

1 **Physical exercise induces hippocampal neurogenesis and prevents cognitive decline**

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26 Abstract

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227 Accumulating evidence from animal and human research indicate that adult hippocampal neurogenesis
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528 plays a key role in cognition. Meanwhile, cognitive decline is well known to associate with ageing-related
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729 neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Therefore,
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1030 prevention of hippocampal neurogenesis reduction should be critical for these diseases. Physical exercise,
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1331 a potent enhancer of adult hippocampal neurogenesis, has emerged as a potential therapy or an adjunctive
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1632 therapeutic strategy for cognitive decline. In this review, we discuss the recent findings on hippocampal
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1833 neurogenesis and the incorporation of new born neurons into the neuronal network in humans and in
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2134 rodents. By focusing on hippocampal neurogenesis, we illustrate the role and possible mechanisms of
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2435 physical exercise in cognition preservation.

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2736 **Keywords:** Neurogenesis; Exercise; Cognition; Brain plasticity; Neurodegenerative disease; Aging
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31 3238 1. Introduction

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3539 Neurogenesis, the production of neural cell-types from neural stem cells (NSCs) or neural progenitor cells
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3840 (NPCs) occurs throughout life [1]. This new conception overturns the long-held dogma that the adult
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4141 brain has no capacity for generating new neurons. Adult neurogenesis has been consistently observed in
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4342 the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate
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4643 gyrus under normal conditions [2]. Neurons born in the SGZ can incorporate into the existing neural
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4944 network of granule cells in the dentate gyrus [3, 4]. Furthermore, new born adult dentate granule cells
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5245 (DGCs) are believed to contribute to hippocampus-dependent functions such as learning and memory [5,
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5446 6] and in particular pattern separation, defined as the ability to transform a set of similar input patterns
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5747 into a less-similar set of output patterns in information processing [7, 8].
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6249 Hippocampal neurogenesis reduction happens in aging-related neurodegenerative diseases, such as
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Alzheimer's disease (AD) and Parkinson's disease (PD), which are accompanied with cognitive decline [9-11]. Hence, promotion of the hippocampal neurogenesis has become a new insight to cure these diseases and to delay or halt brain aging. How to enhance hippocampal neurogenesis has captured the attention of many neuroscientists. Adult neurogenesis in the mammalian brain has been suggested as a dynamic process which is regulated by numerous intrinsic and extrinsic factors [12]. Hippocampal neurogenesis represents the regenerative capacity of adult mammalian brain and a striking form of brain plasticity. Interestingly, recent studies indicate that physical exercise regulates the proliferation, **differentiation**, survival and maturation of NPCs, and support the positive correlation between exercise-induced hippocampal neurogenesis and cognition improvement [13-18].

2. Adult hippocampal neurogenesis in humans and rodents

The existence of adult NSCs in the rodent brain was reported in the 1960s, while the first direct evidence supporting the notion of human adult neurogenesis was discovered in hippocampus in 1998 by using bromodeoxyuridine (BrdU) labeling technique [19]. However, due to safety concerns, it has been difficult to study neurogenesis in humans by BrdU technique. **Thus, the current methods employed to study adult human neurogenesis rely on immunostaining of postmortem brain tissues with endogenous markers, such as glial fibrillary acidic protein (GFAP), for astroglia, and NeuN, calbindin, doublecortin (DCX), Ki67 and, Nestin for neurons [19, 20] or culturing human NPCs isolated from tissue biopsies [21, 22]. A new technique using the natural ¹⁴C abundance in genomic DNA has been developed to determine the neuronal age, which has been integrated into some mathematical models to calculate dynamics of neurogenesis in adult human postmortem hippocampus [23]. Nevertheless, these ex vivo measurements could not provide further information on the possible role of adult neurogenesis. Notably, magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) techniques are thought to be available methods to assess hippocampal neurogenesis in living person [24, 25]. The former detects the neurogenesis by identifying a**

74 NPC-specific metabolic biomarker [24], and the latter tests neurogenesis based on the positive
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275 correlation between MRI measurements of cerebral blood volume and neurogenesis because of their
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576 coupling [25], but the validity and accuracy remain to be determined. Technological limitations halt the
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77 analysis of the functional role of adult hippocampal neurogenesis in humans. To date, it is still difficult to
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1078 study hippocampal neurogenesis directly in living person and a huge amount of studies mainly come from
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1379 rodent experiments.
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1881 The findings of several studies indicate the same location and similar regulation of adult hippocampal
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2182 neurogenesis between humans and other mammals. Firstly, Eriksson et al [19] provided solid evidence
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2483 that adult neurogenesis in humans occurs in the SGZ of dentate gyrus, the same region in which new
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2784 neurons reside in rodents and monkeys [20, 23, 26]. Secondly, the number of new born neurons in human
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3085 dentate gyrus shows a steadily reduction with aging [20, 23]. This parallels with the age-related decrease
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3286 seen in non-human mammals [27, 28] which provides evidence that the regulation of adult hippocampal
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3587 neurogenesis in humans could be similar to that in other mammalian species.
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4089 Given few relevant human studies, it is difficult to compare the number of new adult DGCs between
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4390 humans and non-human mammals. Snyder and Cameron speculated that the true number of new adult
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4691 born DGCs might be significantly higher in humans than in rats, with the reasons that the dosage of BrdU
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4992 conversed from a very small dose used in humans failed to detectably label 40-90% of S-phase cells in
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5293 rodents and that the human subjects were terminally ill and, advanced in age with likely reduced
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5494 neurogenesis [26]. In addition, the turnover rate of DGCs could be higher in humans than in mouse, with
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5795 35% in humans compared to 10% in mouse [23, 29]. Furthermore, the maturation period of the new adult
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6096 born neurons deviates in different species. The maturation period of DGCs in adult macaque monkeys is 6
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6397 times longer than that in adult rodents [30]. The maturation time might be even longer in humans because
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of that the total length of the embryonic neurogenic period is 100d in humans, 60d in monkeys and, 6d in mice, and that the cell cycle of human NPCs is 5 times longer compared with that of other mammals suggesting that NPCs in dentate gyrus divide at a slow rate in humans [30].

In the adult brain, the hippocampus is a critical structure for the formation of certain types of memory [31-33] and mood regulation [34]. A fundamental question has been raised that whether the continuously generated neurons have some specific functions? It is well known that immediate early gene (IEG), such as Arc, Fos, and Egr1 (also known as Zif268), are the indicators of recently activated neurons [35-37]. Therefore, immunofluorescence double labeling of IEG and BrdU has been used to confirm the adult new born neurons contributing to process the hippocampus-dependent information [37, 38]. Furthermore, irradiation and anti-mitotic drugs have been used to assess the contribution of adult new born neurons to animal behaviors and the results revealed that ablation or reduction of adult hippocampal neurogenesis results in functional deficit [39, 40]. A recent study has shown that increasing adult hippocampal neurogenesis is sufficient to reduce anxiety and depression-like behaviors [41]. Collectively, these studies demonstrate that new adult neurons contribute to hippocampus-dependent functions.

3. Integration of adult new born neurons into the existing network

In the past several years, it has become clear that adult generated neurons can form synaptic connections with the existing circuit. In rodents, there are two precursor pools of the dentate gyrus, type 1 (quiescent) and type 2 (latent) NPCs in the SGZ [42, 43]. Type1 NPCs have a radial process and express endogenous progenitor markers of nestin, GFAP, Sox2 [42, 44]. Although type 1 NPCs express the astrocyte marker GFAP, they are morphologically and functionally different from mature astrocytes [45]. The type 2 NPCs have only short horizontal processes and express Sox2 [45]. Type 2 progenitors give rise to astrocytes and granule cells in the dentate gyrus, which could play an important role in early AD process. **It has been**

122 suggested that dysfunctional neurogenesis exacerbates neuronal vulnerability to AD characterized by
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223 deposition of amyloid- β ($A\beta$), a kind of neurotoxicity protein, whereas enhanced neurogenesis represents
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524 an endogenous brain repair mechanism of AD by providing more new neurons to replace the dead or
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825 impaired ones [42, 45].
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1627 The new adult born DGCs bear little resemblance to their mature counterparts and must undergo a
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1928 lengthy process of morphological and physiological maturation [13]. As maturation, the new cells receive
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2429 afferent inputs from local interneurons [4, 46] and entorhinal cortex by perforant path [2, 13], while, their
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2930 efferent outputs project to hilus and CA3 pyramidal neurons by mossy fibres [2, 47]. During the second
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3531 week after birth, the formation of synapses connecting local interneurons and the new granule cells occurs
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4632 [2]. Initially, these synapses are depolarized by gamma-aminobutyric acid (GABA) and are therefore less
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5733 likely to be inhibited by the strong GABAergic inhibition in the dentate gyrus, however, become
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The new adult born DGCs bear little resemblance to their mature counterparts and must undergo a lengthy process of morphological and physiological maturation [13]. As maturation, the new cells receive afferent inputs from local interneurons [4, 46] and entorhinal cortex by perforant path [2, 13], while, their efferent outputs project to hilus and CA3 pyramidal neurons by mossy fibres [2, 47]. During the second week after birth, the formation of synapses connecting local interneurons and the new granule cells occurs [2]. Initially, these synapses are depolarized by gamma-aminobutyric acid (GABA) and are therefore less likely to be inhibited by the strong GABAergic inhibition in the dentate gyrus, however, become indistinct as the neurons maturing [4]. The efferent projections of newborn neurons to the CA3 area also occur at this time [13]. It is worth noting that GABA in the dentate gyrus plays a key role in adult hippocampal neurogenesis through dual regulation of both stem cell activation and neuroblast survival at this time window [46, 48].

Consistent with the formation of dendritic spines, afferent input from entorhinal cortex is lack in these new neurons until after 2 weeks of birth [2]. Originally, the majority of spines on the new granule cells are liable to target axon boutons that already synapse with other existing spines [49]. Furthermore, the mossy fibre boutons of new granule cells initially form synapses with CA3 pyramidal neurons either near existing thorny excrescences or directly with thorny excrescences [47, 50]. It is suggested that both afferent and efferent synapses formation of new adult born granule cells are influenced by synaptic activity. Moreover, approximately half of all neurons die during the first 4 weeks of birth [51, 52] and the

146 basic physiological and morphological properties of the survivors are indistinguishable from their mature
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147 counterparts at 8 weeks of age [2, 53]. Nevertheless, the structural modifications of dendritic spines and
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148 axonal boutons continue to occur as the adult born granule cells become older. Fully maturation of
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149 newborn neurons will take months [13], suggesting that synaptic plasticity of the new neurons will take
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150 quite a long period of time.

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152 Interestingly, accumulating evidence indicates that immature granule cells in the adult dentate gyrus have
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153 specific electrophysiological properties different from their mature counterparts. **In the period between 4
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154 and 6 weeks of age, adult born neurons exhibit enhanced long-term potential (LTP) showing a higher
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155 potential amplitude and a lower induction threshold [54]. In addition, immature neurons are more easily
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156 to be recruited into the neural circuits than their mature counterparts [47, 55, 56].** The aforementioned
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157 findings reveal that young neurons appear to be more excitable than mature neurons and may differ from
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158 their mature counterparts in firing patterns. Increased neurogenesis which induces more new neurons
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159 taking part in the neuronal network may consequently affect the functions of hippocampus because of the
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160 higher activity.

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162 Despite of limited techniques in humans and the deviates between species, there is compelling evidence
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163 on adult hippocampal neurogenesis and integration of the new born neurons (Figure 1). From the synaptic
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164 perspective, the formation of new synapses enhances the plasticity of the pre-synaptic and post-synaptic
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165 neurons. From the neuronal network perspective, the formation of new synapses reflects the formation of
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166 a new neuronal network. A higher excitability of the new neurons makes the neuronal network even more
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167 sensitive to the stimulus, which maybe at least in part accounts for the increase of efficiency in processing
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168 information, thereby contributes to the improvement of hippocampus-dependent functions.

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170 4. Physical exercise improves cognition via inducing hippocampal neurogenesis

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271 There is growing evidence suggest that physical exercise enhances not only the physical health of
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572 individuals but also cognition and other brain functions. Physical exercise improves fitness, memory,
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173 attention and reading, thereby benefits academic achievement in children [57, 58]. A large scale studies
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174 substantiate that cardiovascular fitness positively associated with intelligence [59, 60]. Moreover,
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175 cardiovascular fitness during early adulthood predicts socioeconomic status and educational attainment
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176 later in life [60]. A meta-analysis study has shown that 1 to 12 months of exercise in healthy adults brings
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177 behavioral benefits in memory, attention, processing speed and executive function [61]. In addition, both
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2178 acute and long-term physical exercise leads to improvement in physical performance, executive function
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2179 and global cognition in healthy older adults and older adults with cognitive impairment [62, 63].
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3181 In rodents, voluntary running exercise significantly increases proliferation of NPCs in the dentate gyrus
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3282 [14, 64] and also benefits spatial memory [16]. Moreover, treadmill running (forced exercise) can regulate
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3583 hippocampal neurogenesis through an intensity-dependent manner. It was demonstrated that supra-lactate
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3884 threshold treadmill exercise can significantly increase hippocampal neurogenesis [65], while treadmill
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4185 running below the lactate threshold improves survival and maturation of new born neurons as well as
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4486 benefits spatial memory [15]. Furthermore, wheel running increases spine motility and the mushroom
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4687 spine density as well as enhances spine growth during early maturational stages, thereby, regulates the
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4988 maturation and integration of newborn neurons into the hippocampal circuit [13]. It is strikingly that
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5289 exercise heightens the amplitude of LTP in the dentate gyrus and improves learning characterized by
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5590 faster acquisition and better retention tested in Morris water maze [64, 66]. Thus, physical exercise is
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5791 involved in the regulation of adult hippocampal neurogenesis including proliferation, differentiation,
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6092 survival, maturation and function.
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194 Collectively, above studies demonstrate that exercise benefits cognition in humans as well as in animals
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195 and increases neurogenesis in the dentate gyrus in rodents. However, whether exercise-induced
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196 hippocampal neurogenesis is the underpinning of beneficial effects that physical exercise brings to
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197 cognition? Studies using neurogenesis inhibition and IEG labeling techniques provide us with valuable
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198 information to cut through the fog. Focal irradiation to inhibit hippocampal neurogenesis results in
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199 cognitive deficits, whereas, 3 weeks wheel running ameliorates the impairment [67]. Another study using
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200 a lentiviral approach to block neurogenesis of dentate gyrus showed that blocking hippocampal
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201 neurogenesis impairs cognition in a level-dependent manner, and resulted in spatial memory decrease and
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202 even object recognition impairment [6]. Furthermore, IEG studies confirmed that new DGCs may be
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203 preferentially recruited into circuits, which mediate spatial information processing and memory formation
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204 [5, 38, 68].

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3206 However, other studies draw a different conclusion. It is suggested that ablation of hippocampal
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3207 neurogenesis by focal irradiation impairs contextual fear conditioning and synaptic plasticity in the
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3208 dentate gyrus, but has no effect on spatial learning tested in Morris water maze and Y maze [40].
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209 Swimming in the water maze with or without platform can both increase hippocampal neurogenesis, but
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4210 young neurons are activated only by platform location training [68]. To some degree, these conflicting
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4211 conclusions are interpretable. Spatial processing depends on the dorsal hippocampus, whereas
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4212 anxiety-related behavior relies more on the ventral hippocampus [68]. Different irradiation regions and
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213 degrees of irradiation among the studies could be responsible for the deviation results in cognition [6, 68].
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214 It is also possible that there exist different mechanisms that regulate neurogenesis as well as activate the
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5215 neurons. Neurogenesis is required for some but not other hippocampus-dependent tasks, and is not
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6016 required for tasks that do not involve the hippocampus [69, 70], therefore, the activation of adult born
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217 DGCs is situation-specific [71]. Although swimming is a sensitive stimulus to increase the hippocampal
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218 neurogenesis, but it is not the sensitive stimulus to activate these new adult born neurons.

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220 The techniques of retroviral labeling and rabies virus mediated trans-synaptic retrograde tracing which are
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221 capable to define and quantify new neuron afferent inputs have paved the way for us to further understand
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222 the exercise-induced neurogenesis. **Recent studies have demonstrated that wheel running regulates adult**
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223 **born neuron presynaptic connectivity from local interneurons or long-range projection neurons in**
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224 **subcortical regions [56, 72], and specifically augments the innervations from entorhinal cortex [72].**
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225 Altogether, physical exercise may benefit cognition through increasing adult hippocampal neurogenesis,
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226 upregulation innervations between regions and reorganization of neural network, which represents a form
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227 of structural and network plasticity in hippocampus and other regions so as to refine neural connections.
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228 However, physical exercise-induced neurogenesis is required to contribute to some but not all
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229 hippocampus-dependent cognitions [69, 73]. Recent evidence reveals that new adult born neurons
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230 indirectly encode and store memories by regulating excitation-inhibition balance [74].
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35 36 37 38 **5. Mechanisms of physical exercise induced hippocampal neurogenesis** 39

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233 Neurogenic niche, the microenvironments of SGZ and SVZ, may have specific factors that are permissive
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234 for the differentiation and incorporation of new neurons [45]. Adult progenitor cells derived from
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235 non-neurogenic areas exhibit self-renewal and multi-potentiality once transplanted into a neurogenic brain
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236 area, and can differentiate in a region-specific context, suggesting that the microenvironment has a crucial
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237 role in providing and regulating fate-determining cues in the adult brain [75]. What makes the SGZ
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238 special in supporting the proliferation and differentiation of multi-potent neural progenitors has attracted
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239 the interest of scientists. In addition to progenitors, there are mature neurons, astrocytes, oligodendrocytes,
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240 and endothelial cells [76], which may provide some of the components in the neurogenic niche contribute
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241 to the regulation of physical exercise-induced hippocampal neurogenesis. Figure 2 highlights the
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242 mechanisms of physical exercise in promoting hippocampal neurogenesis.

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244 Astrocytes, the most abundant cell type in the mammalian brain, make connections with neurons by
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245 tripartite synapses [77]. Astrocytes also surround blood vessels by the endfeet, which makes the
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246 astrocytes, neurons and blood vessels working together as functional units [78]. Therefore, astrocytes
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247 serve as bridges, relaying information and transporting substances between blood vessels and neurons. It
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248 is suggested that astrocytes play a key role in promoting the neuronal differentiation of adult hippocampal
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249 NPGs and in the integration of adult new born neurons [79]. There is evidence that exercise significantly
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250 increases the number of astrocytes in hippocampus and other regions of the brain [80, 81], and lengthens
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251 the processes of astrocytes in hippocampus [81]. In addition, exercise can also induce transporters plastic
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252 changes in astrocytes such as improving the expression of glucose transporter1 (GLUT1) to support the
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253 increasing demand of glucose as neural activity enhancement [82]. Collectively, the effects of exercise on
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254 astrocytes may be partly responsible for the underling mechanism of exercise-induced hippocampal
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255 neurogenesis.

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257 The vasculatures of the neurogenic niche regulate neural stem cell behavior by providing circulating and
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258 secreted factors. Various forms of cerebrovascular insufficiency such as reduced blood supply or
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259 disrupted microvascular integrity in cortical regions may occupy an initiating or intermediate position in
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260 the cognitive decline [83]. In addition, proliferating cells and putative neural progenitors in SGZ are
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261 closely associated with the vasculature, indicating that blood-derived factors may have a direct impact on
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262 adult neural progenitors [84]. Indeed, factors such as growth differentiation factor 11 (GDF11) found in
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263 young blood induce vascular remodeling and increase neurogenesis in aging mice [85]. Moreover,
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264 vascular endothelial growth factor (VEGF) a common factor regulating angiogenesis secreted by
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265 endothelial cells, is implicated in improving neurogenesis in the SGZ [86] and exercise-induced
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266 neurogenesis in the hippocampus with improvement cognition acts in part through VEGFR2/Flk-1
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267 signaling [87]. Conversely, blockade of VEGF abolishes exercise-induced neurogenesis [88].
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269 Neurogenic niche are richly innervated by axonal inputs from local interneurons and distant cortical or
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270 subcortical regions [56]. Release of neurotransmitters and other factors by afferent inputs may regulate
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271 precursors at different stages of the stem cell lineage [76]. A number of different neurotransmitters such
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272 as serotonin (5-HT), GABA and glutamate play a role in the exercise-induced hippocampus neurogenesis.
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273 In the adult SGZ, GABA presumably from local interneurons has a depolarization effect on the maturing
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274 granule neurons during the initial period of hippocampal neurogenesis [4]. The GABA-mediated activity
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275 seems to be important for the survival and maturation of adult born DGCs via cyclic AMP response
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276 element-binding protein (CREB) [89]. It is suggested that transcription factor CREB is activated by
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277 exercise-induced brain-derived neurotrophic factor (BDNF) expression and activation of cellular survival
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278 AKT signaling [90]. 5-HT also has an important role in the exercise-induced neurogenesis because
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279 stimulation of the 5-HT₃ receptor promoted neurogenesis and 5-HT₃ receptor subunit deficiency results
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280 in loss of exercise-induced hippocampal neurogenesis and antidepressant effects [91]. One type of the
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281 glutamate receptors, N-methyl-D-aspartate (NMDA) receptor, is involved in the increase of
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282 exercise-induced long-term potentiation (LTP) [92]. LTP induction depends upon the activation of
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283 NMDA receptors, the competitive antagonist could block the effect [92, 93]. In addition, exercise
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284 up-regulates the mRNA levels of NR2b, a subtype of NMDA receptor, and enhances BDNF expression in
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285 the dentate gyrus as well [92], indicating that enhanced secretion of glutamate and BDNF by local
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286 neurons or neurons outside of the neurogenic niche may contribute to the regulation of exercise-induced
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287 hippocampal neurogenesis.
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289 Moreover, Bergami et al recently highlighted that there is a critical time window during the new DGCs
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290 maturation in rodents [56]. In this time period, the new neurons are most sensitive to the stimuli such as
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291 enriched environment and physical exercise and exhibit stronger synaptic plasticity than mature DGCs, as
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292 indicated by the lower threshold for the induction of LTP and higher LTP amplitude [2, 54, 94]. This
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293 transient enhancement in plasticity may provide a fundamental rationale for the timing of exercise
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294 intervention implement which would produce optimal therapeutic effects. Literatures available revealed
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295 that the time window was 2-6 weeks and 4-6 weeks birth age of neurons in mice and in rats respectively
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296 [2, 54, 56]. Notably, if the hypothesis above proved to be correct, the critical time window may be coming
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297 later and time period may be longer in humans than in rodents because of the slower mitotic division rate
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298 and longer maturation time period in humans. Hence, understanding the details of the critical time
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299 window in humans seems important in exercise intervention to delay or halt brain aging and to get best
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300 therapeutic efficacy, as well as to develop adjunctive therapeutic strategies for neurodegenerative diseases
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301 or mental disorders.
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302 **6. Potential therapeutic and preventive implications of physical exercise in cognitive decline of** 33 34 35 303 **aging-related neurodegenerative diseases** 36 37

304 Aging, depression, AD and PD are characteristic of cognitive decline which is one of the major health
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305 challenges faced by modern society. Hippocampal neurogenesis decreases along with age, which may
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306 underlie cognitive impairments associated with aging-related neurodegenerative diseases such as AD and
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307 PD [95]. In addition, hippocampal neurogenesis reduction is a prominent feature in rodent models of
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308 stress and depression [9]. Intriguingly, some anti-depressant treatments result in enhancement of
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309 hippocampal neurogenesis as well as induction of LTP [34, 96]. A growing body of evidence suggests
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310 that promotion of adult hippocampal neurogenesis improves cognition such as pattern separation and
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311 spatial memory [97]. Thus, improvement of hippocampal neurogenesis has the hope to delay or halt
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312 cognitive decline in these diseases.
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Over the last decade, the use of NSCs transplantation to treat cognitive impairment has received growing attention, NSCs transplanted into the hippocampus give rise to neurons, astrocytes and oligodendrocytes [98] and reverse progressive cognitive decline associated with aging [99]. Furthermore, human NSCs injected into the lateral ventricle or transplanted into the hippocampus of aged rats incorporate into the host brain and improve cognition function as assessed by the Morris water maze [100, 101]. However, this novel approach faces several issues such as reliable characterization, experimental reproducibility as well as mitotic capacity [22]. In addition, NSCs transplantation has a quite low rate of efficiency in the aged brain compared to the young [85]. Collectively, it seems a long way to go before NSCs transplantation can be used to cure cognition decline in humans.

Since the goal of stem cell transplantation is to introduce new neurons that could contribute to functional enhancement or reconstruction of impaired neuronal circuitry [10], physical exercise could be an alternative to achieve the goal. As discussed above, age related decline of neurogenesis and cognitive function is associated with reduced blood flow and decreased numbers of NSCs. Interestingly, physical exercise can rejuvenize the neurogenic niche with increased blood flow into brain and enhanced hippocampal neurogenesis and neuronal plasticity, thereby, should counteract the negative effects of aging.

Recent meta-analysis reports unraveled that regular physical activity performed by elderly people plays a certain protective role against AD by improving cognition [102], and suggested that drug therapy for AD and mild cognitive impairment should be combined with exercise intervention [103]. In the Tg4-42 mouse model of AD, physical activity delays hippocampal neurodegeneration and rescues spatial memory deficits [104]. Altogether, physical exercise has emerged as an effective, low-cost, and low-tech way for prevention or slowdown of cognitive decline in aging and aging associated neurodegenerative diseases.

338 7. Conclusions and future directions

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339 Neurogenesis in the hippocampus represents a form of morphological and functional plasticity in the
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340 mammalian adult brain. Activity-dependent regulation of neurogenesis and experience-dependent
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341 participation of adult born DGCs in information processing imply the contribution of adult born DGCs in
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342 hippocampus-dependent functions. Neurogenesis ablation and IEG labeling methods consistently suggest
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343 the involvement of adult born DGCs in learning and memory. Reduction of hippocampal neurogenesis is
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344 always accompanied with cognitive decline in diseases such as depression, AD and PD. Improvement of
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345 hippocampal neurogenesis induced by exercise benefits some but not all hippocampus-dependent
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346 functions. The precise mechanisms of exercise-induced neurogenesis are largely unclear. However,
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347 physical exercise may regulate the overall dynamic balance in the neurogenic niche through increasing
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348 proliferation of astrocytes and enhancing the secretion of some transmitters, growth factors or
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349 neurotrophic factors. The non-invasive imaging techniques have been developed for monitoring
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350 hippocampal neurogenesis in humans [24, 25], despite their validity and precision await further testing.
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351 These techniques pave the ways for us to investigate the functions of hippocampal neurogenesis in living
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352 persons under various physiological or pathological conditions, which will hopefully lead to novel
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353 diagnoses and therapies for neurological disorders.

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355 The potential that adult hippocampal neurogenesis can be manipulated has inspired hope for treatments to
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356 slow or even repair brain damage from diseases or injuries. Exogenous introduction of new neurons by
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357 transplantation of human NSCs [98-100, 105] or perfusion of young blood into the aging brain to
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358 rejuvenate the neurogenic niche seems to be promising techniques in inducing brain plasticity for some
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359 diseases associated with cognitive decline. From this perspective, physical exercise known as a non-drug,
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360 non-invasive, low-cost and low-tech method to induce up-regulation of endogenous neurogenesis in the
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361 hippocampus and appears to be an available alternative therapeutic method. Bare in mind that

hippocampal neurogenesis deviates between species and little information available to know how far the situation in animal models would reflect the conditions in the adult human brain. However, we speculate that neurogenesis generates more adult born DGCs, has slower mitotic division rate, owns higher granule neurons turnover rate and longer maturation time period in humans than in rodents based on the literatures available. Thus, more precise non-invasive techniques are warranted to further investigate hippocampal neurogenesis on physiological and pathological conditions in humans. Moreover, understanding the time window of hippocampal neurogenesis in humans could be important for exercise intervention to delay or halt brain aging, as well as to develop adjunctive therapeutic strategies for neurodegenerative diseases or mental disorders.

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References

- [1]. Pierret C, Morrison JA, Rath P, Zigler RE, Engel LA, Fairchild CL, et al. Developmental cues and persistent neurogenic potential within an in vitro neural niche. *BMC Dev Biol.* 2010;10:5. [PubMed: 20074373]
- [2]. Deng W, Aimone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci.* 2010;11:339-50. [PubMed: 20354534]
- [3]. van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH. Functional neurogenesis in the adult hippocampus. *Nature.* 2002;415:1030-4. [PubMed: 11875571]

- 386 [4]. Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of
1
387 newly generated neurons in the adult brain. *Nature*. 2006;439:589-93. [PubMed: 16341203]
3
4
388 [5]. Kee N, Teixeira CM, Wang AH, Frankland PW. Preferential incorporation of adult-generated granule
6
7
389 cells into spatial memory networks in the dentate gyrus. *Nat Neurosci*. 2007;10:355-62. [PubMed:
8
9
1390 17277773]
11
12
1391 [6]. Jessberger S, Clark RE, Broadbent NJ, Clemenson GD, Jr., Consiglio A, Lie DC, et al. Dentate
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15
1392 gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in
16
17
18
1393 adult rats. *Learn Mem*. 2009;16:147-54. [PubMed: 19181621]
19
20
2194 [7]. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, et al. Increasing adult
22
23
2395 hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*. 2011;472:466-70.
25
26
396 [PubMed: 21460835]
27
28
29
397 [8]. Sahay A, Wilson DA, Hen R. Pattern separation: a common function for new neurons in hippocampus
30
31
3298 and olfactory bulb. *Neuron*. 2011;70:582-8. [PubMed: 21609817]
33
34
3599 [9]. Sahay A, Hen R. Adult hippocampal neurogenesis in depression. *Nat Neurosci*. 2007;10:1110-5.
36
37
400 [PubMed: 17726477]
38
39
40
401 [10]. Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van Praag H. When neurogenesis encounters
41
42
4402 aging and disease. *Trends Neurosci*. 2010;33:569-79. [PubMed: 20961627]
44
45
4603 [11]. Brehmer Y, Kalpouzos G, Wenger E, Lovden M. Plasticity of brain and cognition in older adults.
47
48
4904 *Psychol Res*. 2014;78:790-802. [PubMed: 25261907]
50
51
5205 [12]. Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant
52
53
5406 questions. *Neuron*. 2011;70:687-702. [PubMed: 21609825]
55
56
5707 [13]. Zhao C, Teng EM, Summers RG, Jr., Ming GL, Gage FH. Distinct morphological stages of dentate
58
59
6008 granule neuron maturation in the adult mouse hippocampus. *J Neurosci*. 2006;26:3-11. [PubMed:
61
62
6309 16399667]
64
65

- 410 [14]. Yau SY, Gil-Mohapel J, Christie BR, So KF. Physical exercise-induced adult neurogenesis: a good
1
411 strategy to prevent cognitive decline in neurodegenerative diseases? *Biomed Res Int*.
3
4
412 2014;2014:403120. [PubMed: 24818140]
6
- 7
413 [15]. Inoue K, Okamoto M, Shibato J, Lee MC, Matsui T, Rakwal R, et al. Long-Term Mild, rather than
8
9
10
414 Intense, Exercise Enhances Adult Hippocampal Neurogenesis and Greatly Changes the
11
12
13
415 Transcriptomic Profile of the Hippocampus. *PloS one*. 2015;10:e0128720. [PubMed: 26061528]
14
- 15
416 [16]. Lee MC, Inoue K, Okamoto M, Liu YF, Matsui T, Yook JS, et al. Voluntary resistance running
16
17
18
417 induces increased hippocampal neurogenesis in rats comparable to load-free running. *Neurosci Lett*.
19
20
21
418 2013;537:6-10. [PubMed: 23352660]
22
- 23
24
419 [17]. Sung YH. Effects of treadmill exercise on hippocampal neurogenesis in an MPTP
25
26
420 /probenecid-induced Parkinson's disease mouse model. *J Phys Sci*. 2015;27:3203-6. [PubMed:
27
28
29
421 26644675]
30
- 31
32
422 [18]. Vivar C, Peterson BD, van Praag H. Running rewires the neuronal network of adult-born dentate
33
34
35
423 granule cells. *NeuroImage*. 2016;131:29-41. [PubMed: 26589333]
36
- 37
424 [19]. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al.
38
39
40
425 Neurogenesis in the adult human hippocampus. *Nat Med*. 1998;4:1313-7. [PubMed: 9809557]
41
- 42
426 [20]. Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, et al. Murine features of
43
44
45
427 neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. *PloS one*.
46
47
48
428 2010;5:e8809. [PubMed: 20126454]
49
- 50
51
429 [21]. Roy NS, Wang S, Jiang L, Kang J, Benraiss A, Harrison-Restelli C, et al. In vitro neurogenesis by
52
53
54
430 progenitor cells isolated from the adult human hippocampus. *Nat Med*. 2000;6:271-7. [PubMed:
55
56
431 10700228]
57
- 58
59
432 [22]. Park TI, Monzo H, Mee EW, Bergin PS, Teoh HH, Montgomery JM, et al. Adult human brain neural
60
61
62
433 progenitor cells (NPCs) and fibroblast-like cells have similar properties in vitro but only NPCs
63
64
65

- 434 differentiate into neurons. PloS one. 2012;7:e37742. [PubMed: 22675489]
- 1
435 [23]. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, et al. Dynamics of
3
4
436 hippocampal neurogenesis in adult humans. Cell. 2013;153:1219-27. [PubMed: 23746839]
5
6
- 7
437 [24]. Manganas LN, Zhang X, Li Y, Hazel RD, Smith SD, Wagshul ME, et al. Magnetic resonance
8
9
10
438 spectroscopy identifies neural progenitor cells in the live human brain. Science. 2007;318:980-5.
11
12
1439 [PubMed: 17991865]
14
15
- 16
440 [25]. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. An in vivo
17
18
441 correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A .
19
20
21
442 2007;104:5638-43. [PubMed: 17374720]
22
23
- 2443 [26]. Snyder JS, Cameron HA. Could adult hippocampal neurogenesis be relevant for human behavior?
25
26
444 Behav Brain Res. 2012;227:384-90. [PubMed: 21736900]
27
28
- 29
445 [27]. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat:
30
31
32
446 age-related decrease of neuronal progenitor proliferation. J Neurosci. 1996;16:2027-33. [PubMed:
33
34
447 8604047]
36
37
- 38
448 [28]. Leuner B, Kozorovitskiy Y, Gross CG, Gould E. Diminished adult neurogenesis in the marmoset
39
40
449 brain precedes old age. Proc Natl Acad Sci U S A. 2007;104:17169-73. [PubMed: 17940008]
41
42
- 43
4450 [29]. Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, et al. Roles of
44
45
4451 continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat neurosci.
47
48
4452 2008;11:1153-61. [PubMed: 18758458]
49
50
- 51
453 [30]. Kohler SJ, Williams NI, Stanton GB, Cameron JL, Greenough WT. Maturation time of new granule
52
53
54
454 cells in the dentate gyrus of adult macaque monkeys exceeds six months. Proc Natl Acad Sci U S A.
55
56
455 2011;108:10326-31. [PubMed: 21646517]
58
59
- 60
456 [31]. Squire LR, Genzel L, Wixted JT, Morris RG. Memory consolidation. Cold Spring Harb perspect
61
62
457 Biol. 2015;7:a021766. [PubMed: 26238360]
63
64
65

- 458 [32]. Kim S, Dede AJ, Hopkins RO, Squire LR. Memory, scene construction, and the human
1 hippocampus. *Proc Natl Acad Sci U S A*. 2015;112:4767-72. [PubMed: 25825712]
459
3
- 460 [33]. Dede AJ, Wixted JT, Hopkins RO, Squire LR. Hippocampal damage impairs recognition memory
4
6 broadly, affecting both parameters in two prominent models of memory. *Proc Natl Acad Sci U S A*.
7
8 2013;110:6577-82. [PubMed: 23576763]
9
10
11
12
- 1463 [34]. Sahay A, Hen R. Hippocampal neurogenesis and depression. *Novartis Found Symp*.
14
15 2008;289:152-60; discussion 60-4, 93-5. [PubMed: 18497101]
16
17
- 1865 [35]. Countryman RA, Kaban NL, Colombo PJ. Hippocampal c-fos is necessary for long-term memory of
19
20 a socially transmitted food preference. *Neurobiol Learn Mem*. 2005;84:175-83. [PubMed: 16122949]
21
22
23
- 2467 [36]. Smith CA, Countryman RA, Sahuque LL, Colombo PJ. Time-courses of Fos expression in rat
25
26 hippocampus and neocortex following acquisition and recall of a socially transmitted food preference.
27
28 *Neurobiol Learn Mem*. 2007;88:65-74. [PubMed: 17448703]
29
30
31
- 3470 [37]. Tashiro A, Makino H, Gage FH. Experience-specific functional modification of the dentate gyrus
33
34 through adult neurogenesis: a critical period during an immature stage. *J Neurosci*. 2007;27:3252-9.
35
36 [PubMed: 16906136]
37
38
39
- 4073 [38]. Ramirez-Amaya V, Angulo-Perkins A, Chawla MK, Barnes CA, Rosi S. Sustained transcription of
41
42 the immediate early gene *Arc* in the dentate gyrus after spatial exploration. *J Neurosci*.
43
44 2013;33:1631-9. [PubMed: 23345235]
45
46
47
- 4876 [39]. Snyder JS, Hong NS, McDonald RJ, Wojtowicz JM. A role for adult neurogenesis in spatial
49
50 long-term memory. *Neurosci*. 2005;130:843-52. [PubMed: 15652983]
51
52
53
- 5478 [40]. Saxe MD, Battaglia F, Wang JW, Malleret G, David DJ, Monckton JE, et al. Ablation of
55
56 hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate
57
58 gyrus. *Proc Natl Acad Sci U S A*. 2006;103:17501-6. [PubMed: 17088541]
59
60
61
- 6281 [41]. Hill AS, Sahay A, Hen R. Increasing adult hippocampal neurogenesis is sufficient to reduce anxiety
63
64
65

- 482 and depression-like behaviors. *Neuropsychopharmacology*. 2015;40:2368-78. [PubMed: 25833129]
- 1
483 [42]. Mu Y, Gage FH. Adult hippocampal neurogenesis and its role in Alzheimer's disease. *Mol*
3
4
484 *Neurodegener*. 2011;6:85. [PubMed: 22192775]
- 6
7
485 [43]. Jhaveri DJ, Taylor CJ, Bartlett PF. Activation of different neural precursor populations in the adult
8
9
10
486 hippocampus: does this lead to new neurons with discrete functions? *Dev Neurobiol*.
11
12
13
487 2012;72:1044-58. [PubMed: 22505142]
- 14
15
488 [44]. Hsu YC, Lee DC, Chiu IM. Neural stem cells, neural progenitors, and neurotrophic factors. *Cell*
16
17
18
489 *transplant*. 2007;16:133-50. [PubMed: 17474295]
- 19
20
21
490 [45]. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell*.
22
23
24
491 2008;132:645-60. [PubMed: 18295581]
- 25
26
492 [46]. Song J, Zhong C, Bonaguidi MA, Sun GJ, Hsu D, Gu Y, et al. Neuronal circuitry mechanism
27
28
29
493 regulating adult quiescent neural stem-cell fate decision. *Nature*. 2012;489:150-4. [PubMed:
30
31
32
494 22842902]
- 33
34
495 [47]. Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, et al. Neurons born in the adult
35
36
37
496 dentate gyrus form functional synapses with target cells. *Nat Neurosci*. 2008;11:901-7. [PubMed:
38
39
40
497 18622400]
- 41
42
498 [48]. Song J, Sun J, Moss J, Wen Z, Sun GJ, Hsu D, et al. Parvalbumin interneurons mediate neuronal
43
44
45
499 circuitry-neurogenesis coupling in the adult hippocampus. *Nat Neurosci*. 2013;16:1728-30. [PubMed:
46
47
48
500 24212671]
- 49
50
51
501 [49]. Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, et al. Synapse formation on
52
53
54
502 neurons born in the adult hippocampus. *Nat Neurosci*. 2007;10:727-34. [PubMed: 17486101]
- 55
56
503 [50]. Faulkner RL, Jang MH, Liu XB, Duan X, Sailor KA, Kim JY, et al. Development of hippocampal
57
58
59
504 mossy fiber synaptic outputs by new neurons in the adult brain. *Proc Natl Acad Sci U S A*.
60
61
62
505 2008;105:14157-62. [PubMed: 18780780]
- 63
64
65

- 506 [51]. Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA. Short-term and long-term survival of
1
507 new neurons in the rat dentate gyrus. *J Comp Neurol.* 2003;460:563-72. [PubMed: 12717714]
3
- 508 [52]. McDonald HY, Wojtowicz JM. Dynamics of neurogenesis in the dentate gyrus of adult rats.
4
509 *Neurosci Lett.* 2005;385:70-5. [PubMed: 15967575]
6
- 510 [53]. Schmidt-Hieber C, Jonas P, Bischofberger J. Enhanced synaptic plasticity in newly generated
11
12 granule cells of the adult hippocampus. *Nature.* 2004;429:184-7. [PubMed: 15107864]
13
- 512 [54]. Ge S, Yang CH, Hsu KS, Ming GL, Song H. A critical period for enhanced synaptic plasticity in
15
16 newly generated neurons of the adult brain. *Neuron.* 2007;54:559-66. [PubMed: 17521569]
17
18
19
- 514 [55]. Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH. NMDA-receptor-mediated, cell-specific
22
23 integration of new neurons in adult dentate gyrus. *Nature.* 2006;442:929-33. [PubMed: 16906136]
24
25
- 516 [56]. Bergami M, Masserdotti G, Temprana SG, Motori E, Eriksson TM, Gobel J, et al. A critical period
27
28 for experience-dependent remodeling of adult-born neuron connectivity. *Neuron.* 2015;85:710-7.
29
30
31 [PubMed: 25661179]
32
- 519 [57]. Niederer I, Kriemler S, Gut J, Hartmann T, Schindler C, Barral J, et al. Relationship of aerobic
36
37 fitness and motor skills with memory and attention in preschoolers (Ballabeina): a cross-sectional and
38
39 longitudinal study. *BMC pediatr.* 2011;11:34. [PubMed: 21569343]
40
41
- 522 [58]. Hillman CH, Buck SM, Themanson JR, Pontifex MB, Castelli DM. Aerobic fitness and cognitive
44
45 development: Event-related brain potential and task performance indices of executive control in
46
47 preadolescent children. *Dev Psychol.* 2009;45:114-29. [PubMed: 19209995]
48
49
- 525 [59]. Fedewa AL, Ahn S. The effects of physical activity and physical fitness on children's achievement
52
53 and cognitive outcomes: a meta-analysis. *Res Q Exer Sport.* 2011;82:521-35. [PubMed: 21957711]
54
55
- 527 [60]. Aberg MA, Pedersen NL, Toren K, Svartengren M, Backstrand B, Johnsson T, et al. Cardiovascular
58
59 fitness is associated with cognition in young adulthood. *Proc Natl Acad Sci U S A.*
60
61 2009;106:20906-11. [PubMed: 19948959]
62
63
64
65

- 530 [61]. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic
1
531 exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials.
2
3
4
532 Psychosom Med. 2010;72:239-52. [PubMed: 20223924]
5
6
7
533 [62]. Chu CH, Chen AG, Hung TM, Wang CC, Chang YK. Exercise and fitness modulate cognitive
8
9
10
534 function in older adults. Psychol Aging. 2015;30:842-8. [PubMed: 26652724]
11
12
13
535 [63]. Li F, Harmer P, Liu Y, Chou LS. Tai Ji Quan and global cognitive function in older adults with
14
15
536 cognitive impairment: a pilot study. Arch Gerontol Geriatr. 2014;58:434-9. [PubMed: 24398166]
16
17
18
537 [64]. van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and
19
20
21
538 long-term potentiation in mice. Proc Natl Acad Sci U S A. 1999;96:13427-31. [PubMed: 10557337]
22
23
24
539 [65]. E L, Burns JM, Swerdlow RH. Effect of high-intensity exercise on aged mouse brain mitochondria,
25
26
540 neurogenesis, and inflammation. Neurobiol Aging. 2014;35:2574-83. [PubMed: 25002036]
27
28
29
541 [66]. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal
30
31
32
542 neurogenesis in aged mice. J Neurosci. 2005;25:8680-5. [PubMed: 16177036]
33
34
35
543 [67]. Ji JF, Ji SJ, Sun R, Li K, Zhang Y, Zhang LY, et al. Forced running exercise attenuates hippocampal
36
37
544 neurogenesis impairment and the neurocognitive deficits induced by whole-brain irradiation via the
38
39
40
545 BDNF-mediated pathway. Biochem Biophys Res Commun. 2014;443:646-51. [PubMed: 24333433]
41
42
43
546 [68]. Snyder JS, Radik R, Wojtowicz JM, Cameron HA. Anatomical gradients of adult neurogenesis and
44
45
547 activity: young neurons in the ventral dentate gyrus are activated by water maze training.
46
47
48
548 Hippocampus. 2009;19:360-70. [PubMed: 19004012]
49
50
51
549 [69]. Dupret D, Revest JM, Koehl M, Ichas F, De Giorgi F, Costet P, et al. Spatial relational memory
52
53
54
550 requires hippocampal adult neurogenesis. PloS one. 2008;3:e1959. [PubMed: 18509506]
55
56
57
551 [70]. Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. Neurogenesis in the adult is involved
58
59
552 in the formation of trace memories. Nature. 2001;410:372-6. [PubMed: 11268214]
60
61
62
553 [71]. Trouche S, Bontempi B, Roullet P, Rampon C. Recruitment of adult-generated neurons into
63
64
65

- 554 functional hippocampal networks contributes to updating and strengthening of spatial memory. Proc
1
555 Natl Acad Sci U S A. 2009;106:5919-24. [PubMed: 19321751]
3
4
556 [72]. Vivar C, Peterson BD, van Praag H. Running rewires the neuronal network of adult-born dentate
6
557 granule cells. NeuroImage. 2015. [PubMed: 26589333]
8
9
558 [73]. Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E. Neurogenesis may relate to some but
11
12 not all types of hippocampal-dependent learning. Hippocampus. 2002;12:578-84. [PubMed:
1359 12440573]
14
15
560 [74]. Park EH, Burghardt NS, Dvorak D, Hen R, Fenton AA. Experience-dependent regulation of dentate
18
561 gyrus excitability by adult-born granule cells. J Neurosci. 2015;35:11656-66. [PubMed: 26290242]
19
20
21
562 [75]. Shihabuddin LS, Horner PJ, Ray J, Gage FH. Adult spinal cord stem cells generate neurons after
22
23 transplantation in the adult dentate gyrus. J Neurosci. 2000;20:8727-35. [PubMed: 11102479]
24
25
563 [76]. Riquelme PA, Drapeau E, Doetsch F. Brain micro-ecologies: neural stem cell niches in the adult
26
27 mammalian brain. Philos Trans R Soc Lond B Bio Sci. 2008;363:123-37. [PubMed: 17322003]
28
29
564 [77]. Panatier A, Arizono M, Nagerl UV. Dissecting tripartite synapses with STED microscopy. Philos
30
31 Trans R Soc Lond B Bio Sci. 2014;369:20130597. [PubMed: 25225091]
32
33
565 [78]. Freeman MR. Specification and morphogenesis of astrocytes. Science. 2010;330:774-8. [PubMed:
34
35 21051628]
36
37
566 [79]. Song HJ, Stevens CF, Gage FH. Neural stem cells from adult hippocampus develop essential
38
39 properties of functional CNS neurons. Nat Neurosci. 2002;5:438-45. [PubMed: 11953752]
40
41
567 [80]. Li J, Ding YH, Rafols JA, Lai Q, McAllister JP, 2nd, Ding Y. Increased astrocyte proliferation in rats
42
43 after running exercise. Neurosci Lett. 2005;386:160-4. [PubMed: 16024173]
44
45
568 [81]. Saur L, Baptista PP, de Senna PN, Paim MF, do Nascimento P, Ilha J, et al. Physical exercise
46
47 increases GFAP expression and induces morphological changes in hippocampal astrocytes. Brain
48
49 Struct Funct. 2014;219:293-302. [PubMed: 23288255]
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

- 578 [82]. Allen A, Messier C. Plastic changes in the astrocyte GLUT1 glucose transporter and beta-tubulin
1
279 microtubule protein following voluntary exercise in mice. *Behav Brain Res.* 2013;240:95-102.
3
4
580 [PubMed: 23201358]
6
- 581 [83]. Farkas E, Luiten PG. Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog*
7
8
9
1082 *Neurobiol.* 2001;64:575-611. [PubMed: 11311463]
11
- 1083 [84]. Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *J Comp*
12
13
14
15
1084 *Neurol.* 2000;425:479-94. [PubMed: 10975875]
16
- 1085 [85]. Katsimpardi L, Litterman NK, Schein PA, Miller CM, Loffredo FS, Wojtkiewicz GR, et al. Vascular
17
18
19
20
2186 and neurogenic rejuvenation of the aging mouse brain by young systemic factors. *Science.*
22
23
2487 2014;344:630-4. [PubMed: 24797482]
25
- 2088 [86]. Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF)
26
27
28
29
3089 stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci U S A.* 2002;99:11946-50. [PubMed:
31
32
3390 12181492]
34
- 3091 [87]. Cao L, Jiao X, Zuzga DS, Liu Y, Fong DM, Young D, et al. VEGF links hippocampal activity with
35
36
37
3892 neurogenesis, learning and memory. *Nat Genet.* 2004;36:827-35. [PubMed: 15258583]
39
- 4093 [88]. Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, et al. VEGF is necessary for
41
42
4394 exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci.* 2003;18:2803-12. [PubMed:
44
45
4695 14656329]
47
- 4896 [89]. Jagasia R, Steib K, Englberger E, Herold S, Faus-Kessler T, Saxe M, et al. GABA-cAMP response
49
50
51
5297 element-binding protein signaling regulates maturation and survival of newly generated neurons in the
53
5498 adult hippocampus. *J Neurosci.* 2009;29:7966-77. [PubMed: 19553437]
55
- 5599 [90]. Chen MJ, Russo-Neustadt AA. Running exercise-induced up-regulation of hippocampal
56
57
58
59
6000 brain-derived neurotrophic factor is CREB-dependent. *Hippocampus.* 2009;19:962-72. [PubMed:
61
62
63601 19294650]
64
65

- 602 [91]. Kondo M, Nakamura Y, Ishida Y, Shimada S. The 5-HT₃ receptor is essential for exercise-induced
1
603 hippocampal neurogenesis and antidepressant effects. *Mol Psychiatry*. 2015;20:1428-37. [PubMed:
3
4
604 25403840]
6
- 7
605 [92]. Farmer J, Zhao X, van Praag H, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on
8
9
10
606 synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo.
11
12
13
607 *Neurosci*. 2004;124:71-9. [PubMed: 14960340]
14
- 15
608 [93]. Muller L, Tokay T, Porath K, Kohling R, Kirschstein T. Enhanced NMDA receptor-dependent LTP
16
17
18
609 in the epileptic CA1 area via upregulation of NR2B. *Neurobiol Dis*. 2013;54:183-93. [PubMed:
19
20
21
610 23313317]
22
- 23
611 [94]. Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, et al. Neuronal
24
25
26
612 differentiation in the adult hippocampus recapitulates embryonic development. *J Neurosci*.
27
28
29
613 2005;25:10074-86. [PubMed: 16267214]
30
- 31
32
614 [95]. Couillard-Despres S, Iglseder B, Aigner L. Neurogenesis, cellular plasticity and cognition: the
33
34
35
615 impact of stem cells in the adult and aging brain--a mini-review. *Gerontology*. 2011;57:559-64.
36
37
38
616 [PubMed: 21311170]
39
- 40
617 [96]. David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I, et al. Neurogenesis-dependent
41
42
43
618 and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron*.
44
45
46
619 2009;62:479-93. [PubMed: 19477151]
47
- 48
620 [97]. Clelland CD, Choi M, Romberg C, Clemenson GD, Jr., Fagniere A, Tyers P, et al. A functional role
49
50
51
621 for adult hippocampal neurogenesis in spatial pattern separation. *Science*. 2009;325:210-3. [PubMed:
52
53
54
622 19590004]
55
- 56
623 [98]. Hodges H, Veizovic T, Bray N, French SJ, Rashid TP, Chadwick A, et al. Conditionally immortal
57
58
59
624 neuroepithelial stem cell grafts reverse age-associated memory impairments in rats. *Neurosci*.
60
61
62
625 2000;101:945-55. [PubMed: 11113344]
63
64
65

- 626 [99]. Shetty AK, Rao MS, Hattiangady B. Behavior of hippocampal stem/progenitor cells following
 1
 627 grafting into the injured aged hippocampus. *J Neurosci Res.* 2008;86:3062-74. [PubMed: 18618674]
 3
- 628 [100]. Qu T, Brannen CL, Kim HM, Sugaya K. Human neural stem cells improve cognitive function of
 4
 629 aged brain. *Neuroreport.* 2001;12:1127-32. [PubMed: 11338178]
 7
- 630 [101]. Ager RR, Davis JL, Agazaryan A, Benavente F, Poon WW, LaFerla FM, et al. Human neural stem
 11
 12 cells improve cognition and promote synaptic growth in two complementary transgenic models of
 1631 Alzheimer's disease and neuronal loss. *Hippocampus.* 2015;25:813-26. [PubMed: 25530343]
 14
 15
 1632
- 633 [102]. Santos-Lozano A, Pareja-Galeano H, Sanchis-Gomar F, Quindos-Rubial M, Fiuza-Luces C,
 18
 19
 20
 2134
 22
 23
 2635
 25
 26
 2636
 27
 28
 29
 2637
 30
 31
 3238
 33
 34
 3639
 36
 37
 3640
 38
 39
- 641 [104]. Huttenrauch M, Brauss A, Kurdakova A, Borgers H, Klinker F, Liebetanz D, et al. Physical activity
 42
 4642
 44
 45
 4643
 47
 48
 4644
 50
 51
 645
 52
 53
 54
 646
 55
 56
 5647
 58
- 648 [105]. Dunn HC, Ager RR, Baglietto-Vargas D, Cheng D, Kitazawa M, Cribbs DH, et al. Restoration of
 60
 649
 62
 63
 6450
 65
 65 lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse model. *J
 Alzheimers Dis.* 2015;43:893-903. [PubMed: 25125468]

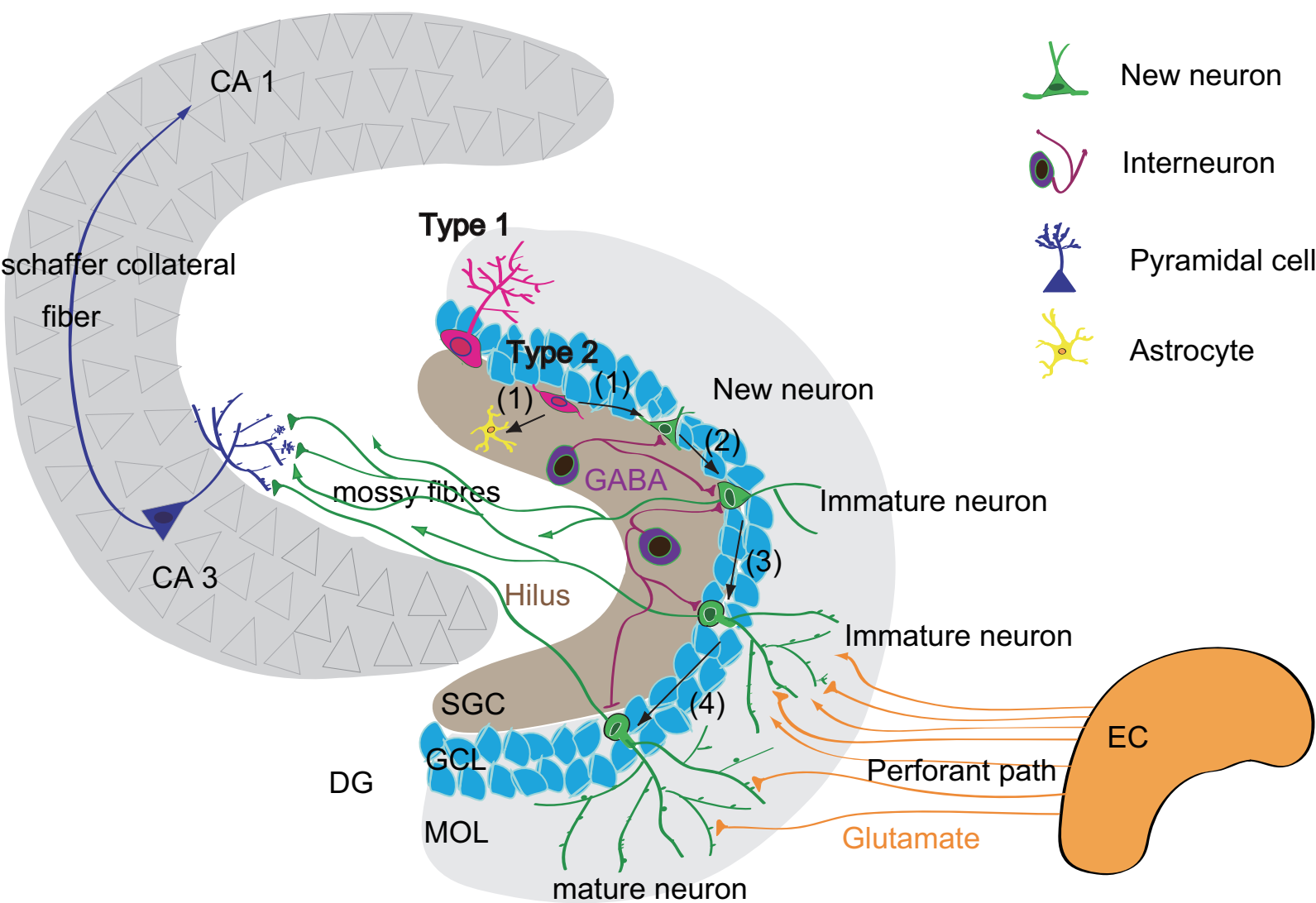
Figure legends

Fig.1. Adult hippocampal neurogenesis and integration of the new born neurons. (1) Type 2 progenitors give rise to astrocytes and granule neurons. (2) Mainly neurite growth and the axons enter the hilus or

651 CA3 area. (3) Spines formation and target axon boutons of perforant path from EC that already synapse
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652 with other spines, and axons of the immature neurons liable to form synapses with or near the thomy
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653 excrescences of the pyramidal cells in CA3. (4) Structural modification on neurite and finally the immature
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654 neurons become fully maturation. Before maturation the new neurons can be depolarized by GABA
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1055 coming from local interneurons, but inhibited by GABA when they maturation. DG, dentate gyrus; SGZ,
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1056 subgranular zone; GCL, granular cell layer; MOL, molecular layer; EC, entorhinal cortex.
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1958 Fig.2. Mechanisms of physical exercise induced hippocampal neurogenesis. In the neurogenic niche of
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2159 the SGZ, physical exercise can regulate functions of both functional unit and local interneurons, which
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2060 up-regulate the energy supply and the release of some regulation factors to improve the hippocampal
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2061 neurogenesis. Physical exercise can also increase the release of neurotransmitters such as glutamate and
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2062 5-HT from cortical area or subcortical area (outside of the niche) to promote hippocampal neurogenesis.
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3063 SGZ, subgranular zone; GDF11, growth differentiation factor 11; CREB, cAMP-response element
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3064 binding protein; VEGF, vascular endothelial growth factor; BDNF, brain-derived neurotrophic factor;
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3065 GABA, gamma-aminobutyric acid; 5-HT, serotonin.
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Neurogenesis and integration of the new neurons



Mechanisms of hippocampal neurogenesis

Physical exercise

