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SPECIAL ISSUE

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Neurogenesis and schizophrenia: dividing neurons in a divided mind?

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Abstract Forty years after the initial discovery of neurogenesis in the postnatal brain of the rat, convincing evidence has been accrued that functional neurons are generated throughout the entire lifespan, particularly in the dentate gyrus (DG) and the subventricular zone (SVZ). This phenomenon has been termed adult neurogenesis (AN) and while it was detected in all examined mammalian species including humans, the physiological role of this process remains unknown. Although a plethora of animal studies indicate an involvement of AN in the pathophysiology of depression, this view has recently kindled considerable controversy. Pertinent studies in humans failed to confirm a role of reduced hippocampal neural stem cell proliferation (NSP) in depression but suggest a contribution to the pathophysiology of schizophrenia. The functional relevance of disturbed AN may encompass erroneous temporal encoding of new memory traces, thereby contributing to cognitive deficits observed in schizophrenia. This AN-hypothesis of schizophrenia is supported by neuroimaging, as well as by several genetically modified rodent models, e.g. *reelin* and *NPAS3* knockout mice. Furthermore, several genes impacting on AN, including *NPAS3*, were also found to be associated with schizophrenia by case-control studies. In conclusion, several lines of evidence suggest that reduced AN may contribute to the etiopathogenesis of schizophrenic disorders, whereas it does not seem to be a critical risk factor for affective disorders.

Key words adult neurogenesis · schizophrenia · candidate genes · neuronal stem cell · psychiatric disorder · postmorten study · NPAS3

Abbreviations: AN: Adult neurogenesis, BDNF: Brain derived neurotrophic factor, BrdU: 5-bromo-2-deoxyuridine, DG: Dentate gyrus, DISC1: Disrupted in schizophrenia 1, ECT: Electroconvulsive treatment, FGF-2: Fibroblast growth factor 2, GCL: Granule cell layer, NMDA: N-methyl-D-asparate, NO: Nitric oxide, NOS-I: Nitric oxide synthase type I (neuronal), NOS-III: Nitric oxide synthase type III (endothelial), NPAS3: Neuronal PAS domain protein 3, NSP: Neural stem cell proliferation, OB: Olfactory bulb, PCP: Phencyclidine, PPI: Pre-pulse startle inhibition, SGZ: Subgranular zone, SVZ: Subventricular zone, TLE: Temporal lobe epilepsy, VEGF: Vascular endothelial growth factor, Wnt: Wingless-type MMTV integration site family, Wnt 3: Wnt member 3

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Introduction

It is now well established that the adult brain has the potential to generate new functional neurons from neural stem cells [35], a phenomenon which has been termed adult neurogenesis (AN). AN has been confirmed in a variety of species and attracted considerable attention in the neuroscience community, especially following the seminal study by Eriksson demonstrating AN in humans [28]. Neuroneogenesis only takes place in few, well-defined brain areas: the subventricular zone (SVZ), i.e. the boundary between the striatum and the lateral ventricle, from where newborn cells migrate along the rostral migratory stream to the olfactory bulb (OB); and the dentate gyrus (DG), where neural stem cells are aligned along the subgranular zone (SGZ). The first step—termed proliferation—of AN is the "unbalanced" or unidirectional division of neural stem cells, to generate another stem cell as well as a neural progenitor cell. The latter starts migrating through the

granule cell layer (GCL) paralleled by differentiation from an undifferentiated neuroblast to a mature neuron; only a few neural progenitor cells transform into glial cells. This second step of AN is usually summarized under the term "survival", as only a small number of newborn cells (~10%) finally undergo terminal differentiation to functional neurons. Two weeks after the formation of the progenitor cell, the immature neuron's dendrites branch and start to receive glutamatergic input from the entorhinal cortex. Finally, the mature neuron is integrated structurally and functionally into pre-existing neural networks [103, 111]. Evidently, the process of AN is fine-tuned requiring complex regulatory mechanisms hitherto incompletely understood.

Even more enigmatic than its regulation are the functional consequences of AN. AN in the DG was linked to hippocampus-dependent learning tasks (for a review see [57]), e.g. spatial learning. However, the state of affairs appears to be more complex (see the contributions of Kempermann et al. and Kuhn et al., in this issue). In summarizing findings from rodent studies, hippocampal AN not surprisingly appears to have a role in specific learning and memory tasks of this very structure, yet its precise role remains uncertain, and even more so in nonhuman primates and humans.

Neurogenesis and depression

With the wide availability of neuroimaging techniques, morphometric studies in psychiatric disorders have become increasingly popular. Consistent across several MRI studies, hippocampal volume was found to be reduced in unipolar depression. Obviously, the question whether or not this is also paralleled by stereological histological measurements in postmortem tissue has been raised; however, only a few studies have addresses this caveat adequately and point to a reduction of neuropil rather than to neurodegeneration. Accordingly, hippocampal cell loss was not detected in postmortem tissue of depressed patients [70, 78]. Nevertheless, the biological mechanism underlying hippocampal atrophy in depression remained uncertain and soon after the discovery of AN in mammals, it became a prime suspect in this respect (see Mahlstedt et al. and Czeh et al. in this issue). Thus, the "neurogenesis hypothesis of depression" has become very popular in the last years, yet there is a considerable controversy (Mahlstedt et al. in this issue). The only study in humans related to this issue (see below), however, did neither made a case for an involvement of AN in the pathogenesis of depression nor in the mechanism of action of antidepressant drugs [93].

The investigation of AN is usually accomplished by immunohistochemical BrdU staining, which is not feasible in humans. Several antibodies have however recently been suggested to substitute for BrdU, including proliferation cell nuclear antigen (PCNA), doublecortin and Ki-67. The latter is expressed in all phases of the cell cycle except G_0, and thus hippocampal Ki-67 immunohistochemistry can be regarded as a surrogate parameter for neural stem cell proliferation (NSP), i.e. the first step of AN. As we could establish Ki-67 staining for human tissue, this enabled us to examine a possible connection between AN and major depression. To do so, we have examined human postmortem tissue obtained from the Stanley Medical Research Institute (http://www.stanleyresearch.org/programs/brain_collection.asp), including 15 specimens each from patients suffering from depression, bipolar disorder, schizophrenia, and controls, by means of Ki-67 immunostaining [93]. Surprisingly, a significant reduction in stem cell proliferation was solely found in schizophrenia (by 63%), which was not affected by drug treatment or any other intervening variable. This finding provided first evidence that AN might be involved in the etiopathogenesis of schizophrenia rather than depression, although replication in independent cohorts is a desideratum. Can this finding of reduced NSP be incorporated in current concepts of schizophrenia pathology?

Neurogenesis and schizophrenia

It is well accepted that schizophrenia is associated with several cognitive deficits, which are stable over time, i.e. trait rather than state dependent suggesting a (fine-) structural, rather than a—although not mutually exclusive—functional basis. A substantial proportion of these altered cognitive processes involves dysfunction of the hippocampus, e.g. impaired verbal memory and learning, which were accordingly found to correlate with changes in hippocampal and/or temporal lobe volume [3]. Beyond these neuropsychological measures in humans, the hippocampal formation was shown in animal studies to serve in online information processing and the multimodal integration of information, thereby producing a cohesive and accurate representation of the environment [107]. Although not yet demonstrated, this function might significantly contribute to dysfunctional information processing in schizophrenia, underlying not only cognitive defects but also delusions and hallucinations. Not unexpected, in conjunction with the dorsolateral prefrontal cortex, the hippocampus is the prime candidate implicated in the pathophysiology of schizophrenia.

Hippocampal volume and schizophrenia: neuroimaging and histopathology

Neuroimaging literature on the volume of the hippocampus is relatively consistent (reviewed by [34]) across various studies in patients suffering from schizophrenia, showing an average hippocampal vol-

ume loss of approximately 4%. A recent meta-analysis of first-episode studies including 300 patients and 287 controls even reported a bilateral atrophy of 8%, suggesting that the volume deficit is not a long-term neuroadaptive consequence of the disorder or its treatment, but underlying the etiology of the disease [105]. Another meta-analysis, scrutinizing voxel-based examination approaches, concluded that in more than 50% of all studies a reduction in the volume of the medial temporal lobe, including the hippocampus, was found [48]. The decrease in hippocampal volume, however, does not appear to be linked to progression over time [23, 24, 105]. Interestingly, hippocampal volume deficits identified in neuroimaging studies correlate with the degree of cognitive dysfunction, namely, memory performance [3].

Assuming that the decrease in hippocampal volume, as evidenced by converging findings from neuroimaging studies, is not due to methodological artefacts, it nevertheless has to be supported by postmortem data in humans. Moreover, the postmortem approach should also provide the means to investigate the nature and possibly the mechanism of disease-associated hippocampal volume change. While initial studies receiving considerable attention indeed demonstrated neuronal cell loss [30], disarray of hippocampal neurons [65] and reduction in neuron soma size [4, 8]. However, findings from subsequent studies are by and large in conflict with these initial reports; especially stereological investigations argued against a reduction in the total count of hippocampal neurons [44, 113], whereas a subset of non-pyramidal CA2 neurons might nevertheless be reduced in number [7]. This contradictory data might be explained by the small number of subjects investigated in these studies, in conjunction with disease heterogeneity. At present, the prevailing notion suggests that disturbances in the neuropil, especially the synaptic machinery, most likely underlie the atrophy found in imaging studies. Thus, although a plethora of human data suggest the hippocampus as a prime suspect in the pathophysiology of schizophrenia, the cellular and molecular underpinnings remain unknown. A disturbance in AN and hence impaired neuronal wiring—reflected by decreased hippocampus volume in MRI scans—would therefore be well compatible with the present state of knowledge.

Psychopharmacology of adult neurogenesis: anti-psychotics

As suggested by a series of studies starting in 2000 [73], all classes of anti-depressants are capable of increasing AN. Antipsychotic drugs however received less attention, probably due to the popular "AN hypothesis of depression". Nevertheless, several rodent studies consistently showed that hippocampal AN is unchanged during treatment with the classical antipsychotic haloperidol; while six studies, encompassing both acute and chronic treatment regimes, showed unchanged levels of stem cell proliferation [42, 59, 73, 100, 112, 114], only one study demonstrated an increase in AN upon treatment [22] as revealed by BrdU staining. The latter experiment was performed in gerbils (while the other investigators used mice and rats), suggesting that species differences might explain this discrepancy. Likewise, the prototypic atypical antipsychotic clozapine did not influence proliferation or survival of newborn cells in the DG [100]. Comparable doses were used in another study, again showing no difference; when low, subtherapeutic doses were applied, the number of BrdU-incorporating cells was doubled upon acute, but not chronic clozapine treatment [42]. This finding still awaits confirmation and it is as yet unclear whether or not this can be extrapolated to human AN. Olanzapine has been tested in three studies. While Kodama and associates demonstrated a significant up-regulation of AN in the DG upon chronic, but not subchronic olanzapine treatment [64], another group failed to do so in a comparable paradigm [114], although the authors denoted that "the data suggests that olanzapine may have some effect in the DG", and, most notably, increased AN in the prefrontal cortex of olanzapine-treated animals was found. Finally, in a head-to-head comparision of olanzapine with risperidone, both failed to increase AN in the DG of treated animals yet stimulated the proliferation of precursor cells in the SVZ [112] suggesting that these compounds stimulate cell proliferation in the rostral migratory stream to replenish OB neurons. Accordingly, a postmortem study found neuronal abnormalities in the OB of schizophrenic patients indicative of a disturbance of cell proliferation [5].

In line with animal data, total lifetime dosage of antipsychotics did also not impact on the level of NSP in our human postmortem study [93]. A large proportion of patients are likely to have received "typical", first-generation antipsychotics during the course of illness. Taken all studies together, a critical review of the published data leads to the conclusion that antipsychotics do not significantly increase AN in the DG, i.e. the very region in which reduced AN was demonstrated in schizophrenia, and that a stimulation of AN does not contribute to their mechanism of action. However, other brain regions implicated in the etiopathogesis of schizophrenia like the amygdala, the striatum or the prefrontal cortex might benefit from increased AN, as they were demonstrated to retain the potential for AN in primates under certain circumstances. The rate of proliferating cells under normal conditions in these areas is much smaller than in the DG [37] and newborn neurons are only of transient existence, which might explain that cortical AN is not detectable in humans [10] by measurement of ^{14}C incorporation. Stem or precursor cells which are

quiescent under resting conditions might nevertheless be targets of proliferation-inducing signals and thereby counter-acting neurodevelopmental malformations observed in schizophrenia [2].

Psychopharmacology of adult neurogenesis: psychoto-mimetics and NMDA signaling

Following the "dopamine hypothesis" of schizophrenia, which is based on the efficiency of dopamine receptor antagonists in the treatment of at least some psychotic symptoms by, the "glutamate hypothesis" of schizophrenia was put forward [76] suggesting that hypoglutamatergic states and impaired NMDA signaling underlie schizophrenia. In agreement with this concept, NMDA receptor antagonists, such as phencyclidine (PCP), the more selective MK-801, and the widely used anesthetic ketamine were shown to induce schizophrenia-like symptoms. Accordingly, PCP or ketamine treatment emerged as animal models of schizophrenia shown to display several key symptoms analogous of schizophrenia in rodents (e.g. impairment of prepulse inhibition [PPI], deficits in social behavior and cognitive dysfunctioning), and a recent study reported that repeated PCP administration decreases AN in the hippocampus of rats [69]. On the other hand, neurogenesis was stimulated 2-fold upon sub-chronic, sub-anesthetic (but not anesthetic; [66]) administration of ketamine [56]. Similar results were obtained with other NDMA site antagonists like MK-801 [36]. In line with this data, direct stimulation of the receptor by injection of NMDA resulted in decreased NSP [14]. While these findings seem at first sight contradict our finding of reduced NSP in schizophrenia in humans, it has to consider that alterations in AN after pharmacological modulation of the NMDA receptor may reflect an acute counter-regulation of glutamatergic hypofunctioning. Cause and effect are likely to be interchanged in the human disease state, which is neurodevelopmental in nature. In line with this notion, it has recently been shown that the proliferation rate of human neural progenitor cells derived from fetal cortex, is stimulated by glutamate but decreased by NMDA antagonists [106].

NMDA signaling and neurogenesis: downstream mechanisms

With respect to possible downstream mechanisms of NMDA receptor activation, there is data implicating at least two pathways in the regulation of AN: the nitric oxide (NO) and Wnt signaling cascades. NO, which has been implicated in the pathophysiology of schizophrenia [9], regulates AN in a complex manner. In hippocampal neurons NO is formed by neuronal nitric oxide synthase (NOS-I) which is the target of NMDA-induced Ca^{2+}-influx, while NOS-III, present in the vasculature, is an alternative source for this gaseous messenger. Since there are tight interactions between the endothelium and neural progenitor cells, thus forming a vascular niche for neurogenesis [83], the latter may be part of a signaling pathway between vasculature and neural stem cells. It was shown that mice lacking NOS-III actually display reduced levels of NSP [95], which appears to be mediated by vascular endothelial growth factor (VEGF) previously shown to stimulate AN [16, 52, 97]. Correspondingly, ECT stimulates VEGF [79] which is paralleled by angiogenesis [46] and increased AN [72, 102]. In summary, a remarkable body of evidence indicates a link between endothelial cells, NOS-III and VEGF with a positive effect on NSP, which can be induced e.g. by ECT.

Matters are more complicated with respect to NOS-I, which is also thought to be a risk gene for schizophrenia [94]. Mice with a knockdown of NOS-I feature cognitive deficits and resulting behavioral changes in several paradigms (Reif et al., in preparation). The effects of NOS-I knockdown on AN however seem to be complex and the findings are somewhat contradictory. Pharmacological studies using NOS inhibitors provided evidence that NOS-I inhibits NSP [77, 82, 84–86]. Systemic administration of a NO donor on the other hand resulted in elevated levels of neurogenesis [116]. Since these studies did not include investigation of survival rates, NSP but not AN was determined. Nevertheless, these experiments favor the conclusion that NOS inhibition results in increased NSP. In NOS-I knockout mice, an ~30% increase of NSP was demonstrated in the DG [82]. In contrast, we found unchanged NSP rates in NOS-I knockout mice using a slightly different injection scheme allowing for a more precise distinction between NSP and survival (Fritzen et al., submitted). Survival was, however, dramatically increased in NOS-I knockouts which is in accordance with data indicating that NO signaling switches surviving newborn cells to terminal neuronal differentiation [18, 19]. NO from NOS-I thus seems to inhibit stem cell survival and to modulate late stages of AN, which comprises both cell survival and neuronal differentiation. As NOS-I in vitro slows down cell proliferation [19], this inhibitory signal is lacking in NOS-I knockdown mice resulting in a substantial increase in the survival of new-born cells.

The wingless-type MMTV integration site family (Wnt) pathway represents the second possibly downstream mediator of NMDA-induced neurogenesis, since hippocampal NMDA activation induces Wnt member 3 (Wnt3) release along with activation of its target genes [17]. Wnt3 in turn was shown to increase NSP in vitro and in vivo, while blockade of Wnt signaling almost completely abolishes hippocampal AN [68]. The Wnt pathway comprises several Wnt gylcoproteins, *frizzled* receptors and three further intracellular mechanisms, of which the canonical pathway—i.e. *disheveled* activation with consecutive

inactivation of the lithium target molecule GSK-3β and resulting β-catenin accumulation—has been implicated in the pathophysiology of schizophrenia by several lines of evidence (e.g. human postmortem expression profiling and neurochemical measures). Together, there is considerable evidence linking Wnt3 with both schizophrenia and neurogenesis [109], thus rendering this signaling pathway an attractive target for investigations into schizophrenia pathogenesis. Candidate gene studies in schizophrenia have only been reported for the FZD3 receptor, which is implicated in the non-canonical, Ca^{2+}-releasing Wnt signaling pathway. Results are controversial, and a recent meta-analysis [51] as well as our own data (Reif et al. submitted) argues against an association of *FZD3* with schizophrenia.

In summary, although the view that altered NMDA receptor-mediated glutamatergic signaling impacting on AN is relevant to the pathophysiology of schizophrenic psychoses is supported by several lines of evidence, the precise mechanisms are unclear. Lessons from genetically modified mice may aid their identification with both NMDA receptor NR1 knockdown and receptor ε1-subunit knockout mice have been proposed as animal models for schizophrenia. To date there is only one series of studies in NMDA receptor ε1 subunit knockout mice, showing unchanged AN under basal conditions [60, 62], whereas the well-described neurogenic effect of exercise was only observable in wild-type, but not knockout animals, suggesting that this is mediated by the NMDA receptor complex [61]. Of related interest, rats exposed to postnatal hypoxia feature impaired startle responses and thus may serve as schizophrenia-like models. These animals display increased NMDA NR1 subunit expression in adulthood in the DG and CA1 field [99]. Experiments on AN in these animals are currently under way and the results may shed light on the link between schizophrenia-like behavior, NDMA signaling and AN. While the NMDA receptor signaling cascade and its role in AN has been extensively investigated by both pharmacological and transgenic methods, several other signaling systems have also been considered in the regulation of neurogenesis. Genetically modified mice serve an important role and a steadily increasing number of knockouts has been evaluated for AN [32]. Among the genes encoding proteins that have been demonstrated to influence AN, some may also play a role in schizophrenia, e.g. fibroblast growth factor 2 (FGF-2), the cannabinoid receptor CB1R and the neurokinin receptor NK1-R. Finally, several other genes deserve a closer look.

Further pathways linking schizophrenia to AN: DISC1

Disrupted-in-schizophrenia 1 (DISC1) was proposed to be a schizophrenia risk gene as it was found to be disrupted by a balanced translocation segregating with schizophrenia in a large Scottish pedigree [74]. In the following years, evidence was accrued that DISC1 also contributes to schizophrenia risk in the general population, since case-control studies found association with both schizophrenia as well as bipolar disorder on the single-marker and the haplotype level; furthermore, linkage to the DISC1 locus was demonstrated (reviewed in [50, 92]). Polymorphisms in DISC1 were not only associated with disease per se, but also with cognitive functioning in schizophrenia [12, 15]. Intriguingly, also normal subjects carrying the *DISC1* Ser704Cys genotype showed smaller hippocampal grey matter volume, less hippocampal fMRI activation during a working memory task and poorer performance in hippocampus-dependent cognitive functions [13]. As DISC1 was located in the limbic system and participates in neurite outgrowth [54, 75, 81] as well as cortical development [53], it is obvious to suspect a role in neurogenesis. Indeed, DISC1 is strongly expressed during all stages of prenatal hippocampal development in mice, but also postnatally in adolescent animals at P35 [6, 101]. Measures on AN or schizophrenia-like phenotypes in DISC1 transgenics have not yet been reported but preliminary findings (reviewed in [50, 80]) argue for disturbed PPI, impairments of social cognition and spatial memory along with enlargement of the lateral ventricles. Thus, *DISC1* polymorphisms may well be connected to disturbed AN.

The reelin story

The extracellular glycoprotein reelin, released from GABAergic interneurons in the adult brain, serves as an important signaling molecule in neuronal migration and differentiation during brain development most probably providing a stop signal to migrating neurons. Mutations in the human reelin-ecoding gene (*RELN*) cause a form of lissencephaly. It was shown that reelin haploinsufficiency is the causative mutation of the reeler mouse [21], an animal model known since the late sixties. These mice display disturbed DG neurogenesis during development, in that granule cells proliferate ectopically and the normal pattern of neurogenesis is reversed [104]. In the recent years, converging lines of evidence argued for a connection of *reelin* and schizophrenia. First, *reelin* expression was found to be decreased in all examined brain regions including the hippocampus in postmortem tissue from schizophrenic patients [41, 49] accompanied by corresponding reductions in reelin immunopositive hippocampal neurons [31, 63]. Case-control association studies yielded largely negative results, rendering it unlikely that *RELN* variation contributes to the genetic liability towards schizophrenia. Epigenetic mechanisms are more likely to play a role, as the RELN promoter is hypermethylated in schizophrenic patients [40].

Paralleling these findings, the reeler mouse has been proposed as an animal model for schizophrenia. These mice display decreased reelin expression along with neuroanatomical abnormalities reminiscent of neuropathological findings in psychosis [20]. These findings need to be critically viewed as the behavioral phenotype of reeler mice is not suggestive of schizophrenia-like behavior [91], although phenotypical traits include marked cognitive defects, such as impaired contextual fear conditioning, a hippocampus-dependent task. Interestingly, L-methionine treatment of both wildtype and reeler mice resulted in PPI disruption and reduced reelin expression, paralleled by reelin promoter hypermethylation [110]. This course of action was suggested to mimic the epigenetic down-regulation of RELN in schizophrenic patients [25]. The link between schizophrenia, reelin deficiency, and AN is further underscored by two recent studies demonstrating reduced and disorganized (i.e. newborn cells are not aligned along the SGZ, but scattered all over the DG) AN in reeler mice [58, 115].

Defective migration of hippocampal granule cells, called granular cell dispersion, is observed in tissue from patients suffering from temporal lobe epilepsy (TLE) and suggested to be due to local reelin deficiency [33]. Interestingly, kainate injection in the hippocampus of rats, serving as a model for TLE, causes an increase in NSP [39]. However, granule cell dispersion induced by kainate lesioning is not due to increased AN but rather to displacement of mature granule cells, most probably caused by decreased reelin levels [45]. Likewise, no NSP as detected by Ki-67 staining was found in hippocampus tissue from patients with TLE [29]. Granule cell dispersion in TLE, and kainate injection alike, does not appear to be due to impaired AN despite the observed decrease of reelin, thus arguing against a role of reelin in NSP. Nevertheless, epigenetically influenced and reelin-induced pathology of granular cell migration may contribute to the pathophysiology of schizophrenia.

From depression to schizophrenia: BDNF

Despite the fact that the neurotrophin BDNF has primarily been implicated in depression, evidence is accumulating that it also contributes to the pathophysiology of schizophrenia. Case-control studies e.g. suggested an association of BDNF polymorphisms not only with bipolar disorder, but also schizophrenic psychoses [38]. At the functional level *BDNF* variation was shown to influence episodic memory, hippocampal volume and brain activation as revealed by fMRI in both healthy volunteers and schizophrenic patients [11, 26, 43, 87]. Group x genotype interaction effects were however not observed [47, 108]. This suggests that *BDNF* genotype may not increase the risk for schizophrenia per se, but acts as a disease modifier by contributing to hippocampal pathology.

Since *BDNF* knockout mice are not viable, experiments are restricted to heterozygous *BDNF* ± mutants. These mice probably display reductions in NSP, but definitely in stem cell survival [67, 96]. Accordingly, BDNF injection into the hippocampus results in increased neurogenesis of granule cells [98]. Furthermore, the AN-enhancing effect of the antidepressant imipramine requires the presence of BDNF for sustained survival of newborn cells implying that antidepressants do not increase AN directly but rather stimulate neuronal turnover [96]. All in all, these data are suggestive of a close link between AN, BDNF, and schizophrenia, especially with respect to the survival of newborn cells.

A new player: NPAS3

Given the likely genetic influence on the reduction in hippocampal volume in schizophrenia, identification of genes related to schizophrenia influencing both hippocampal morphology and AN may represent the ultimate proof for the AN hypothesis of schizophrenia. The transcription factor neuronal PAS domain protein 3 (NPAS3), expressed in interneurons, may meet these criteria [89]. The first hint that NPAS3 plays a role in schizophrenia came from a family in which disruption of *NPAS3* on chromosome 14q13 segregates with disease [55]. The second line of evidence is derived from rodent studies: NPAS3 knockout mice display several schizophrenia-like behavioral abnormalities, such as diminished PPI, impaired social recognition, deficits in learning tests, stereotypic behavior at weaning, and increased locomotor activity in the Open Field paradigm [27]. This is accompanied by a reduction of hippocampal reelin and the FGF-2 receptor expression. Moreover, NPAS3 knockout mice feature a marked reduction (84%) in hippocampal AN [90] correlating with the thickness of the GCL. The decrease of AN is reversible upon ECT. Whether the NPAS3 pathway also contributes to the genetic liability for schizophrenia in the general population is unclear, however, preliminary communications already indicated an association of NPAS3 variation with schizophrenia [71, 88]. Studies are under way in our laboratory which investigate whether this also correlates with hippocampus volume or NSP.

Taken together, the findings implicate several pathways in both schizophrenia and alterations in AN (Fig 1): NMDA signaling with downstream activation of NOS; the Wnt pathway; reelin hypermethylation leading to reelin downregulation; the schizophrenia candidate genes *DISC1* and *BDNF*; and, finally, *NPAS3* and its signaling cascade. Future research will investigate whether these genes convey a genetic risk to schizophrenia, whether they are correlated to AN and/or hippocampal volume in postmortem tissue, and if they impact on structural or functional variation of the hippocampus in neuroimaging studies.

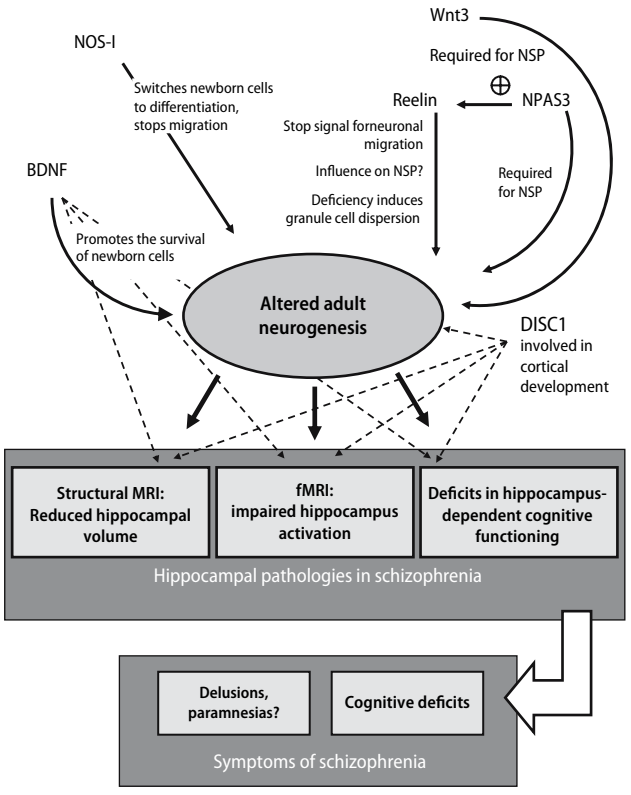

Fig. 1 Signaling pathways influencing adult neurogenesis (AN), illustrating how AN may contribute to schizophrenia. Candidate genes depicted in red are associated with schizophrenia in human studies, using either case-control association or postmortem approaches

Concluding remarks: Consequences of altered adult neurogenesis in schizophrenia

With the summary above we gathered a remarkable body of evidence for a hippocampal pathology underlying schizophrenia, which may—at least in part—encompass altered AN. Reduced NSP is unlikely to contribute only to cognitive impairment in hippocampus-dependent tasks observed in schizophrenia, but also to other characteristics of schizophrenic psychoses. Considering the critical role of the hippocampus in integrating multimodal cues [107], disturbed AN may result in corresponding deficits. In this context, a recent hypothesis by Gage and associates is of related interest [1].

They proposed that AN assists the encoding of time in the formation of new, multimodal memories thus enabling cohesive temporal associations. Given that a disruption of AN thus might cause erroneous temporal encoding of new memory content, it can be speculated that disturbed AN not only contributes to schizophrenia-related deficits in episodic memory, but also to deranged emotional coding of reality perception and consecutive formation of delusions or paramnesias.

Finally, one should NSP not only consider a target for future drugs: learning, exercise and enriched environment are environmental factors which increase AN cost-effectively and free of any side effects. This directly points towards non-pharmacological treatment of schizophrenic patients in terms of optimized environmental conditions, which are a desideratum but unfortunately not always present in psychiatric care.

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