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Review

Insult-induced aberrant hippocampal neurogenesis: Functional consequences and possible therapeutic strategies

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ABSTRACT

Adult hippocampal neurogenesis plays a critical role in a wide spectrum of hippocampus-dependent functions. Brain pathologies that involve the hippocampus like epilepsy, stroke, and traumatic brain injury, are commonly associated with cognitive impairments and mood disorders. These insults can affect neural stem cells and the subsequent neurogenic cascade in the hippocampus, resulting in the induction of aberrant neurogenesis, which is thought to compromise hippocampal network function, thereby hampering hippocampus-dependent behavior.

We here summarize recent preclinical literature on hippocampal insult-induced changes in neurogenesis and based on that, we propose that normalizing aberrant neurogenesis post-insult may help to prevent or rescue behavioral deficits which could help develop novel therapeutic strategies.

1. Introduction

Although considered non-existent for decades, the occurrence and controlled regulation of hippocampal neurogenesis in the adult mammalian brain has now been broadly accepted in the field [1]. This form of brain plasticity has received extensive attention after identification of various hormonal and environmental regulators [2–4]. This interest further increased following the (re-)confirmation of neurogenesis in human brain [5–7], that was paralleled by an intense debate over optimal detection methods, tissue preservation and a possible functional role in human brain recently [8–12].

Adult hippocampal neurogenesis (AHN) is driven by a neural stem cell (NSC) pool in the subgranular zone (SGZ) of the dentate gyrus (DG). NSCs are commonly found in a quiescent state, but upon activation they give rise to neural progenitor cells that divide and produce neuroblasts. In turn, these neuroblasts differentiate into immature neurons (Fig. 1), that, over the course of several weeks, transform into fully functional

granule neurons and integrate into the existing hippocampal network [13,14]. Granule neurons in the DG are the first relay station in the information flow entering the hippocampus and their firing rate is under a strong inhibitory control from different types of local interneurons, constituting a robust electrophysiological filter or “gating” function which, when disrupted by insults such as traumatic brain injury (TBI) or status epilepticus, leads to hippocampal network hyperexcitability and memory dysfunction [15–17]. The development and functional integration of newborn granule cells originated from AHN is controlled locally by GABA-ergic interneurons, such as parvalbumin γ -aminobutyric acid-releasing interneurons, and glutamatergic interneurons such as mossy cells [18–21] demonstrating that a delicate balance in excitation and inhibition is crucial for the physiological “on demand” contribution of AHN to hippocampal plasticity [22].

The production of newborn neurons decreases slowly with age [10,23–25] possibly due to changes in the vasculature or neurogenic niche [26,27], the systemic environment [28], or the limited

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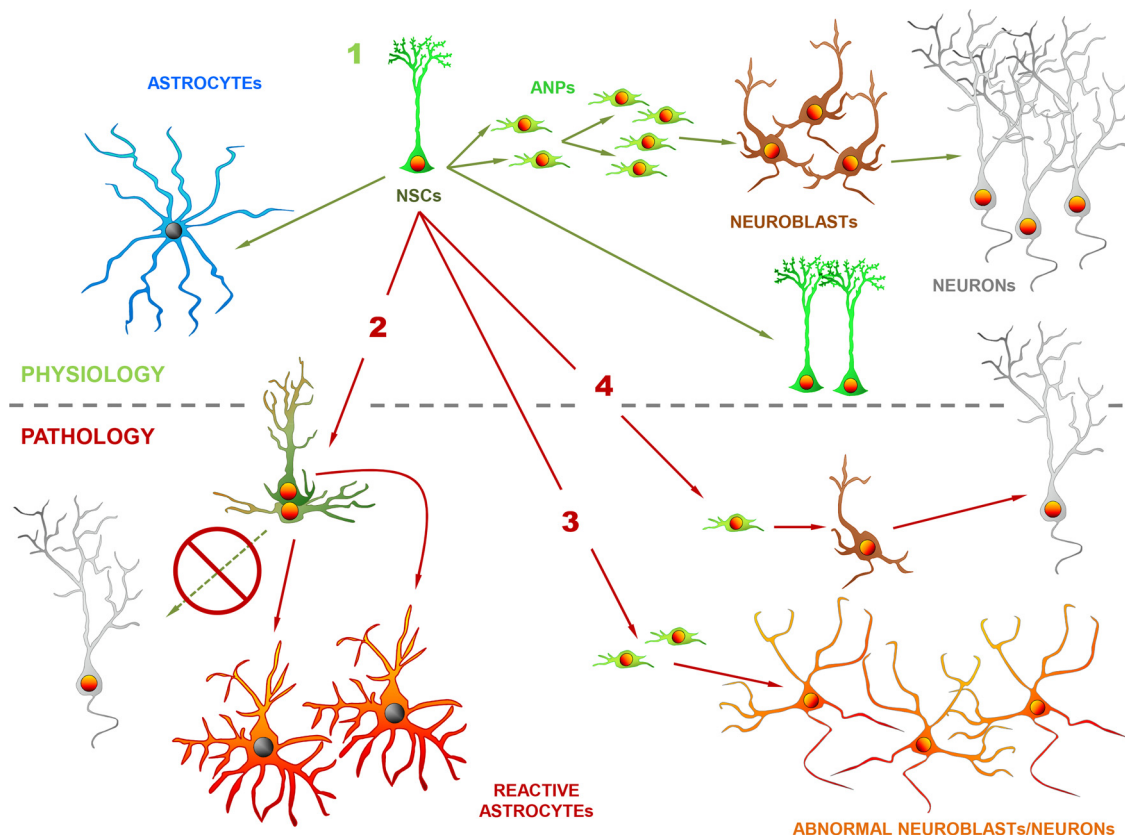


Fig. 1. Normal and aberrant neurogenesis. In physiological conditions (1) NSCs divide asymmetrically to generate neuronal precursors that divide and differentiate into neurons [13,14]. NSCs can also generate astrocytes and divide symmetrically to produce more NSCs. In pathological conditions, such as epilepsy, traumatic brain injury or stroke, adult hippocampal neurogenesis can be deregulated in different ways: (2) NSCs can abandon neurogenesis almost completely as they become reactive NSCs (React-NSCs) that ultimately convert into reactive astrocytes [58,72]. (3) Production (sometimes in excess) of new neurons with altered morphological and electrophysiological properties is also possible [65,66,68,70,71,134]. (4) Neurogenesis can be diminished either because proliferative capacity of NSCs and/or activated neuronal precursors (ANPs) is compromised, or because an initial increase in NSC activation provokes the depletion of the NSC population [55,58–61,64].

regenerative capacity of NSCs [29]. Over time, this is thought to result in a depletion of the stem cell pool, although the production of new neurons can still be increased in the senescent brain by manipulating glucocorticoids [30–32], neurosteroids [33], or exposing animals to physical activity [34] or an enriched environment [34,35]. Experimental studies in rodents have shown that AHN critically contributes to complex memory processes, such as navigating through space [36–38], behavioural pattern separation [39–41], remembering [42], forgetting [43], anxiety [44], and drug addiction [45]. Interestingly, during aging the extent of memory impairment has been quantitatively linked to the rate of neurogenesis [46].

In addition to environmental stimuli, AHN is tightly regulated by cell-intrinsic and extrinsic molecular signals, such as growth factors, transcription factors, adhesion molecules, neurotransmitters, hormones and epigenetic regulators (Reviewed in [47–49]). This tight regulation of the neurogenesis cascade is likely aimed at maintaining a steady rate of neuron production throughout life. Changes in intrinsic programs and external environment with ageing together may lead to memory deficits [27].

Over the years, multiple pathologies, i.e. epileptic seizures, stroke, and TBI, were demonstrated to affect the hippocampal neurogenic cascade in multiple ways. These alterations have been primarily identified in epilepsy models and captured under the umbrella term “aberrant neurogenesis” [50], encompassing a variety of abnormal outcomes of, and changes in, the neurogenic cascade (Fig. 1) and in the morphology and location of newborn granule neurons, which are fundamentally different from the outcome of physiologically reactive AHN. Here, we use these as examples to discuss recent advances in this field.

2. Aberrant AHN and functional implications

Since AHN is a multi-step process that includes NSC activation, proliferation, apoptotic selection, migration and neuronal differentiation, each individual stage is sensitive to dysregulation in a pathological environment or following specific insults. This can result in multiple (dys)functional outcomes such as: an excessive activation of NSCs [58,60]; alterations in NSC fate [58,59]; downregulation of the proliferative capacity of NSCs, neural progenitor cells or neuroblasts [55,59,61]; an abnormal development and length of the dendritic tree of newborn neurons [57,62] and ectopic migration of newborn neurons [53] (summarized in Table 1). In particular, the development of abnormal dendritic trees may be a significant feature of aberrant neurogenesis, since low synaptic connectivity prevents immature neurons from responding to cortical activity [63]. Overall, these abnormalities result in the generation of newborn neurons with altered properties, which in turn can alter their integration in, and functional contributions to the preexisting hippocampal network. Since AHN is located in the DG, i.e. the start of the trisynaptic circuit, changes in their properties will influence CA3 and subsequent CA1 projections, thereby affecting hippocampal network function and ultimately, cognition. Moreover, adding substantial numbers of NSC-derived reactive astrocytes to the neuronal population of the DG will likely also induce profound changes in functioning of the hippocampal circuit.

One of the most common pathologies studied in relation to AHN is epilepsy and the occurrence of epileptic seizures. Despite the variability in literature largely derived from the wide range of experimental epilepsy models, it is well established that convulsive epileptic seizures initially increase the rate of neurogenesis, which is then followed by a

Table 1
Overview of aberrant neurogenic phenotypes and associated cognitive deficits associated with epileptic seizures, stroke, and TBI.

Pathology	Model	Time point	Aberrant phenotype	Cognitive deficits	Reference	
Epileptic seizures	Pilocarpine-SE (Rat)	1d– 27 d	Transient increased proliferation, Ectopic newborn neurons	Not assessed	[55]	
	Systemic kainic acid-SE (Rat)	3 wk -1 yr	Increased numbers of newborn neurons (3-5wks after SE), Basal dendrites, Ectopic newborn neurons, Increased mushroom spines	Not assessed	[131]	
	Intrahippocampal kainic acid-SE (mouse)	3, 7, 50 d	Increased NSC proliferation, Induction of reactive NSCs, Depletion of the NSC pool at 50 days	Not assessed	[58]	
	Intrahippocampal kainic acid, non-convulsive seizures (mouse)	3 d	Increased neuroblast proliferation, Induction of reactive NSCs, Loss of neurogenic NSCs	Not assessed	[59]	
	Pilocarpine-SE (mouse)	6 wk	Increased newborn neurons, Ectopic newborn neurons	Impaired Novel-Object location memory	[126]	
	Pilocarpine-SE and kainic acid-SE (rat)	1-21 months	Ectopic hilar newborn neurons, Basal dendrites	Not assessed	[52]	
	Pilocarpine-SE (rat)	2-17 months	Ectopic hilar newborn neurons	Not assessed	[53]	
	Intra-amygdala kainic acid SE (mouse)	9 d	Increased proliferation, Increased newborn neurons	Not assessed	[54]	
	Intrahippocampal kainic acid-SE (mouse)	2 wk	Basal dendrites	Not assessed	[56]	
	Systemic kainic acid-SE (mouse)	4 d	Increased NSC proliferation	Not assessed	[60]	
	Systemic kainic acid-SE (rat)	7, 28 d	Increased proliferation, Increased newborn neurons, Basal dendrites	Impaired novel object recognition	[50]	
	Systemic kainic acid-SE (mouse)	3 d	Increased NSC proliferation	Not assessed	[64]	
	Pilocarpine-SE (rat)	14, 28 d	Increased proliferation, Ectopic newborn neurons	Not assessed	[122]	
	Electrical kindling (rat)	18 d	Increased newborn neurons, Basal dendrites	Not assessed	[123]	
	Pilocarpine-SE (mouse)	4 wk	Basal dendrites, Ectopic newborn neurons	Impaired Morris Water Maze acquisition learning	[125]	
	Stroke	Cerebral artery occlusion (mouse)	7, 14 d	Increased proliferation, Increased newborn neurons	Impaired long-term memory retention and impaired spatial memory	[68]
		Cerebral artery occlusion (mouse)	7 wk	Increased newborn neurons, Ectopic newborn neurons, Basal dendrites	Impaired spatial memory	[69]
	TBI	Photothrombosis & cerebral artery occlusion (rats)	6 wk	Ectopic newborn neurons, Basal dendrites	Not assessed	[70]
Cerebral artery occlusion (mouse)		6d, 5 wk	Increased proliferation, Increased newborn neurons	Not assessed	[132]	
ET-1-induced cerebral artery occlusion (mouse)		7, 10 d	Induction of reactive NSCs	Not assessed	[72]	
Controlled cortical impact (mouse)		1-3.7 d	Increased NSC proliferation	Not assessed	[133]	
Controlled cortical impact (mouse)		1-28 d	Transient increased proliferation, Decreased newborn neurons	Not assessed	[94]	
Controlled cortical impact (mouse)		1-8 wk	Ectopic newborn neurons, Impaired dendritic arborization	Not assessed	[95]	
Controlled cortical impact (mouse)		2, 4 wk	Increased newborn neurons, Ectopic newborn neurons, Increased dendritic complexity	Not assessed	[96]	
Fluid Percussion (mice)		1, 7 d	Increased newborn neurons, Ectopic newborn neurons,	Not assessed	[97]	
Controlled cortical impact (rat)		1-21 d	Transient increased proliferation Increased newborn neurons	Not assessed	[98]	
TBI (human)		< 1 d	Increased NSC proliferation	Not assessed	[100]	
Controlled cortical impact (mouse)	Controlled cortical impact (mouse)	2 d	Increased proliferation, Severity-dependent increased newborn neurons	Not assessed	[104]	
	Controlled cortical impact (mouse)	3, 7, 30, 90 d	Increased proliferation, Transient increased newborn neurons	Not assessed	[105]	
	Controlled cortical impact (mouse)					

long-lasting decline [55,60,61,64]. In addition, neurons born during and after the seizures display morphological and functional alterations. In fact, the concept of aberrant neurogenesis was first described in the context of seizure-associated plasticity that lead to long-lasting structural changes in hippocampal morphology [50]. Furthermore, the hyperactivation of NSCs induced by seizures eventually exhausts the NSC pool and leads to a strong and long-lasting decrease in AHN at later stages [58].

The hyperactivation of NSCs as a phenomenon per se has only recently been studied in more detail. Upon activation by strong stimuli, like convulsive seizures, NSCs do not only enter the cell cycle in much larger numbers, they also shift their division mode from asymmetric to symmetric division, and with an important change: after seizures, NSCs transform into reactive NSCs (React-NSCs) in a seemingly similar manner as astrocytes do when they convert into reactive astrocytes. React-NSCs become multibranching and extend basal prolongations as they move away from the SGZ in an upward direction after which they locate throughout the entire GCL up into the molecular layer. Their prolongations are much thicker than the normal single radial process and the fine 'broccoli-like' arborization that normal NSCs develop as they migrate into the molecular layer, is lost. Furthermore, React-NSCs overexpress GFAP and nestin. Thus, React-NSCs divide symmetrically at the cost of maintaining a neuronal progenitor cell pool and in turn, seem to further differentiate into reactive astrocytes, thereby contributing to increased astrogliosis [58].

Besides the loss of NSCs and the induction of astrogliosis, other alterations are observed in the newly generated neurons after seizure onset. One of the most striking and consistent observations has been the ectopic displacement of such cells to the outer layers of the granule cell layer (GCL), the molecular layer (ML), or the hilus of the DG. Next to this ectopic location, these neurons also show altered dendritic arborization, including the generation of basal dendrites. Together, these phenomena are thought to change local neuronal rewiring and hence the structural and functional organization of the hippocampal network. Furthermore, several studies have highlighted neuron-intrinsic alterations in baseline excitability, which potentially could contribute to the formation of a pro-epileptogenic microenvironment known to facilitate recurrent seizures [65,66].

Epileptic seizures comprise a wide variety of pathologies, with convulsive seizures being mostly studied. Recently, however, several studies have addressed the effects of less severe, non-convulsive, seizures on several aspects of the neurogenic cascade. These studies have shown that also non-convulsive seizures induce aberrant neurogenesis, though not all outcome parameters have been addressed thus far. Even epileptiform activity *per se*, as characterized by burst discharges and interictal spikes e.g., and an abnormal increase in neuronal activity that does not trigger seizures of any kind, already affects neurogenesis [58]. Non-convulsive seizures induce neuroblast proliferation, reactive NSCs and decrease the total NSC pool shortly after seizure onset, but this occurs to a lesser extent than after convulsive seizures [58,59,67]. As the long-term development and subsequent integration of the newborn neurons was not assessed in these studies, it remains still unknown whether some of these changes are transient or compensated for by other phases, and thus whether or not the entire neurogenic process can be considered aberrant.

Interestingly, many of the hallmarks of aberrant neurogenesis, including increased numbers of newborn granule cells, ectopic granule cells, malformations of the dendritic tree and synapse composition, have also been observed after other comparable brain insults, such as stroke [68–71]. They seem to depend on the severity, location and size of the stroke lesion [70], suggesting that aberrant neurogenesis may be a common pathological substrate for several types of brain insults. Furthermore, the induction of reactive astrocytes derived from React-NSCs has also been confirmed after stroke [72], suggesting that the induction of React-NSC may be a characteristic feature of aberrant AHN.

Several models of epilepsy in mice show a massive inflammatory response in brain areas affected during the onset and propagation of epileptic activity [73–77]. However, the production of these proinflammatory molecules is also accompanied by the synthesis of other anti-inflammatory mediators which avoid the possible harmful effects [78]. For example, neurons upregulate IL-1 and TNF-alpha receptors during seizures [79,80]. Therefore, when this delicate balance between pro- and anti-inflammatory molecules is affected, a loop of neuronal hyperexcitation and neuroinflammation may be generated, which may contribute to the development of chronic seizures: neuronal excitotoxicity provokes glial and NSC-mediated proinflammatory reactivity which in turn promotes seizures, further neuronal excitotoxicity and NSC-derived reactive astrocytes (RAs) [58]. RAs are essential players in epilepsy-related neuroinflammation. In normal conditions astrocytes regulate ion levels (especially potassium), the amount of interstitial liquid and glutamate levels at the synapses. These capabilities are lost or altered in RAs, which in turn can contribute to perpetuation of seizures [81]. In fact, the induction of RAs in a healthy brain is enough to trigger epileptic seizures [82]. This effect may be due to ionic imbalance that facilitates neuronal depolarization and glutamate persistence for longer time in the synaptic cleft as RAs fail to remove it, thus lowering the threshold for the synchronous hyperexcitation that characterizes epilepsy. In addition, astrocytes use glutamate to generate glutamine via glutamine synthetase. Glutamine is required by neurons to synthesize GABA. In a proinflammatory context, RAs may not only capture less glutamate but also have diminished expression of glutamine synthetase [83] and therefore the amount of GABA is decreased, as has been shown in human epileptic tissue of hippocampal sclerosis [84]. The contribution of microglia in epilepsy is also slowly being revealed in the last years. One of the possible mechanisms involved could be altered synaptic pruning as shown in a model of Rett syndrome [85] or after an upregulation of the complement components [86]. More recently, it has been shown how the natural capacity of microglia to phagocytose cell debris is impaired due to seizures and therefore dead neurons and their toxic remains accumulate. This impairment is at least partially mediated by altered ATP widespread release during seizures, which disrupts ATP basal microgradients fundamental for microglia recognition of apoptotic cells [87]. As the blood brain barrier (BBB) is altered after seizures, blood-to-brain extravasation of peripheral immune cells is possible. Although in the previously mentioned report [87] both monocyte and neutrophil invasion were ruled out in a mice model of MTLE, this cellular invasion has been shown to be relevant in epilepsy experimentally induced by a viral infection [88]. In this case, the main contribution to neuroinflammation by infiltrating macrophages is caused by their elevated release of cytokines (especially interleukin-6, IL-6), a biological response also triggered in microglia [89]. Microglial phagocytic capacity is also known to be changed by insults to the brain. While in physiological conditions only a little proportion of the microglia show active phagocytosis, their phagocytic index increases after exposing them to an inflammatory challenge in vitro, which may be in order to maintain the phagocytosis/apoptosis coupling ratio. However, this microglial phagocytosis shows a chronic impairment in an experimental model of MTLE which leads to the accumulation of apoptotic cells contributing to the development of an inflammatory response [87].

Though not studied in as much detail as epileptic seizures, it has become clear that also traumatic brain injury (TBI) strongly affects the hippocampus. Following an initial insult, like physical injury to the cortex e.g., its secondary damage involves local inflammation, excitotoxicity and other long-term changes that are triggered by the initial trauma [90–92]. Shortly after TBI, astrogliosis is observed in the hippocampus, although it is not yet clear whether there is a contribution from TBI-induced React-NSCs or whether it is fully dependent on resident astrocytes.

Even more so than for experimental seizures, experimental TBI comprises a wide range of models which provoke different effects and,

not unexpectedly, different and even opposing results have been reported in the literature regarding changes in neurogenesis. In general, and comparable to epileptic seizures, TBI also induces proliferation in the SGZ of the DG, which returns to baseline levels 1–2 weeks post trauma [93,94]. The newborn neurons studied after TBI also share several features with those observed after seizures, such as an ectopic location and aberrant dendritic development [95–97]. This phenotype clearly resembles the aberrant neurogenesis that is observed after epileptic seizures and stroke, and thus one can hypothesize that similar downstream mechanisms may underlie these phenomena in these different pathologies.

While initial effects of TBI on AHN have been extensively characterized in rodent models [98,99], recent evidence indicates that TBI may also induce neurogenesis in the human brain [100]. Interestingly, TBI induces increased migration of adult-born immature neurons, one of the typical hallmarks of the aberrant neurogenesis that is also observed after seizures. Although these atypical, immature neurons do become mature and differentiate into granular neurons, their ectopic location remains limited to the outer GCL, with a reduced dendritic complexity after TBI [95,96]. Electrophysiological characterization of granule cells after TBI has further revealed increased excitability, both cell-intrinsic as well as cell-extrinsic by decreased inhibitory synaptic input and decreased feed-forward inhibition on granule cells [100–103]. Importantly, the severity of TBI determined its effects on AHN: while mild TBI did not affect measures like NSC proliferation, immature neuron numbers or newly-generated mature neurons, moderate TBI also promoted NSC proliferation but did not increase neurogenesis. Severe TBI again increased NSC proliferation as well as the numbers of immature neurons and newly-generated mature neurons, thereby resembling the differences observed before between strong convulsive seizures and milder, non-convulsive ones [104]. Consistent with earlier findings on the effects of seizures on radial glia-like Type-1 NSCs in the hippocampus [60], TBI particularly activates the proliferation of quiescent Type 1 cells [93] and undermines their long-term neurogenic potential [105]. Although astrogenic React-NSCs are induced after both convulsive and non-convulsive seizures [58,59], their induction by TBI has not yet been characterized.

Hippocampal neurogenesis plays a crucial role in a wide array of behaviours and in agreement, both epileptic seizures, stroke, and TBI have been associated with cognitive deficits over time [106–108]. This has led to the hypothesis that prevention of insult-induced alterations in the hippocampal neurogenic cascade could possibly rescue at least some of the cognitive deficits common to these types of pathologies.

Several studies have identified some of the possible molecular mechanisms involved in aberrant AHN, among which the Wnt signaling pathway seems to be a central contributor [109,110]. In addition, other studies have found a consistent upregulation of microRNAs associated with seizure-induced aberrant AHN (reviewed in [48]). In particular, the synergistic action of the microRNAs miR-124 and miR-137 seems to be a relevant regulator of aberrant AHN [59,111]. Although the molecular mechanisms involved have not been extensively characterized, mitochondrial (oxidative) pathways seem likely to be involved [111,112], some of which are linked to adequate lineage progression of adult NSCs [113]. 3 previous single-cell RNA sequencing studies have identified a common group of genes expressed in mouse hippocampal NSCs [114–116] (Supplementary Table 1), from which we generated a list of genes that are predicted to be common targets for both miR-124 and miR-137 using mirWalk 2.0, a comprehensive atlas of microRNA-target interactions [117] (Supplementary Table 2) and used it to obtain a list of 1018 genes expressed in NSCs that are predicted to be common targets for both microRNAs (Supplementary Table 3). Gene ontology analyses using The PANTHER (Protein ANalysis THrough Evolutionary Relationships) Classification System, Version 14 [118] identified a list of 18 significantly overrepresented and 6 significantly underrepresented biological pathways (BPs, Fig. 2A). Interestingly, the top overrepresented BP (FDR corrected p value = 2.45 E-3) was

mitochondrial fatty acid beta-oxidation (FAO), a BP previously identified as key regulator of adult NSC activity [119]. 7 genes involved in FAO were predicted as common miR-124 and miR-137 targets (Fig. 2B). Previous studies have shown that cytokine-mediated astrocyte activation in the striatum is linked to enhanced FAO and increased astrocyte resistance to (metabolic) insults [120], pointing at FAO as a possible candidate molecular pathway for further studies aimed to understand the regulation of NSC by neurological insults.

3. The hippocampal neurogenic cascade as potential therapeutic target

Effects of aberrant neurogenesis on cognition have been extensively characterized. However, the shift from neurogenesis towards astrogenesis, due to the induction of React-NSCs, has not been studied in great detail. Interestingly, astrogliosis in the hippocampus has been shown to drive the formation of chronic epileptic seizures, possibly by deregulation of the tripartite synapse and hence the electric homeostasis of the neuronal-glia network [82].

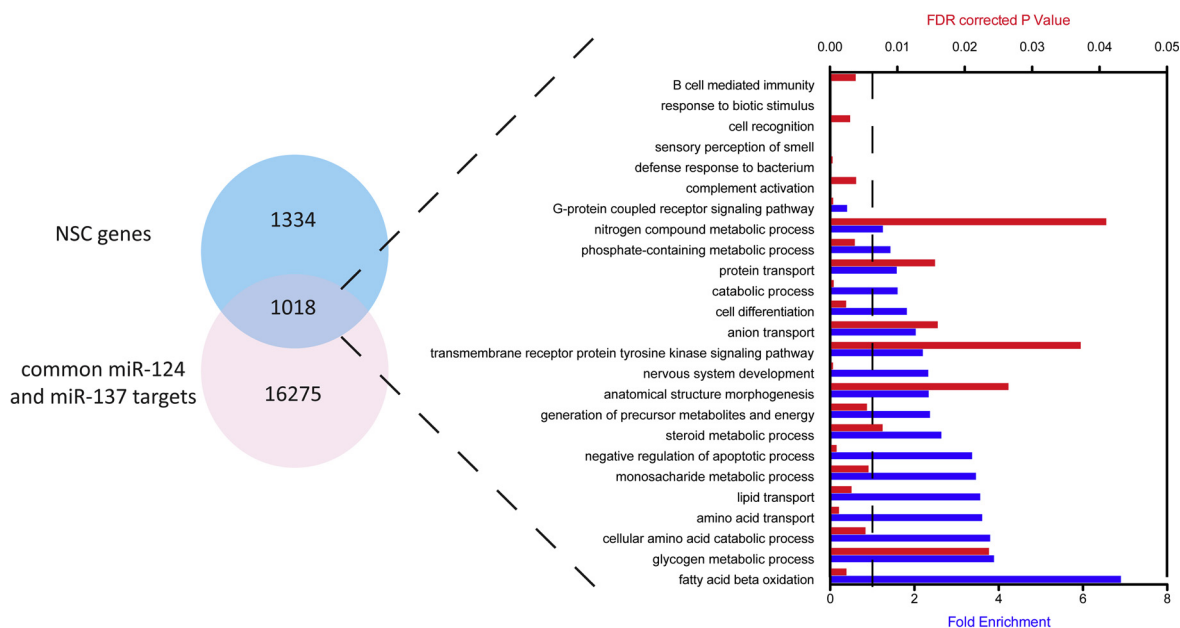
As a significant number of TBI patients suffer from post-traumatic epileptic seizures [121], which has also been shown in established rodent models, these studies together raise the question whether inhibiting the induction of aberrant neurogenesis and astrogliosis could be a potential therapeutic target to prevent or rescue the secondary cognitive deficits and occurrence of post-traumatic epilepsy.

Several studies have attempted to inhibit neurogenesis using approaches like irradiation, but altogether failed to reach a consensus on the role of neurogenesis in seizure development and cognitive impairment, possibly due to differences in spatiotemporal design and readouts and the choice of behavioral paradigm [122–125]. The most compelling evidence linking aberrant neurogenesis to cognitive deficits in relation to epilepsy comes from a study that used a genetic approach to ablate neurogenesis in the DG, shortly prior to the chemical induction of epileptic seizures by means of pilocarpine. Mice with intact neurogenesis showed cognitive deficits and chronic spontaneous seizures, which could both be rescued by the genetic ablation of neurogenesis [126]. Inhibiting neurogenesis to prevent cognitive deficits was recently shown to also be a promising strategy after stroke [68].

To date, most studies addressing aberrant neurogenesis in the context of the 3 brain disorders discussed here have been exploratory approaches using a complete inhibition of the neurogenic cascade in order to understand the molecular mechanisms behind this pathological shift in stem cell fate decisions and aberrant neurogenesis. These studies have been of great value, as they have given the field new approaches to tackle the induction of aberrant neurogenesis. In order to work towards translational therapeutic strategies, one must consider strategies that are solely aimed at preventing the shift from healthy neurogenesis towards aberrant neurogenesis, maintaining a healthy baseline level of neurogenesis that will be crucial for proper cognitive functions, instead of complete inhibition of the neurogenic cascade, which in itself will hamper cognitive processes.

We have recently employed such a non-genetic approach using microRNA interference *in vivo* [59]. Our study identified non-convulsive seizure-induced changes in NSCs that resulted in a shift from neurogenesis towards reactive astrogenesis. In a first attempt to rescue the seizure-induced effects on NSCs and their progeny, we infused anti-microRNA oligonucleotides (AMOs) to simultaneously inhibit miR-124 and miR-137 specifically and found that this intervention blocked or reversed several seizure-induced alterations in NSCs. Although we did not address the effects of miR-124 and miR-137 AMOs on long-term seizure outcomes, the contribution of aberrant new neurons to hippocampal circuits or cognition, recent studies have demonstrated the effectiveness of AMOs targeting miR-135a and miR-134 to reduce spontaneous recurrent seizures in experimental models of epilepsy [127,128] and to identify a role for miR-22 in aberrant neurogenesis after status epilepticus, where miR-22 AMOs exacerbated the ectopic

A



B

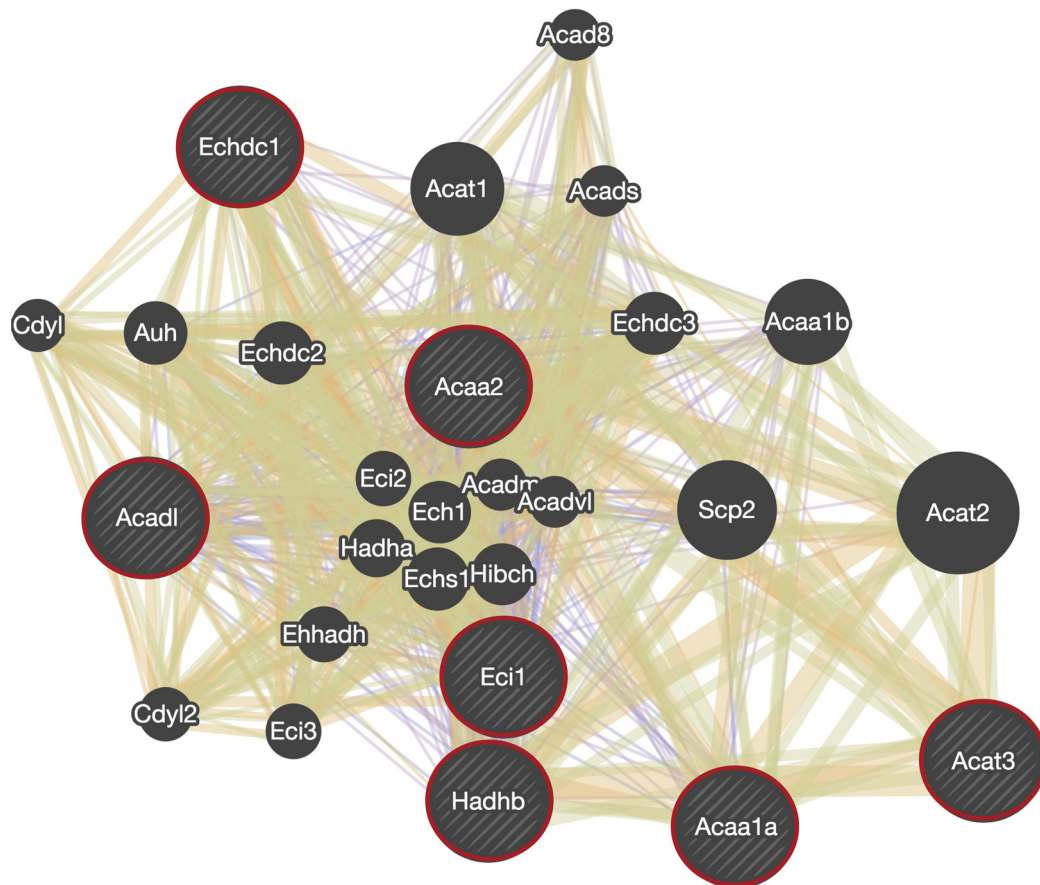


Fig. 2. Bioinformatic analysis of putative common miR-124 and -137 targets indicates fatty acid beta oxidation as a potential regulatory pathway involved in the therapeutic effects of the antagomir treatment.

A) Venn diagram of genes expressed in hippocampal NSCs mapped against putative common targets of miR-124 and -137 reveals 1018 putative candidate genes. Panther GO analysis identified 18 overrepresented biological processes, of which fatty acid beta oxidation was the highest overrepresented within our sample. **B)** Genemania pathway analysis of fatty acid beta oxidation. Out of the total 22 genes involved in the pathway, 7 genes (striped pattern) were predicted common targets of both miRNAs.

migration of newborn neurons [129]. Overall, these results underscore the potential of AMOs as experimental tools that could be further developed towards future therapeutic strategies to counteract the deleterious effects of brain insults.

4. Future perspectives

During recent years, it has become clear that insult-induced aberrant neurogenesis is detrimental to hippocampal function and results in cognitive deficits. First attempts to rescue the induction of aberrant neurogenesis have recently been employed, but we are still a long way from fully understanding the process, its consequences, and thus potential therapeutic targets and strategies. Instead of a complete inhibition of the full neurogenic cascade, rather individual stages of the neurogenic process might be worthwhile to consider as potential targets (i.e. NSC hyperactivation, the induction of React-NSCs, or the differentiation and integration phase of the newborn neurons (Fig. 1). It will be crucial in the coming years to also focus more on the epigenetic dysregulation of the neurogenic cascade upon the induction of pathology, as this will help to identify novel therapeutic approaches with a higher clinical translational value that can be employed to prevent cognitive deficits.

The gap from preclinically used approaches to the clinic is still significant, but the use of RNA interference is a first step. The temporary nature of RNA interference compared to genetic approaches provides powerful, specific tools with more translational value. Recently, the first clinical RNA interference approach has been approved by the FDA [130], giving way for the further development of such approaches, that one day may hopefully be able to help prevent the comorbid cognitive deficits associated with the devastating pathologies of epilepsy, stroke and TBI.

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