. Also, the function and properties of the newborn cells, for instance their responsiveness to positive stimuli such as exercise in adult life [198], may have been altered for life, often in a sex-specific manner [199–201].

Recent findings by [202] are further consistent with such concepts also in humans. They quantified neural progenitor cells (NPCs), granular neurons, glia and dentate gyrus volume in hippocampi of four groups of drug-free, neuropathology-free subjects and compared patients with major depression who committed suicide and control subjects with and without early life stress (before the age of 15). Their results show that resilience to early life stress involved a larger dentate gyrus, whereas a smaller volume with fewer granular neurons and NPCs was found in the depressed/suicide group [202]. Together with related imaging findings [195], this is one of the first anatomical studies indicating that lasting effects of early life stress on neurogenesis and structural hippocampal measures may also be present in humans and in relation to psychopathology.

Clearly, the recent publication of several notable papers surrounding the [27] paper ([28,50,59]; [31,66,70,203,69,16,32,33,67,68,250]) has re-established human neurogenesis as a vibrant and major field, with important implications for cognition and brain disorders. Since the dentate gyrus has now been implicated in at least some of the cognitive deficits associated with AD, future studies may help to understand whether the 'programming' of neurogenesis by early life stress is indeed involved in the vulnerability to develop later psychopathologies [202] or AD [177], and whether this could underlie aspects of 'cognitive reserve' [204].

The concept of '*reserve*' is based on the individual variation in vulnerability and resilience for age-related cognitive decline. It stems from observations that, given a comparable pathological load, some individuals perform better than others in cognitive tasks. One hypothesis presumes that depending on the presence of stimulating and challenging conditions during critical periods of brain development and/or early life, a better 'trained' and more 'flexible' brain may emerge with, for instance, more available connections, hubs and/or an enhanced level of overall plasticity. This higher capacity to circumvent the functional consequences of emerging AD neuropathology may then represent a larger 'reserve', that would take longer to deteriorate functionally, which may thereby delay the deleterious consequences that accompany ageing and postpone the age of onset of AD, as discussed recently both from a preclinical and conceptual perspective [177,204,205]. While it is interesting that 'reserve' can now be quantitatively expressed using a neuroimaging approach [206], it awaits to be studied whether such changes indeed involve the DG and/or neurogenesis, if they indeed depend on specific early life conditions, and whether they can also be modified or rescued by adult experiences.

7. Future molecular, cellular and imaging approaches

With the growing availability of well-characterized human brain tissues in brain biobanks worldwide, improved and standardized tissue processing and immunocytochemical protocols will help to further answer important research questions from a histological perspective. To fully understand adult neurogenesis, it will be essential to further characterize the neural stem cell and progenitor developmental stages, their molecular determinants as well as the cellular and molecular composition of the neurogenic niche at discrete time points over the lifespan. With the current development of advanced molecular sequencing techniques and the availability of GWAS data and database access, the possibility to characterize neurogenesis in the human brain at *single-cell or single-nucleus* level becomes very attractive [11].

Specific protocols are already available for rodent material and have allowed us to establish gene expression profiles specific to neuronal precursors or stem cells in the rodent hippocampus (see [207]). Following isolation of the dentate gyrus cell populations, single-cell RNA sequencing (scRNAseq) of the hippocampal niche can be performed and a comprehensive description of all dentate gyrus cells is feasible based on the identification of distinct cell type-specific markers [208]. Already, scRNAseq of the dentate gyrus along with pseudo-time analysis has identified heterogeneous populations of NSCs and NPCs in rodents [208–211]. The implications of these findings for the understanding of NSC activation and adult neurogenesis, and its functional relevance, and whether a comparable diversity of adult hippocampal NSCs exists in the human brain, remain to be determined. Recent, large scale efforts have reported related single-cell molecular changes in human brain and described comprehensive genomic resources in relation to development and disease (see references in [162,212–215];).

Notably, single-nucleus RNA sequencing (snRNAseq), which enables analysis of single nuclei isolated from frozen or fixed tissue and the enrichment of rare, labeled cell populations by fluorescence-activated cell sorting (FACS), points to a spatial diversity of neurogenesis in the adult dentate gyrus in mice [11]. However, confounding factors related to cell type marker specificity may pose specific hurdles to the interpretation of data derived from scRNAseq or snRNAseq rodent studies.

The identification of NSC- and/or NPC-specific transcriptomic markers has proven particularly challenging, often resulting in the inability to distinguish adult NSC clusters in the dentate gyrus from astrocytes or other niche resident cell populations [208,211]. Emerging markers able to better discriminate between adult NSCs and other related cell lineages, like astrocytes, include *Vnn1*, *Hopx*, *Thrsp* and *Id3,* among others [209,216]. Along the same lines, these studies revealed that genes previously presumed to be unique to astrocytes, such as *Apoe*, are highly expressed in adult hippocampal NSCs and can even be used as markers of stemness ([208,211]; see also; http://linnarssonlab.org/dentate/). Alluding to putative functional implications of these observations, the ApoE4 isoform constitutes the most prevalent genetic risk of AD, whereas ApoE was recently shown to regulate the functional integration of adult-born hippocampal neurons into the dentate network [217].

Given some of the noticeable technical advantages of snRNAseq over scRNAseq, including reduced dissociation bias, compatibility with frozen and fixed samples, and the elimination of dissociation-induced transcriptional stress responses, together with their comparable transcript detection power in certain tissue preparations [218], it is anticipated that snRNAseq and/or the development of high-definition spatial transcriptomics [219] will pave the way for future studies aimed to understand the functions of human adult hippocampal NSCs. Such studies may shed new light on the developmental stages and transcriptional dynamics of NSCs, progenitors, and their subtypes. Also, by comparing perinatal, juvenile and adult mice, the molecular dynamics and diversity of dentate gyrus cell types could be revealed and shifts in the molecular identity of quiescent and proliferating radial glia *vs* adult granule cells could be identified and monitored in relation to developmental and chronological age.

Fundamental similarities have already been described for postnatal and adult neurogenesis in the rodent hippocampus [209] and interesting results have been obtained for human brain as well [212,215,220]. Importantly, transcriptomic analyses in human and non-human primate brain tissue and cerebral organoids also revealed certain evolutionary and molecular constraints to orthologous gene expression across species, pointing towards particular human-specific neurogenic traits [221,222].

Together, these findings corroborate previous histological evidence and support a unique role for neurogenesis in human brain specification, physiology and disease. The holistic view of the cellular and molecular complexity in the mammalian brain that emerges from the

recent scRNAseq and snRNAseq studies will enable us to systematically interrogate the molecular and cellular regulators of the hippocampal neurogenic niche upon physiological aging and in neurodegeneration. Appreciating the contribution of distinct cellular populations to the 'fitness' of the niche and understanding the mechanistic underpinnings of the interaction between NSCs, NPCs and other niche residing cells, like microglia and astrocytes, will be of particular importance herein.

Interestingly, NSCs and NPCs have been shown to exert immunomodulatory functions, which they gradually lose upon aging or with disease progression in AD mice [223,224]. Conversely, deficits in hippocampal neurogenesis could be rescued by depletion of microglia in a genetic mouse model of AD [225]. These observations along with the emerging roles of microglia in aging and AD brain, emphasize the need to systematically study the aging or diseased hippocampal niche as a complex multicellular system.

Although several technical and statistical drawbacks still exist, and a side-to-side comparison between scRNAseq and snRNAseq data in human brain tissue is currently pending, existing evidence suggests that the profiles of single cells largely resemble the patterns obtained after sequencing of single nuclei. This allows for profiling of human tissues archived in brain biobanks worldwide, which may help to advance the field as such profiling of newborn cells will allow better characterization of the different types of neuroblasts and their progression through the neurogenic lineage in the human hippocampus. Applying scRNAseq and/or spatial transcriptomics [219] to investigate transcriptome changes in an age range of post-mortem human hippocampi might also help to identify novel specific markers of hippocampal neurogenesis and address aspects of the relative age of the newborn cells and their proportions in the hippocampus at different ages.

More specifically, single-cell interrogation of the aging or diseased adult hippocampal niche in human brain may also allow the dissection of non cell-autonomous senescence- or neurodegeneration-related molecular regulators of adult neurogenesis, adding to the list of neurotrophic factors, proinflammatory stimuli, amyloid beta, systemic cues and others. Moreover, in addition to DCX, PSA-NCAM, SOX-2 or PROX1, these molecular approaches may result in other suitable, and possibly more stable, markers that could be used to uniquely identify and/or selectively label neuronal precursors or young neurons. Particularly with respect to neurodegeneration and given the mechanistic pleiotropy and pathophysiological complexity of neurodegenerative disorders, mapping the scRNAseq data to their functional [215] and spatial [226] context will be crucial, as it can provide invaluable insights into the role of adult neurogenesis in physiological and pathological aging.

On the other side of the spectrum, non-invasive *imaging and biomarker studies* utilizing magnetic resonance spectroscopy (MRS) could help investigate changes in neurogenesis related metabolites in the live human hippocampus in relation to specific challenges, tasks, or disease states. MRS was used before to examine neural stem cells and neurogenesis. In a series of *in vitro* and *in vivo* studies, Manganas et al., [140] showed that, in particular, a lipid-signal is enriched in the human hippocampus *in vivo*. In extensive validation experiments, the authors examined several types of stem and precursor cells, cells undergoing neuronal differentiation, and a variety of post-mitotic cells *in vitro* and found a selective enrichment of a lipid-rich signal in the stem/progenitor population, but not in other cell types such as astrocytes and neurons. Similarly, the changes in lipid signal were of a similar magnitude after ECS stimulation *in vivo* as after histological analysis of the BrdU-positive cells in the postmortem brains of the same animals [140].

Based on these data, the authors hypothesized that the lipid signal is enriched in human neural stem/progenitor cells and would therefore be more abundant in the hippocampus than in other brain regions where these cells do not reside. Indeed, MRS in a cohort of pre-pubertal, post-pubertal and young adults found abundant signal in the hippocampus compared to cortical/white matter. This report received criticism as methodology used to detect the lipid signal required high technical expertise and was not automated, thus introducing bias from the operator. Moreover, it extracted the signal from a very noisy area of the spectra without *a priori* knowledge on the type of molecule being detected. Over the past decade, however, these criticisms are being addressed and this emerging technology has been making progress toward more robust and automated studies in humans [141,227–229,153,230].

While providing an indirect measure of human neurogenesis *in vivo*, MRS could thus be a valuable tool to study its relation to pattern separation, stress, cognition, mental health and lifestyle and some attempts in that direction have been made [134,155,231,232]. In this respect and in terms of biomarkers, the recent links between stem cell metabolism [233] and fatty acid metabolism are very interesting. Clearly, stem cells utilize a unique source of energy and their energy metabolism likely requires specific lipids. Advanced MRS approaches for the detection of such *in vivo* neurogenic biomarkers will prove to be very valuable. Ultimately, for any measure of hippocampal neurogenesis, it would be informative to combine with measures of functional brain activity.

8. Open questions

Looking forward, we can conclude that following yet another dynamic phase in this field's development, the occurrence of adult neurogenesis in the human brain has been (re-)established. Yet, aside from methodological and functional aspects, many open conceptual questions remain. For one, the differences between developmentally-generated and adult-generated newborn cells is relevant as these cells may have quite different properties and capacities [234–237], but are likely hard to distinguish from one another using current histological methods in human brain. Based on rodent studies, many of the newborn cells are adult-generated, but a considerable proportion of the granule neurons present in the adult human hippocampus has likely been generated around birth, while also specific subsets may die [235]. The birth rate of these cells likely decreases with advancing age and at least in rodents, the process of neurogenesis in the developing dentate gyrus undergoes a transformation from the embryonic to the postnatal period around P14, which is coupled with an increase in neural stem cell differentiation towards neuroblasts rather than glia [209] while also complex migratory patterns are seen [237].

The developmental time window of newborn neurons differs between species and most likely also decreases at a different speed during the lifespan of an individual [203]. As these young, presumably still immature, granule neurons have different properties compared to the older and later-born granule cells, and are relatively more numerous early in life, this implies that young granule cells can also make a unique contribution to hippocampal circuits. Relative to the rate of neurogenesis in rodents, newborn neurons in humans may go through a more extended period of *maturation* (order of months), during which time this subset of cells may retain an enhanced plasticity and could serve important functions within the hippocampal network. Whereas the continued addition of new neurons may provide plasticity in adult rodents, the prolonged development of neurons born earlier in life could provide similar levels of plasticity in adult humans without the effort to produce entirely new population of cells (see also [66]).

Another possibility is that granule cells born in adulthood never become truly identical to those born during early development. One function of the early postnatal hippocampal neurogenesis may be the weakening of existing memories and information storage in favor of strengthening the ability to learn new knowledge and to acquire new information through a rapid and continuous generation of large number of new granule neurons. Hence, it will be important to understand to what extent the different populations of newborn cells, born at different ages, may contribute to overall dentate or hippocampal functions, and to what extent they, and the circuitry they reside in, are influenced by the addition of later born adult-generated neurons, and/or emerging pathology.

In the absence of the BrdU or viral-mediated birth-dating approaches, as are traditionally used in animal models, the identification of additional markers or tools may help determine the birth date or age of individual newborn cells in humans. Whether these originate from the single-cell sequencing approaches or from further development and testing of new antibodies, it will be important to develop them for application on human postmortem brain tissues, with all the necessary methodological requirements as discussed above.

Regarding open questions for the field, first and foremost, it is unclear whether human neurogenesis is regulated to the same extent and by the same environmental and molecular factors as those known from rodent studies. Which molecular factors define the neurogenic niche in humans? How is the integration of stem cells into the existing human hippocampal circuitry enabled? Which factors determine their initial and long-term survival? What is their functional role? How can adult-generated neurons modulate hippocampal network functions in humans?

It further remains elusive how neurogenesis, or the lack of it, can contribute to pathologies that originate in, or relate to, the dentate gyrus, from epilepsy to AD? Based on [32], adult neurogenesis appears to be reduced already early in AD, so a better understanding of their (causal) involvement in diseases like cognitive decline and dementia, but also anxiety and major depression, is needed. Does an early decline in neurogenesis reflect an increased disease vulnerability and if so, is the neural stem cell population 'primed' and affected in AD early on? Intriguingly, the N-methyl-D-aspartate receptor antagonist, memantine, which is currently prescribed as an AD medication, has been shown to increase the number of hippocampal NSCs and adult-born neurons in preclinical rodent studies [238,239], providing indirect evidence for the possible benefits of therapeutically targeting adult neurogenesis in AD.

What role does neurogenesis, and its stimulation during critical periods, play in modulating the hippocampal circuit [240] and in building or preserving a cognitive reserve and later resilience to disease? In contrast, exposure to early life stress or early inflammation during critical periods could suppress neurogenesis in a lasting manner and pose a risk for disease development later in life [241]. Can hence an early stimulation of neurogenesis be protective in this respect and would harnessing or restoring neurogenesis before disease onset or during disease progression (in AD, for example) have the potential to enhance the 'fitness of the niche' and of the hippocampal circuitry as a whole? In rodents, recent evidence indicates that adult neurogenesis modulates DG inputs [240], induces global remapping in the dentate gyrus [242] and can protect the hippocampus from neuronal injury following severe seizures [243]. Reversely, early seizure activity depleted NSCs, impairing cognition in an AD model [244].

These, and many other questions are still open, yet intriguing, challenging and exciting. Together with novel experimental approaches, as discussed above, they will help set the stage for a better comprehension and utilization of human hippocampal neurogenesis to its fullest potential, *i.e.* understanding its contribution to human hippocampal functions and related disorders like depression and dementia.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bbr.2019.112458.

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