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SPECIAL ISSUE

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Changes in neurogenesis in dementia and Alzheimer mouse models: are they functionally relevant?

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Abstract Alzheimer's disease and related dementias are devastating disorders that lead to the progressive decline of cognitive functions. Characteristic features are severe brain atrophy, paralleled by accumulation of beta amyloid and neurofibrillary tangles. With the discovery of neurogenesis in the adult brain, the hopes have risen that these neurodegenerative conditions could be overcome, or at least ameliorated, by the generation of new neurons. The location of the adult neurogenic zones in the hippocampus and the lateral ventricle wall, close to corpus callosum and neocortex, indicates strategic positions for potential repair processes. However, we also need to consider that the generation of new neurons is possibly involved in cognitive functions and could, therefore, be influenced by disease pathology. Moreover, aberrant neurogenic mechanisms could even be a part of the pathological events of neurodegenerative diseases. It is the scope of this review to summarize and analyze the recent data from neurogenesis research with respect to Alzheimer's disease and its animal models.

Key words Alzheimer's disease · neuronal progenitor cells · amyloid precursor protein · tau · presenilin

Introduction

In this review, we will discuss recent studies on the role of adult neurogenesis in dementia and Alzheimer-related mouse models, as well as focus on the functional relevance of these findings where possible.

Dementia is a devastating disorder affecting millions of patients in the Western world, resulting in progressive memory loss and cognitive deficits. The most common form is *sporadic* Alzheimer's disease (AD), which is characterized by the abundant presence of beta-amyloid peptide (Aß)-containing senile plaques, derived from amyloid precursor protein (APP), as well as many neurofibrillary tangles (NFTs), mainly consisting of hyperphosphorylated tau protein. Early onset and familial forms of AD are caused by mutations in APP, presenilin1 or 2 (PS1/2), resulting in the overproduction of fibrillogenic Aß species. Alterations in APP and protein tau processing cause accumulation of aberrant amyloid and hyperphosphorylated tau species. These induce progressive neuronal dysfunction and degeneration, resulting in cognitive deficits, DNA damage, brain atrophy and eventually cell death in a limited number of brain areas [61, 67, 68]. Furthermore, AD is, a heterogeneous disorder with a wide variation in age of onset, disease duration and neuropathology and, in many instances, plaque load does not necessarily correlate with the patients symptoms. Despite considerable progress in understanding the biochemical, genetic and molecular mechanisms underlying AD, knowledge of its etiology is still very

Abbreviations: AD: Alzheimer's disease, APP: amyloid precursor protein, Aß: beta amyloid peptide, BDNF: brain derived neurotrophic factor, BrdU: bromo-deoxyuridine, CA: cornu ammonis, CNS: central nervous system, DCX: doublecortin, DG: dentate gyrus, FGF-2: fibroblast growth factor 2, IGF-1: insulin-like growth factor 1, LTP: long-term potentiation, MAP: microtubule-associated protein, NFT: neurofibrillary tangle, PCNA: proliferating cell nuclear antigen, PDGF: platelet-derived growth factor, PS: presenilin, RMS: rostral migratory stream, SGZ: subgranular zone, SVZ: subventricular zone, VEGF: vascular endothelial growth factor

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poor and effective treatment or prevention of the disease remains elusive.

Despite various strategies aimed to slow down or stop the degenerative process of amyloid accumulation and/or the associated inflammatory processes, current research strategies focus on the regeneration of damaged tissue. This could potentially take place by utilizing the therapeutic potential of stem cells and introducing or recruiting them into damaged brain regions and to stimulate differentiation into new neurons. Since the proper delivery of exogenous neural stem cells to restricted areas of the affected AD brain still remains a major challenge, the discovery of ongoing neurogenesis and endogenous stem cells in the adult brain and their regenerative potential holds considerable promise for restoring neuronal populations and regeneration of functional neural circuits. Various studies have now shown that it is specifically the local microenvironment within the brain that determines the neurogenic potential and phenotypic differentiation properties of endogenous, as well as exogenously transplanted, stem cells. Hence, it is critical to first obtain a proper understanding of the effects of the AD disease process and its main mediators on the endogenous stem cell population.

Hippocampal Neurogenesis

The hippocampus, which is severely affected in dementia, is well known for its involvement in cognitive processes, such as learning and memory [47]. It is unique in that it is one of the very few brain regions where neurogenesis continues to occur in the adult [4]. Progenitor cells located in the subgranular zone (SGZ) of the adult hippocampal dentate gyrus (DG) undergo extensive proliferation before they migrate into the granular cell layer [59]. In young adult rats, approximately 9000 new cells are born per day per dentate gyrus. Many of these adult-generated cells die within the first few weeks [19, 28]. This selection is probably determined by local neuronal activity and trophic support [29]. Significant proportions of the new cells survive and differentiate into mature neurons that are functionally active and incorporated into the hippocampal circuitry. In addition to the dentate gyrus, neurogenesis occurs in the subventricular zone (SVZ) of the lateral ventricle. Here, committed progenitor cells migrate via the rostral migratory stream (RMS) into the olfactory bulb where they differentiate into interneurons that are involved in olfactory discrimination learning [3, 37].

Even though adult dentate neurogenesis is prominent in young rodents, the amount of neuronal progenitors rapidly decreases over the following months [12, 59, 45, 58, 76] and is present at much lower levels in adult and particularly aged animals. Additional studies have shown that similar levels exist in older primates [41, 57]. The very few studies on this subject indicate that the adult and elderly human brain is no exception in this respect [8, 10, 30, 35].

Regulation of neurogenesis

Adult neurogenesis is controlled by a wide array of intrinsic growth factors, hormones and environmental factors. Environmental factors, such as enriched environmental housing, learning experiences, or physical exercise stimulate neurogenesis; however, aging, glucocorticoid hormones or stress potently inhibit neurogenesis. It is important to note that a variety of stimuli can affect different stages of the neurogenic process [54], each targeting a specific developmental stage during the maturation of adult-generated cells.

Consistent with the vital role of the hippocampus in cognition, many studies have found changes in adult neurogenesis to be paralleled by changes in hippocampal functional plasticity and/or learning and memory performance [54]. Given the functional incorporation of adult generated cells in the hippocampal circuit [100], and observations that hippocampal learning also increases neurogenesis, it has been proposed that adult neurogenesis directly, or indirectly, contributes to adaptations in hippocampal functioning. Conversely, any pathological alteration within the trisynaptic hippocampal circuit can induce changes in neurogenesis. Of the many regulatory stimuli, neurogenesis is also spontaneously stimulated by hippocampal or cortical damage, for example, by acute excitotoxic, ischaemic or epileptic insults [9, 26, 48, 51, 80]. Some of the regulatory factors involved could be hypoxia-inducible peptides such as BDNF, IGF-1, FGF-2 and VEGF. These growth factors are upregulated after ischemic damage [38, 55, 82, 88]. In addition, they are known stimulators of adult neurogenesis [1, 60, 87, 111]. Although it is not known whether neurogenesis is also upregulated after *chronic* lesions, or during "slow" neurodegenerative processes such as expected to occur in AD, it has been speculated that either aberrant or reduced neurogenetic responses are involved in the cellular pathology in AD.

Cell cycle markers in AD brain

Of particular interest are observations on the re-expression of unique cell cycle proteins that are associated with specific stages of the cell cycle and are found, in particular in the hippocampus [6, 16, 56, 72, 77, 93, 101, 107]. In AD, neurons containing neurofibrillary tangles, in both the structurally dynamic dentate gyrus, as well as in the more "stable" cornu ammonis (CA) area, were shown to co-express various cyclins, mitotic phosphoepitopes and cyclin-

dependent kinases [6, 15, 56, 72, 93, 101]. This phenomenon has initially been interpreted as endangered or damaged neurons that attempt to re-enter the cell cycle [16, 46, 56, 93]. Subsequently, the hypothesis was put forward that re-expression of cell cycle markers such as PCNA and cyclins, could also be part of a more general regenerative process that, in principle, may lead to the production of new neurons in the adult brain.

Thus far, the supporting evidence from mouse models demonstrates that the induction of cell cycle changes after the onset of amyloid pathology is limited [108]. This could depend on the limited age of the rodent species studied, or on the artificial condition of transgene-controlled protein expression that is intrinsically different from the human situation. Re-expression of these markers in mature neurons in the human brain may either induce an abortive exit of the cell cycle and induce apoptosis, or alternatively, lead to long-lasting cell cycle arrest, which would cause permanent cellular dysfunction. As it has not yet been convincingly shown that neurons in the adult brain are capable of mitosis, cell cycle protein expression in mature neurons is regarded as a generalized and maladaptive response of cells "stuck" in a cycle they can not complete, thereby causing cell death [107]. The question of whether or not the disease process induces compensatory birth of new neurons or specific changes in dentate neurogenesis in AD and related mouse models still needs to be addressed.

Neurogenesis in Alzheimer brain

As of yet, only a few studies have reported changes in the expression of immature neuronal markers in AD. One report showed increases in various immature neuronal markers in a cohort of senile AD cases, suggesting that neurogenesis could be increased in AD [50]. In another study, in a younger cohort of presenile patients in which the disease is more severe and often runs a faster course, these results could not be replicated [10]. Here, the number of cells expressing the cell cycle marker Ki-67 was significantly increased. However, more detailed analysis revealed that this was largely due to proliferation in non-neuronal compartments, such as glia and the vasculature, and that differences in the main neuronal layers of the dentate gyrus and the CA region between the groups were not found.

Additional causes for these discrepancies could be due to the age difference between the cohorts. Senile dementia is generally associated with a slower deterioration of cognition over time, whereas presenile dementia often presents much more severe pathology, and reactions to hippocampal injury are expected to be more prominent in the younger group. Regardless, no indications were found for increases in neurogenesis in presenile AD [10]. It should be noted that also methodological issues of postmortem delay and fixation time could have been responsible for these results. One example is the detection of the double-cortin (DCX)-expressing young neuronal population, which was reported to accurately reflect adult neurogenesis levels in rodents [14, 25, 84]. Unlike BrdU, detection of DCX does not require injections of BrdU in live subjects, which makes DCX a promising putative marker for neurogenesis in the postmortem brain. Quantification of DCX in the Jin et al. [50] paper was, however, based solely on Western-blot analyses of only a selection of patients. Unfortunately no anatomical quantification was available for the DCX-positive cells. Furthermore, DCX, like many other microtubule-associated proteins [95], was found to be very sensitive to degradation during postmortem delay [10] and as such, this marker may not be very reliable for the detection of quantitative differences in neurogenesis in the human brain. In any case, careful matching of patients and controls for postmortem delay is required.

Given these methodological pitfalls, the limited availability, the medication of each individual and the "end-stage" quality of human postmortem AD tissue, various groups have taken another approach by focusing on mice models that overexpress selective AD-related proteins, such as APP, PS or tau [for reviews see 40, 94]. Although aspects of redundancy and indirect effects are important, these models not only recapitulate various aspects of AD and frontal temporal lobe dementia, but may also provide a basis to address the issue of cause and effect, as well as the temporal aspects of neurogenesis in relation to the onset of neuropathology and neuronal dysfunction. The study of neurogenesis in human brain material has not only several methodological limitations, commonly used immunohistochemical methods for studying neurogenesis, such as timed BrdU injections and subsequent stereological quantifications, are ethically difficult and technically complicated to perform in human brain tissue. It is currently impossible to address whether changes in neurogenesis have contributed to amyloid-mediated neurodegeneration, whether they are a direct result of the initial pathology or of other causes, such as a non-permissive local microenvironment.

Neurogenesis and AD mouse models: APP and presenilins

In an attempt to link changes in neurogenesis to specific aspects of the disease, such as tauopathy or amyloid pathology, various mouse models of AD have recently been studied [40, 71, 94]. The majority of these have been APP- and/or PS1-based mouse models, and to a lesser extent tau transgenic mice. An alteration in neurogenesis is to be expected in AD mouse models for a number of reasons. Even though

the exact cause of the age-associated decline in neurogenesis remains to be determined, the loss of growth factors from the local hippocampal microenvironment, such as FGF-2, IGF-1, BDNF and VEGF, which are potent stimulators of adult hippocampal neurogenesis and neural stem cell growth in vitro, indicates a reduced neurogenic potential with age [42, 90]. This bears considerable relevance for AD, where many of these growth factors are reduced in their expression as well. Given the stimulatory effects of various growth factors and also of Aß (see below) on stem cells in vitro, this could provide a putative mechanism for an impairment of neurogenesis in AD.

Similar arguments hold for the prominent loss of cholinergic neurons and innervation in AD, which may contribute to impaired neurogenesis [23, 75, 98]. Even though the exact function of APP remains elusive, presenilin 1 (PS1) not only has a well-established role in gamma-secretase cleavage, but is also known for its prominent role in regulating beta-catenin, a protein involved in Wnt signaling, which is known to regulate hippocampal neurogenesis [65]. In addition, neurogenesis may be changed in mutant AD mice due to a 'loss of function' of normal sAPP and PS1. We will first discuss APP and PS1 mutant or deletion studies.

Neurogenesis in the hippocampal dentate gyrus is decreased in mice overexpressing the APP (Tg2576) mutation [33, 34]. Neurogenesis has been found to be unaltered as long as Aβ pathology is absent; however it decreases as soon as plaque pathology becomes evident, either in an Aβ peptide injection model or in a mouse model expressing the APP mutant under control of the platelet-derived growth factor promoter (PDGF-APP)[34, 44]. In contrast to the decrease in the number of dividing cells within the SGZ, PDGF-APP mice had significantly increased numbers of immature neurons in the outer portion of the granule cell layer. Whether the occurrence of these ectopic cells is due to abnormal APP function awaits further study, but changes in this subregion may at least explain some of the discrepancies with previous studies that combined all dentate gyrus subregions in their quantitative analysis. In other mouse models carrying 3 mutated PS1 variants M146V, P117 or A246E), neurogenesis was also found to be decreased [22, 102, 104].

Together, these studies suggest that Aβ pathology decreases, rather than increases [49, 108] neurogenesis. However, it is, important to note that changes in neurogenesis depend on the pathological state [34, 44], an assumption that is further supported by studies of Wen et al., who reported increases in hippocampal neurogenesis in a cohort of mice overexpressing wildtype, but not mutated (P117L) PS1 [103]. In a later study the same authors found decreased neurogenesis in mice overexpressing mutant PS1 whereas no effect of wildtype PS1 over-expression was found [104]. The only difference between these studies was the age of the animals, which was higher in their 2004 paper. Hence, effects of wildtype PS1 on neurogenesis is either positive or neutral, whereas mutated PS1 had a neutral or negative effect on neurogenesis. The difference within one genotype depends on the age of the animals, suggesting a clear age-dependency for the effects of PS1 on neurogenesis. Interestingly, it has been shown that aggregated Aβ 42, and not the soluble and smaller forms of Aβ, can increase neurogenesis in vivo and exerts neurogenic effects on stem cells in vitro [66, 79]. Moreover, infusions of APP into the lateral ventricle increased neurogenesis [18] and it has been suggested that neurogenesis in the SVZ might be regulated by astroglial expression of APP [109]. But negative effects of Aß 42 on progenitor cell in vitro were also reported [43, 44].

Modulation of Neurogenesis; Enriched Environment

Under normal conditions, environmental enrichment serves to increase hippocampal neurogenesis; however, in PS1 knockout mice, which produce less amyloid, there was no increase in hippocampal neurogenesis after enrichment. This reduction was mainly due to a reduced proliferation, rather than the survival of the newborn cells [36]. Interestingly, this was paralleled by tau hyperphosphorylation, neuronal atrophy, increased astrogliosis, and associated with a reduced clearance of hippocampal memory traces. These data correlate with in vitro findings of increased neuronal differentiation of stem cells after Aß stimulation [66], but they differ from results showing that Aβ pathology reduces neurogenesis in vivo [33, 34, 44, 102]. It is, however, important to note that no pathology is present in PS1-deficient mice [18, 36, 109] (Fig. 1). Considering the roles of both APP and PS1 in embryonic development, e.g., as regulators of Wnt signaling [20–22, 105], both genes are likely to be of general importance during developmental and adult neurogenesis. Therefore, stimulatory effects of APP on increased neurogenesis could reflect a developmental role rather than a pathological one. A developmental role is further supported by the fact that the total number of neurons was found to be increased at 8 months of age (no pathology present) in the neocortex of mice overexpressing the swedish mutation (APP23 mice). However, at 27 months of age, these mice have developed a considerable plaque load that negatively correlated with the number of neurons [13].

In conclusion, the effect of increased or mutated Aβ production on neurogenesis appears to depend on two factors: the developmental stage of the animal and the presence or absence of pathology. Obviously, these two parameters are not independent of each other, since most PS1 or APP mutated mice show increased pathology with age. Altered APP or PS1

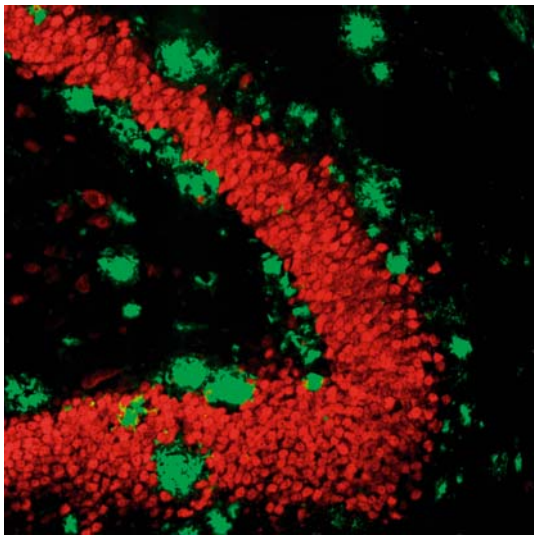

Fig. 1 Plaque formation in the dentate gyrus of a 9-month-old transgenic mouse expressing mutant APP and PS1 under the Thy-1 promoter. Interestingly, plaques (green) occur rather surrounding than inside the granule cell layer. Neuronal cell bodies (red) are visualized with an antibody against the pan-neuronal marker protein NeuN. Image size: 400x400 μm

expression can increase neurogenesis in younger animals when Aβ pathology is still absent; however, it decreases neurogenesis in later stages when Aβ pathology is present.

In contrast to these studies, Jin and colleagues have shown an increase in hippocampal neurogenesis of PDGF promoter-APP transgenic mice that bear both the Swedish and Indiana mutations [49]. These effects were found both at 3 months of age, still in the absence of plaques, and at 1 year of age, at which time the hippocampus contained many plaques. Of importance, a considerable number of BrdU positive cells in the hilus and molecular layer appear to contribute to the total number of newborn cells [34, 49]. This study differs even further from others with reference to the SVZ, where at 3 months of age, no difference was found in the number of dividing cells; however, a significant increase was detected at 1 year of age [49]. These data suggest quite the opposite hypothesis, namely that amyloid pathology, at least to the extent that it is derived from 2 different APP mutations, increases neurogenesis.

Interestingly, various cell-cycle events were found to be increased in different strains of APPswe mutant mice [108], which resembles the situation in human AD where ectopic expression of cell cycle markers has been reported repeatedly and mostly coincided with post-mitotic neurons. Therefore, in contrast to the conclusion of Jin et al. [50], an alternative explanation is the expression of cell cycle markers in dying cells. This also suggests that amyloid affects cell division rather than survival of neurons.

If we were to translate the data from animal models to the familial human AD situation, one would expect neurogenesis to be decreased rather than increased, with APP and/or PS1 as risk factors. Clearly, this contrasts from recent literature where neurogenesis was reported to be either increased or unaffected in a sporadic, senile cohort [50] or in a presenile cohort [10] respectively. Aside from different methodologies, one obvious explanation could be that human AD pathology is more complex than altered APP expression alone, and e.g. also changes in tau expression are implicated. Moreover, although APP pathology may not directly stimulate neurogenesis, the resulting neuronal dysfuntion, damage, and cell loss could increase cell birth in an indirect manner, similar to other brain injuries, e.g., ischemia.

Protein tau and neurogenesis

Considering the wealth of data on neurogenesis in relation to amyloid pathology, remarkably few studies have addressed the possible link between protein tau and neurogenesis. This is especially striking since an extensive in vitro literature suggests a prominent role for tau, as well as other microtubule-associated proteins (MAPs), in structural plasticity during neuronal development, including processes as tightly linked to neurogenesis as cytokinesis, neuronal maturation and neuritic outgrowth [5, 17, 39, 91]. Furthermore, tau phosphorylation, as it occurs in AD, closely resembles tau phosphorylation during mitosis [27, 32, 83]. Moreover, many of the cell cycle alterations in AD have been linked to tangle pathology [16, 46, 56, 93]. Together, this strongly suggests an important role for tau in mitosis and neurogenesis.

It is thought that for mitosis to occur, microtubule growth must take place rapidly, without the microtubules losing their flexibility, otherwise the event could turn catastrophic, resulting in a rapid shrinkage of microtubule length. According to the current "search and capture" model, the plus ends of microtubules grow randomly out of the centrosome and capture the duplicated chromosome. When this takes place, the microtubules are stabilized; however, without stabilization, the spindle pole collapses and the microtubules shrink back to the centrosome [73, 74]. Whereas the recently discovered microtubule XMAP215 facilitates both growth and shrinkage, wild type tau protein facilitates growth, as well as rigidity of microtubules, thus preventing the occurrence of microtubule catastrophe and shrinkage [78]. Taken together, these data suggest that a possible role for tau in mitosis is likely to be an inhibitory one.

In vivo, the tau mutation P301S was found to be associated with overexpression of the cell cycle-dependent kinase inhibitors p21/Cip1 and p27/Kip1 [31]. Moreover, the tau P301L mutation leads to a changed regulation of cyclins, inducing cell cycle arrest in G2 and M phase [110]. In contrast, a recent study focused on mutant tau P301L in young mice

and failed to show any effect on neurogenesis; however, significant increases were found in longterm potentiation, that were associated with improved cognitive performance in the hippocampal-dependent object recognition task [11]. This is one of the first studies in which changes in neurogenesis and functionally-relevant changes in the hippocampus, i.e. LTP and cognition, have not been linked with one another. These data further suggest that in the absence of age-related accumulation of tau phosphorylation, this familial tau mutation may not impair learning and memory, but rather improve it at young ages.

Therefore, independent of neurogenesis, protein tau plays an important role in neuronal processes underlying hippocampal memory. Conversely, it may not be the tau mutation per se, but rather the ensuing hyperphosphorylation, that is responsible for the cognitive decline observed in tauopathies. Taken together, the abovementioned data suggest that overexpression of wildtype or mutated tau is unlikely to promote neurogenesis. However, reduced tau expression may be associated with increased neurogenesis, at least within a specific postnatal period [89]. This is consistent with the inhibitory role of tau during mitosis, as suggested by others [31, 78, 110].

The fact that tau can inhibit neurogenesis does not imply that neurogenesis is inhibited in AD, where overexpression of tau occurs. In AD, a large proportion of tau is thought to be hyperphosphorylated, which may lead to reduced microtubule binding and could, therefore, result in reduced neuronal functioning. And finally, this could possibly lead to increased neurogenesis. While altered APP processing is likely to decrease neurogenesis, increased tau phosphorylation may actually result in the opposite effect. To test these hypotheses, it would be interesting to study the effect of tau phosphorylation on mitosis in various models, e.g., hippocampal cultures or in vivo.

Preventive strategies for AD and neurogenesis

Although there is currently no cure for AD, significant progress has been made in defining lifestyle conditions that promote healthy brain aging and, to some extent, delay the onset of AD. In clinical studies, poor social interaction, physical exercise, nutrition and cognitive stimulation have been singled out to be risk factors of AD onset and progression [7, 62, 86, 92]. In parallel, experimental studies found positive effects of enriched environment, physical exercise and caloric restriction on accumulation of plaques in transgenic AD models [2, 63, 81, 106]. Although the functional link to neurogenesis and other forms of structural plasticity is not fully established, it is again intriguing to note that all of these lifestyle factors are prominent stimulators of adult hippocampal neurogenesis [52, 53, 64, 99] as well as other forms of plasticity [24, 69, 85, 96, 97]. It is, therefore, crucial that patients are made aware of the beneficial effects of these lifestyle parameters on neuroplasticity and disease onset, even if definitive proof of beneficial effects of increased neurogenesis in AD has not yet been provided [70].

Concluding statement

The complex changes that occur during the course of AD are likely to disturb the microenvironment in which neurons are generated from neuronal progenitor cells. We reviewed conflicting data on altered progenitor activity and neurogenesis. The discrepancies between these studies can be attributed to multiple factors, such as different phases of AD progression, animal models, as well as methodological and analytical tools. The accumulation of amyloid plaques and fibrillary tangles are hallmarks of AD; however, additional pathological mechanisms, such as altered neurotransmission and inflammation, could very well contribute to the varied neurogenic response. Whether the changes in neurogenesis are functionally relevant, and whether neurogenesis improved through pharmacological intervention could make a difference for the progression of AD, remains open. Current approaches to increase or decrease adult neurogenesis show a covariation with other forms of plasticity, e.g., at the level of the synapse, dendrite and glial cells, which makes it difficult to prove functional relevance of neurogenesis. Nevertheless, pharmacological or physiological improvement of neuroplasticity per se, including increased neurogenesis, is worth pursuing in order to ameliorate the cognitive deficits of these severe disorders.

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