The Benefits of Exercise on Structural and Functional Plasticity in the Rodent Hippocampus of Different Disease Models

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Abstract. In this review, the benefits of physical exercise on structural and functional plasticity in the hippocampus are discussed. The evidence is clear that voluntary exercise in rats and mice can lead to increases in hippocampal neurogenesis and enhanced synaptic plasticity which ultimately result in improved performance in hippocampal-dependent tasks. Furthermore, in models of neurological disorders, including fetal alcohol spectrum disorders, traumatic brain injury, stroke, and neurodegenerative disorders including Alzheimer's, Parkinson's and Huntington's disease exercise can also elicit beneficial effects on hippocampal function. Ultimately this review highlights the multiple benefits of exercise on hippocampal function in both the healthy and the diseased brain.

Keywords: Exercise, hippocampus, *Cornu Ammonis*, dentate gyrus, neurogenesis, synaptic plasticity, behaviour

ABBREVIATIONS

AD	Alzheimer's disease
BDNF	brain derived neurotrophic factor
CA	*Cornu* Ammonis
CFC	contextual fear conditioning
DGC	dentate granule cell
DG	dentate gyrus
EC	entorhinal cortex
fMRI	functional magnetic resonance imaging
GABA	gamma amino butyric acid
GCL	granule cell layer
HD	Huntington disease
LPP	lateral perforant path
LTD	long-term depression
LTP	long-term potentiation
MPP	medial perforant path
MWM	Morris water maze
NMDA	N-methyl D-aspartate
PD	Parkinson's disease
PND	postnatal day
RAM	radial arm maze
TBI	traumatic brain injury

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INTRODUCTION

The hippocampus is a bilateral structure that is found in the medial temporal lobe of the mammalian brain and is considered part of the limbic system.

The hippocampus consists of the dentate gyrus (DG), the *Cornu Ammonis* (CA) 1 and CA3 regions (also known as the hippocampus proper) and the subiculum (reviewed by [1]). The hippocampus has been the focus of intensive research due to its important role in learning and memory, particularly that associated with declarative (i.e., explicit) and spatial memory [1].

The hippocampus displays both structural and functional plasticity into adulthood. This plasticity can be positively manipulated by interventions such as physical exercise. In this review we summarize the benefits of voluntary physical exercise on hippocampal neurogenesis (which is referred to structural plasticity in this review), and function (which is referred to synaptic plasticity and behavioral improvement in this review) in rodents. We also review the potential benefits of physical exercise on hippocampal plasticity in rodent models of neurological disorders, including traumatic brain injury, stroke and neurodevelopmental and neurodegenerative disorders. For purposes of simplicity, we have focused on studies utilizing rats and mice and where voluntary physical exercise paradigms have been employed. Finally, we have limited our review to studies examining adult animals, except for the section on neurodegenerative diseases. While exercise has also been shown to be beneficial in juvenile and aging animals [2–7], these studies are outside the scope of this review.

The hippocampus

Information flow in the hippocampus

Information flow in the hippocampus is generally unidirectional and is known as the trisynaptic circuit [8] (Fig. 1). The first connection in the trisynaptic circuit originates from Layer II of the entorhinal cortex (EC) and projects to the DG via a group of fibres known as the perforant path. The fibres synapse on the dendrites of the dentate granule cells (DGCs) located in the molecular cell layer. There are two subdivisions of the perforant path: medial (MPP) and lateral (LPP). The MPP originates in the medial EC and projects to the middle one-third of the molecular cell layer, whereas the LPP originates in the lateral EC and projects to the outermost third of the molecular cell layer. Both the MPP and LPP provide excitatory input onto the DGCs but are physiologically distinct and have different short-term and long-term plasticity properties [9–11]. The MPP and LPP are the major inputs of cortical information into the hippocampus and the DGCs play an important role in processing and filtering information before it is sent to other regions of
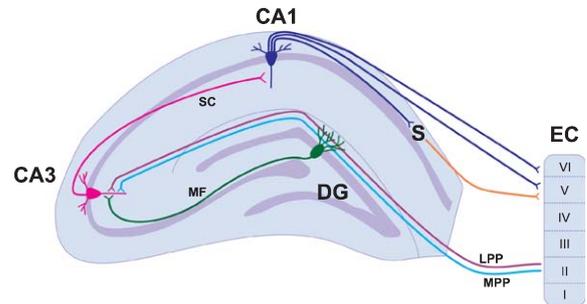

Fig. 1. A simplified hippocampal circuitry illustrating trisynaptic and monosynaptic circuits. The basic circuitry of the hippocampus is commonly termed the trisynaptic circuit. Layer II of the entorhinal cortex provides input to the granule cells of the dentate gyrus via the medial (light blue) and lateral (purple) perforant paths. The dentate granule cells project to pyramidal cells of the CA3 via the mossy fibre pathway (green). CA3 pyramidal neurons project to the CA1 via schaffer collaterals (pink). The CA1 pyramidal cells project to both the subiculum and to layers V and VI of the entorhinal cortex. Abbreviations: *Cornu Ammonis* (CA); Dentate Gyrus (DG); Entorhinal Cortex (EC); Lateral Perforant Path (LPP); Medial Perforant Path (LPP); Mossy Fibres (MF); Schaffer Collaterals (SC); Subiculum (S).

the hippocampus via the trisynaptic circuit [8]. From the DG, DGC axons project onto pyramidal cells in the CA3 region of the hippocampus (Fig. 1). This pathway is unique in that the bundles of axons are unmyelinated and are therefore known as the mossy fibres. The third component of the trisynaptic circuit is the CA3 to CA1 projection known as the Schaffer Collaterals. Pyramidal cells of the CA3 send axons into the stratum radiatum and stratum oriens of the CA1 and innervate apical and basal dendrites of the CA1 pyramidal cells [1]. The CA1 then projects information to the subiculum and both the CA1 and the subiculum project fibres back to Layers V and VI of the EC to complete the cortical information loop (Fig. 1). It should be noted that the CA1 also receives projections from the EC and this pathway is known as the temporoammonic pathway [1]. These projections arise from layers III and V of the EC. This pathway may play a more prominent role in stress and anxiety related behaviours as opposed to spatial memory [12] (which is discussed below (Section 1.1.2)).

The role of the hippocampus in spatial memory

In the 1950s, Dr. William Scoville performed a bilateral limbic surgery on patient Henry Molasion (commonly known as H.M.), giving the first real insight into the function of the hippocampus [13]. In order to treat H.M.'s recurrent seizures, the hippocampus, amygdala, collateral sulcus, perihinal cortex, EC and the medial mammillary nucleus, were

removed [14]. Following surgery, H.M was afflicted with severe memory deficits; he lacked the ability to form and retain long-term memories of new facts (semantic memory) and events (episodic memory). This was the first case where a strong link was made between the hippocampus and explicit (i.e. intentional and conscious) memory.

Numerous studies have now refined the role of the hippocampus in the formation and maintenance of explicit spatial memory [15, 16]. In the 1980's, Dr Richard Morris created the Morris water maze (MWM) test with the purpose of training rodents to learn the spatial location of a hidden platform submerged in cloudy water as a test for hippocampal function [17]. He observed that hippocampal lesions significantly impaired performance in this task [17].

Other studies have identified place cells in the hippocampus, which has led to the cognitive map theory of hippocampal function [18, 19]. These are cells that become active when a rodent is in a specific location in a specific environment [18] and such cells have also been detected in humans [20]. The presence of place cells within the hippocampus provides evidence that this structure organizes and stores stimuli with respect to a spatial framework (i.e. a cognitive map) and may be used for spatial navigation [21, 22]. Indeed, recent studies have suggested that the hippocampal formation acts as a network that encodes events and their contexts, with each distinct region playing a specific but complementary role in the processing of spatial information.

Within this scenario, the DG is believed to play a unique role in spatial pattern separation (reviewed by [23]). Spatial pattern separation is the enhancement of contrast between two similar spatial patterns or events. At the neuronal level this is thought to occur either through change in neuronal firing rate or through the firing of different neuronal sets [24, 25]. The DGCs display sparse firing characteristics and there are very few connections between DGCs and CA3 pyramidal cells [26], which make the DG optimally structured for spatial pattern separation. Furthermore, the existence of populations of DGCs that fire only when a rodent is in a given environment indicate that the DG contains place fields that are important for pattern separation [27–29].

The CA3 region has been implicated in spatial pattern completion – the capacity to retrieve previously stored information when presented with partial or incomplete inputs [30]. Evidence for this comes from studies where mice that lacked N-methyl-D-aspartate (NMDA) receptor expression in the CA3 were trained

on the MWM. While these mice were able to perform the task as well as control mice, if the external environment was altered by removing a subset of the external cues so the mice only had an incomplete set of visual cues to recall the location of the platform, deficits in performance were observed [31]. These results indicate that the ability to use partial/incomplete spatial input was compromised and implicate the CA3 in spatial pattern completion.

The CA1 region of the hippocampus has been implicated in the processing of the temporal order of spatial patterns or events. This function is important to ensure that spatial events separated by time are encoded with minimum overlap [32]. The CA1 region also plays a major role in spatial memory (see Section 3.2.1) and contextual fear conditioning (see Section 3.2.2) and is the most widely studied area of the hippocampus [1]. Ablating or impairing the function of the CA1 region leads to deficits in delayed spatial discrimination [33], Morris Water Maze performance [34], temporal ordering tasks [35], and contextual fear conditioning [36] in rodents and spatial memory impairments in monkeys [37].

Together, the three major regions of the hippocampus – the DG, CA3 and CA1 encode spatial memory, but each region has its own distinct role within this function. The DG is associated with pattern separation, the CA3 with spatial pattern completion, and the CA1 with temporal order processing. The three regions work in concert to encode spatial memory.

Structural and functional plasticity in the hippocampus

The hippocampus is a dynamic structure that displays both structural and functional plasticity. Structural plasticity can occur through the process of adult hippocampal neurogenesis which occurs only in the DG sub-region of the hippocampus [38, 39]. Through this process new neurons are produced and integrated into existing CNS circuitry throughout the life span. Progenitor cells create neuroblasts in the subgranular zone of the DG that migrate into the granule cell layer (GCL) and differentiate into DGCs (reviewed by [40]). These new neurons incorporate themselves into existing neuronal circuits and display action potentials and functional synaptic inputs similar to DG granule cells formed during the developmental period (reviewed by [41]).

Functional, or synaptic, plasticity in the hippocampus is the process by which neurons alter their ability to communicate with one another. Enhancing synaptic efficacy, also known as long-term potentiation (LTP),

is largely dependent upon kinase activation and protein synthesis, and serves as the primary biological mechanism for understanding how learning and memory processes operate in the brain [42, 43]. Long-term depression (LTD) is the opposite of LTP and is characterized by a decrease in synaptic efficacy [43, 44]. This process has been linked to forgetting.

PHYSICAL EXERCISE-INDUCED ENHANCEMENTS IN STRUCTURAL PLASTICITY IN THE HIPPOCAMPUS

The beneficial effects of physical exercise on adult hippocampal neurogenesis were first reported by van Praag et al., (1999) showing that voluntary wheel running promotes hippocampal neurogenesis in adult mice [45]. A positive correlation between running distance and levels of hippocampal neurogenesis has been repeatedly demonstrated in mice [46–48]. Notably, enhancement of neurogenesis by running can be affected by variables including genetic background [48, 49], age [4, 50], form of running (forced vs. voluntary; 39, 45–47), housing environment (single or group housing; [54], and duration (days to months) of exercise training [7, 47, 55]. Despite the variability among different studies, exercise-induced enhancements in hippocampal neurogenesis have been consistently reported in mice and rats in the literature [4, 5, 45–49, 52, 56–58, 54, 59] (Table 1).

The pioneer study by van Praag and colleagues (1999) indicated that long-term voluntary wheel running for 2 to 4 months significantly increased the process of neuronal survival in female adult C57 mice and concurrently enhanced synaptic plasticity and learning and memory performance in the MWM [45]. Further studies by this group have also found significant increases in neuronal differentiation and survival following 45 days voluntary wheel running in both young and aged C57B/L male mice [5].

Recent studies have revealed that physical exercise exerts its promoting effects on cells at different stages of neurogenesis. In adult male and female C57B/L mice, voluntary running increases the number of proliferating cells with a peak occurring after 3-days of short-term running, followed by a return to basal levels after 32 [60] or 35 days of running [61]. Conversely, significant increases in differentiating neuronal cells can only be observed after 10 days of running [7]. These data indicate that voluntary running-induced cell proliferation occurs only in the initial period of running, and longer periods of running mainly promote neuronal differentiation and survival rate of newborn neurons.

Adult neurogenesis is derived from self-renewing neural stem cells (type-1 cells, radial glial-like stem cells: nestin and GFAP positive), which can give rise to intermediate progenitor cells (type-2a cells: nestin positive, GFAP negative) that undergo amplification and acquire neural cell fate to neural progenitors (type 2b cells: nestin and doublecortin positive). These neural progenitors will then differentiate into migrating neuroblasts (type-3 cells: nestin negative, doublecortin positive) that exit cell cycle to become post-mitotic neurons (reviewed by [62]). It is elusive whether running induces adult neurogenesis by influencing proliferation or survival of distinct populations of precursor cells or both. Suh and colleagues (2007) reported that voluntary wheel running activated proliferation of early lineage radial glial-like stem cells [63], which is echoed by the findings of Bednarczyk et al., [64] showing an increase in the number of early lineage stems cells which are Ki67 (a endogenous marker for proliferating cells) and GFAP positive. Similar results were also reported by Lugert et al., (2010) who showed that running activates quiescent radial precursor cells to enter into the cell cycle [65]. In female adult C57BL/1 mice, voluntary wheel running for 7 days induces a transient increase in proliferative precursor cells as well as a reduced portion of DCX positive type-2b/3 cells that re-entered S-phase [61], suggesting that running induces neurogenesis not only by enhancing cell proliferation, but also by promoting cell cycle exit of progenitor cells. Farioli-Vecchioli and colleagues have shown that 12-days of running shortens the cell cycle of NeuroD1-positive progenitor cells (type-2b and -3) in wild-type mice, and also appears to shorten the length of the S-phase as well as the length of the whole cell cycle of both GFAP and Sox2 positive neural stem cells and NeuroD1-positive progenitors in Btg1-null mice that lack the anti-proliferative gene Btg1 [66]. Conversely, Fischer and colleagues only observed a trend towards a shorter cell cycle length in mice showing increased cell proliferation following 5- days of running, and concluded that the effect of running on progenitor cell proliferation was not caused by shortening of cell cycle length [67]. The contradictory results reported by Fischer et al., [67] and Farioli-Vecchioli et al., [66] may be due to the fact that the cell cycle length was examined on the entire proliferating population vs. specific progenitor cell populations. Furthermore, the duration of running (5 days vs 12 days) could have impacted these results. Taken together, running may exert its pro-neurogenic effect

Table 1
Effect of voluntary running on hippocampal plasticity in healthy rodents

Hippocampal neurogenesis

Animal age	Species	Running period	Markers examined	Effect of running	Reference
3 months old	Mouse	12 days	BrdU (Proliferation and Survival) NeuN (neurogenesis)	Increased cell proliferation, cell survival and net neurogenesis	van Praag et al., 1999
3 months old	Mouse	30 days	BrdU (survival) BrdU/NeuN (neuronal differentiation)	Increased cell survival and neuronal differentiation	van Praag et al., 1999
3 months old or 19 months old	Mouse	45 days	BrdU (survival) BrdU/NeuN/S100β triple labeling	Increased cell survival and neuronal differentiation	van Praag et al., 2005
6–8 weeks old	Mouse selectively bred for high levels of running	40 days	BrdU (survival) BrdU/Neuro/ S100β triple labeling	Increased cell proliferation, survival and neuronal differentiation	Rhodes et al., 2003
6 weeks old	Mouse	12 days or 19 days	BrdU (survival) PCNA (cell proliferation)	Increased cell proliferation after 14 days running, Increased cell survival in after both 14 days and 19 days of running	Synder et al., 2009
3 months old	Mouse	12 days	BrdU(Proliferation and survival)	Increased cell proliferation and survival	Brown et al., 2003
8-9 weeks old	Mouse	14 days	BrdU, Ki67 (cell proliferation) DCX (neurogenesis) BrdU/DCX (neuronal differentiation)	Increased cell proliferation, neuronal differentiation and net neurogenesis	Yau et al., 2014
8 weeks old	Mouse	24 hours, 3 days, 7 days or 35 days	BrdU, IdU, CldU	Increased cell proliferation at 24 hours, 3 days and 7 days (peak at 3 days). Return to baseline at 35 days	Brandt et al., 2010
12 weeks old	Transgenic mouse expressing GFP driven by nestin gene promotor	4 weeks	BrdU and nestin-GFP positive cells	Specific increase in type 2b transient amplifying progenitor cells	Kronenberg et al., 2003

(Continued)

Table 1
(Continued)

74 days at end of experiment	Mouse	3, 10 or 32 days	BrdU, Ki67, DCX, calretinin	Increased cell proliferation at 3 days and 10 days (peak at 3 days). Returned to baseline at 35 days. DCX and Calretinin increased at 10 days and 32 days.	Kronenberg et al., 2006
2 months old	Mouse	12 days	BrdU and PCNA (cell proliferation)	Increased cell proliferation	Kannangara et al., 2009
6–8 weeks old	Rat	7 days or 28 days	Brdu (cell proliferation) BrdU/DCX (neuronal differentiation)	Increased cell proliferation and differentiation following 28 days of running	Yau et al., 2012
6–8 weeks old	Rat	14 days	BrdU (cell proliferation) BrdU/DCX co-labeling (Neuronal differentiation)	Increased cell proliferation and neuronal differentiation	Yau et al., 2011
2 months old	Rat	3, 7, 14, 28, 56 days	Ki 67 (cell proliferation) NeuroD (neuronal differentiation)	Increased cell proliferation after 3,7 or 28 days of running Increased neuronal differentiation after 14 or 28 days of running	Patten et al., 2013

Hippocampal synaptic plasticity

Animal age	Species	Running period	Area(s) analyzed	Effect of running	Reference
3 months old	Mouse	30 days	DG and CA1 *In vitro*	Enhanced LTP in the DG, but not CA1	Van Praag et al., 1999
2 months old	Rat	3, 7, 14, 28, 56 days	DG *In vivo*	Enhanced LTP following 56 days of running	Patten et al., 2013
Adult (exact age not specified)	Rat	7+ days	DG *In vivo*	Enhanced STP and LTP, reduced threshold for LTP	Farmer et al., 2004
3–5 weeks old	Mouse	7–10 days	DG *In vitro*	Enhanced LTP, no effect on LTD, both abolished by NR2A blockade	Vasuta et al., 2007

Hippocampal dependent behavior

Animal age	Species	Running period	Behavioral test	Effect of running	Reference
3 months old	Mouse	30 days	MWM	Rapid acquisition (day 3), better memory in probe test	Van Praag et al., 1999

(Continued)

Table 1
(Continued)

2 months old	Rat	3 weeks	MWM	Rapid acquisition (day 2)	Adlard et al., 2004
6–8 weeks old	Mouse	34 days	MWM	Rapid acquisition in control runners but not selectively-bred runners	Rhodes et al., 2003
3 months old	Rat	1 week	MWM	CAMKII blockade improves acquisition in runners but impairs memory on probe test	Vaynman et al., 2007
~7–9 weeks old	Rat	30 days	Contextual fear conditioning	Increased freezing 24hr later	Baruch et al., 2004
~4–6 weeks old	Rat	8 weeks	Contextual fear conditioning	Increased freezing 24hr later, most freezing in rats that ran the most	Burghardt et al., 2006
Adult (exact age not specified)	Rat	6 weeks	Contextual fear conditioning	Increased freezing when running occurred before conditioning but no effect when running occurred between conditioning and testing	Greenwood et al., 2009
2 months old	Mouse	3 weeks	Contextual fear conditioning	Reduced fear memory in runners	Akers et al., 2014
6–8 weeks old	Mouse	5 weeks	Contextual fear conditioning	No effect on memory expression, speed up decay rate of hippocampal dependency of memory	Kitamura et al., 2009
5 months old	Rat	7 weeks	Radial arm maze	Fewer trials to criterion	Anderson et al., 2000
10 weeks old	Mouse	14 days	Y-Maze	Rapid acquisition by trial 2, after learning in non-runners, 14 days of running improved memory retention	Van der Borght et al., 2006

Abbreviations: BrdU, bromodeoxyuridine; CA, *Cornu Ammonis*; DG, dentate gyrus; DCX, doublecortin; MWM, Morris Water Maze; PCNA, proliferating cell nuclear antigen.

by cell cycle shortening on specific subpopulations of neural stem cells and its effect may depend on duration of running.

Prolonged wheel running also increases the number of neuroblasts and mature neurons in the DG [64]. Of note, the presence of a running wheel itself is a form of environmental enrichment which can promote the processes of adult neurogenesis, because both locked wheel and running wheel mice show increases in proliferating cells as indicated by significant increases in co-labeled Ki67 and GFAP positive cells [68]. Importantly, Bednarczyk and colleagues reported that increased number of neuroblasts (DCX positive cells) and newborn neurons (co-labeled with BrdU and NeuN) were only observed in running mice, but not in the mice with locked wheels, indicating that running is needed to increase maturation and survival of post-mitotic neuroblasts. Taken together, there appear to be running-independent and -dependent stages of adult hippocampal neurogenesis [68].

Environmental enrichment that includes supplying cages with toys, tunnels and running wheels induces robust increases in cell proliferation and neurogenesis [69]. However, a recent study has indicated that the running wheel is the critical stimulus for inducing neurogenesis in an enriched environment [70]. When mice are exposed sequentially to the running and then the environment enrichment, there is an additive increase in neurogenesis [71]. Increasing the pool of proliferating precursor cells by running together with an appropriate survival-promoting stimulus such as environmental enrichment follows the idea that the combination of exercise and environmental enrichment may potentially lead to more adult neurogenesis which may benefit hippocampal function.

PHYSICAL EXERCISE-INDUCED ENHANCEMENTS IN FUNCTIONAL PLASTICITY IN THE HIPPOCAMPUS

Synaptic plasticity

Synaptic plasticity refers to changes in neural communication as a result of experience, and can be measured throughout the brain. Two forms of synaptic plasticity have been assessed in the hippocampus, LTP, commonly associated with memory formation, and LTD, which has more recently been associated with memory clearance or forgetting.

The effects of exercise on synaptic plasticity in the hippocampus have been understudied (reviewed by [72]) despite the fact that exercise can reliably enhance performance on a range of hippocampal behaviors

(see Section 3.2). The effects of exercise on *in vitro* hippocampal synaptic plasticity were first shown in female mice in 1999 [45], where one week of voluntary wheel running resulted in greater LTP in the DG. These findings were replicated both *in vivo* and *in vitro* in male rats where voluntary and forced running enhanced LTP in the DG [59, 73, 74] and CA3 [75]. In the DG, exercise may enhance LTP by lowering the induction threshold for LTP, though the mechanism for this change in induction threshold is unknown [73].

Interestingly, in van Praag's seminal study of female mice, there was no effect of wheel running on CA1 LTP [45]. Conversely, forced exercise in sleep-deprived rats overcame impairments in *in vivo* late-phase LTP in the CA1 to the level of non-sleep deprived rats [76]. Interestingly, in this study forced exercise had no effect on CA1 LTP in healthy rats, suggesting that exercise-mediated enhancements of LTP in the CA1 are only evident in models where CA1 LTP is already depleted such as in sleep deprivation, aging and neurodegenerative disease [76–78] (see section 4.4). While these regional differences between DG and CA1 LTP were originally thought to be a direct result of increased neurogenesis following exercise, this group later showed that new neurons display enhanced LTP induction and only develop normal synaptic responses when they are 4-5 weeks old [79].

Bidirectional plasticity

More recently, studies of the effects of exercise on bidirectional plasticity have emerged. Vasuta et al., [80] studied exercise-induced changes in *in vitro* synaptic plasticity in the mouse DG, and the contributions of different NMDAR-subunits on these physiological changes. The effects of voluntary wheel running on DG LTP were replicated, however wheel running had no effect on DG LTD. LTP in the DG is generally NMDAR-dependent [73], however until 2007, the physiological contributions of the different NMDAR subunits on exercise-mediated plasticity were unknown. In this study, selective NR2A or NR2B blockade abolished DG LTP in non-exercised mice. In exercised animals, however, only NR2A blockade abolished DG LTP, and NR2B blockade significantly reduced, but did not block DG LTP. Conversely, neither exercise nor selective blockade of NR2A or NR2B subunits had an effect on DG LTD in sedentary animals, but NR2A blockade abolished LTD while NR2B blockade left LTD intact in exercised mice. Interestingly, while exercise increases NR2B mRNA specifically in the DG region, it does not affect NR1 or NR2A subunit mRNA nor either of these subunits in the CA1

region [73]. Together, these data indicate a unique role for the NR2A subunit in both LTP and LTD in the DG that emerges following exercise.

A great disparity exists in the study of hippocampal physiology following exercise in non-diseased animals. The exercise-induced changes in NMDAR-subunit composition in the hippocampus discussed here are likely just one component of the benefits of exercise, as others have reported increases in dendritic complexity [81] and neurotrophic factors [82] to name a few, which all have implications on synaptic plasticity in the hippocampus [83, 84]. Indeed, there are many mechanisms that may underlie the exercise-induced changes (or lack thereof) in synaptic plasticity in different sub-regions of the hippocampus (many of which are reviewed in this issue) however more work must be done in order to fully understand how each of these putative mechanisms contributes to exercise-induced hippocampal plasticity.

Behavioral plasticity

The effect of voluntary wheel running on hippocampal-dependent behaviors has been extensively studied in both healthy and diseased rodents. Here, we will summarize the most commonly used behaviors in the study of exercise in healthy animals.

Morris water maze

The Morris water maze task (MWM) is a classic hippocampal behavioral task that has been modified in order to assess different aspects and types of memory such as working memory, long-term memory acquisition, and retrieval. Fundamentally, in this task, animals are placed in a pool of opaque water, and must use distal visual cues in order to locate a hidden platform where they may escape the water. Following multiple learning trials over multiple days, the swim path or latency to reach the platform can be measured as an indication of spatial memory acquisition. The platform can be removed for a probe trial where the time spent searching the trained platform location can be assessed to measure reference memory.

The MWM is the most studied behavioral task in exercise literature. Runners acquire the MWM task more readily than non-runners, where by the third day of training, runners take a more direct path and take less time to reach the platform than non-runners [45]. At the time of the probe trial, runners spend a significantly greater proportion of time in the correct quadrant, than incorrect quadrants, and the improvements in performance in runners were paralleled by increases in

hippocampal neurogenesis. The rapid acquisition of the MWM task by runners has been extensively replicated [46, 85], and this acquisition by runners may be more rapid than mice housed in enriched environments [70], though together, environmental enrichment and exercise might have additive effects on behavioral improvement in the MWM [71]. Curiously, when hippocampal neurogenesis is disrupted by irradiation, running-induced improvements in performance in the MWM are no longer evident [86].

Fear conditioning

In contextual fear conditioning (CFC) tasks, an animal is conditioned to fear a context by providing a tone followed by a footshock. After a pre-determined delay, the animal is returned to the fearful context without the footshock, and the freezing response to either the context or the tone in that context is measured. This behavioral task requires the activity of the amygdala, hippocampus, as well as frontal and cingulate cortices (reviewed by [87]).

CFC has been commonly used to assess learning and memory improvements following exercise. Following 30 days of voluntary wheel running, male rats exhibited more freezing in the fearful context when returned to that context 24 hours after footshock training [88]. This evidence of increased freezing to the fearful context has been reported in other groups following exercise [89, 90]. In a study by Burghardt et al., [89] male rats that ran voluntarily froze more than rats that were in the locked control condition, indicating that the voluntary aspect of exercise plays a role in this type of learning. There also appears to be a sensitive period during which voluntary exercise has an effect on this fear conditioning, where running between footshock training and testing has no effect on freezing times, while running before training results in increased freezing to the fearful context [90]. Unlike spatial memories in the MWM, the exercise-mediated behavioral improvements in CFC are not dependent on intact hippocampal neurogenesis [86].

Arm mazes

The radial arm maze (RAM) is a spatial memory task that is sensitive to hippocampal damage. This task can be modified for a multitude of memory types and has classically been used to assess working memory. For this version of the task, the animal can exit a central zone and visit a multitude of arms (from 8–48) in order to collect a food or water reward located at the end of each rewarded arm. The animal must remember which

arms it has already visited in order to not visit the same arm again.

Female rats that underwent voluntary wheel running required fewer trials to reach criterion than their non-runner counterparts [91]. Similarly, in male rats, runners made fewer reference errors and more correct choices than non-runners [92].

The Y maze is another spatial memory task where animals must make a choice to pick either the left or right arm in order to receive a reward at the end of one arm, which is hidden from the view of the animal. As in the MWM, runner mice showed rapid acquisition of the Y-maze task, reaching over 80% correct arm choices by the second trial during the first training session [93]. Once non-runners had learned the Y-maze task, and were allowed 14 days of voluntary running, they had better memory retention than mice that did not run at all. In this same task, when, after the 14-day running (or non-running) delay, the reward location was reversed, those mice that ran acquired the reversal learning task more rapidly [93].

Novel object recognition

Novel object recognition is another classic hippocampal-dependent task (reviewed by [94]), which has been used to study different types of memory. In its most simple version, animals are allowed to freely explore an environment containing two identical objects followed by a pre-determined interval before being returned to the environment for a test phase. In the test phase, one of the familiar objects is replaced with a novel object, which the animal will spend more time investigating if it remembers the familiar object. This task is known to require the intact function of both the hippocampus and the perirhinal cortex in rats [95, 96].

Voluntary wheel running also has been shown to improve novel object recognition in mice [97] and rats [77, 98] where improved performance was correlated with increases in BDNF expression in the perirhinal cortex [98]. There also appears to be a temporal relationship between the time that exercise stops and the behavioral test begins, where testing immediately after exercise produces the greatest improvements in object recognition and BDNF expression in the hippocampus and perirhinal cortex [99].

Learning and forgetting of
hippocampus-dependent memories

New avenues of study have sought to understand the relationship between neurogenesis and forgetting (see [100] for a review). Feng et al., (2001) demonstrated

that impaired neurogenesis causes increased memory retention in the CFC task, suggesting that hippocampal neurogenesis may play a role in memory clearance [101]. Similarly, when hippocampal neurogenesis is ablated, working memory was improved in the RAM [102]. This ablation of hippocampal neurogenesis slows the decay of the hippocampal dependency of remote CFC memories, whereas in controls, remote CFC memories become less hippocampal dependent over time. Running increases the rate at which these CFC memories become hippocampal independent without affecting the expression of the memory, an effect that is blocked by irradiation [103]. Most recently Akers et al., (2014) have shown a clear link between neurogenesis and forgetting where running induced forgetting of a CFC task in adult mice. Using guinea pigs and degus, species that both have low levels of postnatal neurogenesis, they showed intact memory retention except when neurogenesis was stimulated by memantine [104]. Together these studies begin to suggest a role for neurogenesis and memory retention and clearance in the hippocampus.

EFFECTS OF EXERCISE IN NEUROLOGICAL DISORDERS

Fetal alcohol spectrum disorders

Ethanol can cause significant damage to the fetus [105, 106] and can result in fetal alcohol spectrum disorders (FASD) with the extent of damage caused by ethanol varying due to the timing, frequency and volume of ethanol consumed, as well as the genetics and metabolism of the mother.

FASD can be modelled in rodents using a variety of methodologies which are outlined in recent reviews from our laboratory [107, 108]. The most commonly used methods are the liquid diet model where a pregnant dam receives a liquid diet containing 36% (v/v) ethanol throughout pregnancy, and the gavage model where ethanol is administered via oral intubation.

FASD and structural plasticity

FASD can lead to a variety of structural deficits in the hippocampus including decreases in adult hippocampal neurogenesis [109–113]. The effect of exercise has been examined in a variety of models of FASD to determine whether beneficial effects on neurogenesis and neuron structure occur [111, 114, 115].

Redila et al., (2006) were the first to show that decreases in cell proliferation that occur with prenatal

ethanol exposure can be rescued in rats with one week of exercise [115]. Using a different model of FASD, where animals were exposed to ethanol during the third trimester equivalent (corresponding to PND1-10 in the rat), Helfer et al., (2009) found that 12 days of voluntary running wheel exercise during adolescence increased proliferation of cells in the DG, but long-term survival of these neurons was not increased [111]. It is important to note that in this study, baseline levels of proliferation and neurogenesis were comparable between the control and the ethanol-exposed animals, which differs from the study by Redila et al. (2006).

The effect of exercise on neurogenesis was also examined using the gavage model where ethanol was administered throughout all three trimester equivalents [114]. Ethanol exposure reduced cell proliferation and increased early neuronal maturation, but did not affect cell survival [114]. When ethanol exposed animals were given access to voluntary running wheels for 12 days beginning at PND 48, increases in cell proliferation and maturation were observed which indicates that despite deficits caused by ethanol exposure, the brain still has the capacity to respond to the beneficial effects of exercise [114]. Remarkably, increases in the proliferation marker Ki67 were actually much greater in ethanol exposed animals than in control animals following exercise. This may be linked to the fact that ethanol exposed animals ran significantly more than controls, which could indicate a hyperactive phenotype in these animals [114].

These varied results between studies are probably due to the different models of ethanol exposure employed. However, results from Helfer et al., (2009) and Boehme et al., (2011) suggest that while exercise may be able to stimulate proliferation and differentiation, additional therapies may need to be utilized to ensure that the new neurons are able to survive and integrate into functional networks of the hippocampus. For example, Hamilton et al., (2014) combined exercise followed by environmental enrichment. Using BrdU labeling, the authors found that ethanol-exposed animals had lower rates of cell survival than control animals. However, in ethanol-exposed animals who were given voluntary access to a running wheel (started at PND 30 for 12 days) followed by access to an enriched environment (from PND 42 – 72), the levels of cell survival were comparable to those of control animals [110]. These results indicate that both exercise and enrichment may be needed in order to enhance cell proliferation as well as cell survival.

FASD and synaptic plasticity

Ethanol exposure causes long lasting deficits in synaptic plasticity in the DG – in particular, LTP is decreased in adolescent and adult male offspring [116–121]. Interestingly, in females, LTP in the DG is increased in adolescent animals, and there are no differences in LTP between control and ethanol-exposed offspring in adulthood [117,121–123]. Only one study has examined the effect of exercise on synaptic plasticity in the DG of animals exposed to ethanol during development. Only males were examined in this study, but the results clearly indicate that access to a running wheel from PND 28 – 60 (32 days), was enough to completely reverse the deficits in LTP observed in the ethanol-exposed offspring [118].

FASD and behaviour

Learning and memory and executive function are impaired in individuals with FASD [124–127]. Functional brain abnormalities can be examined in human populations using functional MRI (fMRI) technology. fMRI has been used to examine spatial working memory in adults and children with FASD, and impairments compared to control subjects are commonly observed [128, 129]. fMRI has also indicated that subjects with FASD exhibit abnormal patterns of brain activation during tasks involving verbal learning [130], verbal working memory [131], and visual working memory [132].

There is a multitude of data indicating that learning and memory, particularly spatial, reference, and working memory, are impaired in animals that were exposed to ethanol during development. Deficits in the MWM where animals show impairments in spatial acquisition, reference and place memory are observed in animals when ethanol exposure occurs both in the prenatal [118, 133–141] and postnatal [142–148] periods.

Only two studies to date have examined the effects of exercise on behaviour in the MWM in animals with FASD. Christie et al., (2005) examined the effects of voluntary wheel running from PND 54 – 64 in animals where the liquid diet model of ethanol administration was used. In this study, the two trial version of the MWM was conducted over a five day period, and both reference and working memory were assessed. Animals exposed to ethanol displayed significant deficits in both reference and working memory when compared to control groups; however, this deficit was completely reversed in the animals that were allowed access to a running wheel [118]. Similar findings were obtained by Thomas et al., (2008) using the postnatal gavage model of ethanol exposure (3rd trimester equivalent).

In this study, animals were allowed access to a running wheel from PND 21 – 51 and then from PND 52 – 57 they were tested in the MWM (4 trials a day, plus a probe trial on the final day). Ethanol-exposed animals that did not exercise had significant deficits in performance, however, these deficits were greatly reduced in the animals allowed access to a running wheel [147]. Performance in the probe trial was not affected by ethanol-exposure; however, exercise also increased performance in this task in both ethanol-exposed and control animals.

The effect of exercise on other hippocampal behaviours has also been examined using the gavage model of FASD. Schreiber et al., (2012) have shown that neonatal ethanol exposure causes significant deficits in CFC tasks [149]. Interestingly, if ethanol-exposed animals were given access to a running wheel from PND 30 – 42 and then environmental enrichment from PND 42 – 72, these deficits in behaviour were not overcome [149]. In contrast, a similar study from the same laboratory showed that exercise could benefit other forms of contextual fear conditioning [110]. Ethanol-exposure causes deficits in trace eyeblink conditioning [150] and a variant of contextual fear conditioning called the context pre-exposure facilitation effect [112, 151]. Hamilton et al., (2014) examined the effects of exercise (PND 30 – 42) followed by environmental enrichment (PND 42 – 72) on these behaviours following ethanol-exposure from PND 4 – 9. They determined that the combination of exercise and enrichment was able to overcome the deficits induced by neonatal ethanol exposure [110].

Other behavioural phenotypes which may be mediated through the hippocampus and are common with FASD include increased depression and anxiety [152–155]. Brocardo et al., (2012) showed that animals exposed to ethanol throughout all three trimester equivalents (i.e. GD 1–21 plus PND 4–10) using the gavage model have increased depression-like and anxiety-like behaviours. These effects were present in both male and female offspring. A cohort of ethanol-exposed animals was given access to a running wheel for 12 days from PND 48 – 60 and at PND 60 was tested for anxiety and depression-like behaviours. Exercise did not rescue anxiety-like behaviours measured using the elevated plus maze in male or female offspring [156]. Ethanol-exposed females showed increased depressive-like behaviour in the forced swim test when compared to control groups. This effect was not rescued by exercise [156]. In males, a similar increase in depression-like behaviours was observed following ethanol-exposure, however, unlike in females, this

effect could be rescued by exercise [156]. This study suggests that gender may play a role in response to exercise-elicited antidepressant effect in ethanol-exposed rats.

Summary

FASD causes a variety of perturbations in hippocampal structure and function which translate into deficits in hippocampal behaviour. Reductions in neurogenesis are commonly observed which may underlie the deficits in synaptic plasticity and hippocampal behaviour.

Although limited, there are a handful of studies which have examined the benefits of exercise in FASD and the results from these studies provide evidence that exercise may be able to overcome these structural and functional deficits in the hippocampus, to a point where ethanol-exposed animals can no longer be distinguished from control animals. These improvements also appear to translate into positive behavioural changes suggesting that exercise may be beneficial in overcoming some of the learning and memory deficits associated with FASD. However, it is important to note that exercise may not be beneficial for all behavioural phenotypes exhibited in animals exposed to ethanol during the perinatal period [149, 156]. Furthermore, studies like those of Brocardo et al., (2012) emphasize the importance of examining both males and females, because sex-specific differences in the effects of ethanol, and the benefits of exercise, may be observed.

Traumatic brain injury

Traumatic brain injury (TBI) can occur when the head hits, or is hit by an object. Up to 1.7 million incident or recurrent TBIs occur annually in the US, most commonly caused by falls, vehicular accidents, assault, and sports injuries [157]. Direct mechanical insult to brain tissue caused by the initial impact, skull fracture, or penetrating injury, along with the stretching and shearing of cell processes and vasculature, result in a cascade of pathophysiological processes throughout the brain that can cause immediate and persistent symptoms. Impaired learning and memory are common symptoms of TBI, regardless of the type or severity of injury. Despite its central, and therefore relatively protected location, changes in hippocampal volume have been reported in humans and rodents after TBI [158–161], suggesting it is susceptible to damage by secondary injury mechanisms, which likely contribute to persistent learning and memory impairment

resulting from TBI (reviewed by [162]). It is an important goal of experimental animal models of TBI to identify mechanisms underlying TBI symptoms like learning and memory impairment, and to identify interventions that can treat them (for a review of animal models of TBI see [163]). Owing to the heterogeneity of this type of injury, there has been great difficulty in finding effective treatments. The potential to promote structural and functional plasticity in the hippocampus makes exercise an attractive means of rescuing cognitive deficits arising from TBI.

Structural and functional plasticity in TBI

There is a paucity of information available on how exercise directly affects hippocampal structure and functional plasticity following TBI; however emerging evidence shows that initiating moderate exercise after a short recovery period may elevate levels of plasticity-promoting proteins and reduce cognitive deficits after experimental TBI in rodents. These effects are consistently mediated by elevations in the neurotrophin BDNF.

An important focus of this research is to establish a timeline to determine when exercise becomes restorative after TBI, as there is evidence that intense physical and cognitive exertion in the acute recovery phase may exacerbate TBI pathology and increase symptom severity [164]. Due to the heterogeneity in exercise paradigms between studies there is controversy over the optimal time to initiate an exercise intervention, but the majority of literature suggests that delaying the onset of exercise is beneficial. In a mouse model of TBI, MWM performance impairments were rescued, CREB and BDNF expression were elevated, and hippocampal neurogenesis was increased by seven days of voluntary wheel running initiated 5 weeks, but not 1 week post-injury [165]. In rats, however, seven days of voluntary wheel running initiated three days after TBI elevated hippocampal BDNF levels, and ameliorated the TBI-induced increase in hippocampal myelin-associated glycoprotein (MAG) and Nogo-A, which are proteins that inhibit axonal growth [166]. Another group found that adult male rats showed reduced deficits in acquisition of spatial reference memory the MWM and elevated hippocampal BDNF when given access to a running wheel 14–20 days after mild TBI [167, 168]. However, when running wheel access was provided 0–6 days post-injury MWM impairments were increased, and BDNF levels were not changed [168]. In these paradigms, administration of a BDNF inactivator prior to exercise attenuated enhancements in MWM performance

[167] and elevations in plasticity related proteins [166].

Injury severity may dictate when it is best to begin an exercise intervention after TBI. In adult male rats, exercise-induced elevations in BDNF were seen when running wheel access was provided at 14–20 days after a mild TBI, but when a moderate TBI was induced, BDNF was only elevated when access to the running wheel was withheld until 30–36 days post-injury [169]. Interestingly, the same group also found that hippocampal BDNF was elevated after voluntary running 0–7 days after moderate TBI, though they noted that injured animals ran significantly less than controls [170]. This highlights an important challenge in this area of research, as injured animals are more likely to abstain from voluntary running, making it difficult to control for exercise duration and exertion. It is possible that in paradigms where voluntary exercise is initiated immediately after TBI, injured rats abstained from exercise during the initial period where they were more vulnerable to sustain further damage.

Summary

The available literature collectively suggests that delayed exercise after TBI can reduce learning and memory impairment, and elevate plasticity-related proteins in the hippocampus. However, there is a paucity of information on precisely how elevated neurotrophins affect structural plasticity and improve behavioural recovery after brain injury. Insight in this matter could be gained through histological and electrophysiological analysis of hippocampal tissue in order to determine whether these exercise-mediate changes correlate with changes in structural and functional plasticity.

Stroke

Ischemic and hemorrhagic stroke occur when blood circulation to a certain area of the brain is restricted due to vessel blockade or rupture, respectively. This produces metabolic distress, tissue damage and cell death in the affected area. Stroke is an extremely prevalent condition, affecting up to 800 000 Americans annually [171]. Depending on which area of the brain is affected, symptomology can include debilitating and persistent impairment to cognitive, motor, visual, auditory, and speech function. When the affected area includes the hippocampus, learning and memory can be severely impaired (reviewed by [172]). Stroke often results in motor deficits, and the potential for exercise to induce plasticity in sensory and motor cortices, and

improve functional recovery in motor tasks has been well studied [173–175]. There is evidence that exercise can augment hippocampal plasticity after stroke as well. However, the information available on the therapeutic effects of voluntary exercise is extremely limited, likely due to difficulty implementing voluntary exercise paradigms in motor-impaired animals. Where voluntary exercise paradigms have been used, outcome measures primarily focuses on exercise mediated elevation in hippocampal plasticity-related proteins, indicating there is a need for further research directly measuring how exercise affects structural and functional plasticity in the hippocampus.

Structural and functional plasticity in stroke

Motor deficits resulting from stroke complicate the application of an exercise intervention. This is an important consideration, as controls may exercise more vigorously or longer duration in voluntary exercise paradigms, but forced exercise may not produce equivalent results. For this reason, information on how voluntary exercise affects structural and functional plasticity in the hippocampus is extremely limited. In a mouse model of ischemic stroke, voluntary wheel running, but not forced swimming, rescued memory impairments in the MWM. This was accompanied by elevated CREB phosphorylation, and increased survival of adult generated neurons in the hippocampus [176]. Another mouse model found that 42 days of voluntary wheel running was sufficient to increase hippocampal neurogenesis and reduce learning impairments in the MWM after ischemia [177].

There is evidence that voluntary running elevates hippocampal BDNF after ischemic stroke, but more research is needed to determine if this effect translates into changes in hippocampal plasticity or cognitive outcome [174, 175].

Summary

Physical activity has the potential to improve stroke outcome by augmenting hippocampal plasticity, but there is a lack of information on how exercise-mediated improvements in cognition and changes in plasticity related proteins correlate with structural and functional changes in the hippocampus. Ongoing research should attempt to establish how exercise-mediated behavioral recovery and neurotrophin expression correlate with neurogenic changes and electrophysiological analysis of hippocampal tissue.

Neurodegenerative disorders

Neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), constitute a heterogeneous group of disorders that commonly display a characteristic progressive loss of structure and/or function of populations of neurons and glia in the CNS [178]. This neuronal degeneration primarily affects specific neuronal populations, which include cortical and hippocampal neurons in AD [179], dopaminergic neurons in PD [180], and striatal gamma-aminobutyric acid (GABA)ergic neurons in HD (reviewed by [181]). Clinically, these diseases are predominantly adult onset and show chronic progression of cognitive deficits.

Animal models of neurodegenerative diseases provide valuable tools in assessing therapeutic strategies for these disorders. Bearing in mind the well-defined benefits of physical exercise on cognitive function, it is reasonable to consider that exercise may in fact be used as a strategy to prevent or impair the cognitive decline associated with age-related neurodegenerative diseases. In this section, we review the influence of voluntary exercise on structural and functional plasticity in adult-aged rodent models of AD, PD, and HD.

Alzheimer's disease

AD, the leading cause of dementia in the elderly, is an age-related, irreversible neurodegenerative disorder clinically characterized by progressive memory loss and multiple cognitive deficits (reviewed by [182]). Important neuropathological hallmarks of AD in the brain include the gradual accumulation of extracellular plaque depositions composed of amyloid-beta (Aβ) peptide, the formation of neurofibrillary tangles (NFT) consisting of hyperphosphorylated tau protein, and substantial neuronal death [183, 184]. The etiology of AD is not yet known, however two competing hypotheses exist. In the Amyloid hypothesis, Aβ plaques are considered to be the causal component in AD pathogenesis [185]. The second theory, the Presenilin hypothesis, is based on loss-of-function presenilin mutations that lead to neurodegeneration and memory impairment in AD [186]. Despite this controversy, the hippocampus is known to be particularly vulnerable to AD, and is one of the first regions to be affected [187].

AD and structural plasticity

Studies of adult hippocampal neurogenesis in a variety of available transgenic rodent models of AD (reviewed by [188]) have generated contradictory results [156, 189]. Decreases in neurogenesis were

reported in transgenic or knock-in mice carrying the PDAPP mutation [190], the Swedish mutation in the APP gene [191–194], PS1 gene mutations [193–196], as well as in double-transgenic mice for APP and PS1 [193, 194]. APP, PS1, and tau protein triple-transgenic mice also show deficits in neurogenesis [197]. In contrast, transgenic mice that express APP with the Swedish, Dutch, and London mutations [198], or with the Swedish and Indiana mutations [199, 200] were found to have increased hippocampal neurogenesis. Discrepancies in the literature are likely based on a variety of factors such as transgenic model used, stage of disease progression, and difference in protocols used to evaluate neurogenesis.

A successful treatment for AD has yet to be developed. A putative lifestyle treatment is exercise, which has been shown to promote neurogenesis in rodent models of AD. APPswe-PS1ΔE9 mice provided 10 weeks of voluntary wheel running showed enhanced levels of hippocampal neurogenesis. Moreover, running significantly prevented neuronal cell loss in the DG and CA3 hippocampal subregions, but did not affect the CA1 [201]. In the Tg2576 AD model, voluntary runners were found to have greater hippocampal volume compared to sedentary littermates following 16 weeks of access to wheel running [202]. An age-dependent effect of voluntary wheel running was found in the APP23 AD mouse model, where 10 days of exercise induced an increase in adult hippocampal neurogenesis in 18 month-old animals, but had no effect in the 6 month-old cohort [203]. These findings suggest the ability of the AD brain to upregulate cell proliferation and neuronal differentiation in response to voluntary physical exercise.

AD and functional plasticity

García-Mesa *et al.* (2011) used electrophysiology to investigate synaptic function and plasticity in 3xTg-AD mice that were subjected to 6-month wheel running treatment. LTP could not be produced in the 3xTg-AD animals, while exercise was found to only weakly protect the impairment of LTP induction at the CA1-medial prefrontal cortex synapse [204]. Considering the limited evidence available that examines the role of exercise on synaptic plasticity in AD, the remainder of this section focuses primarily on hippocampal behaviour. Various transgenic mouse models of AD show deficits in several hippocampal-dependent learning and memory tasks, such as object recognition, spatial learning, and fear conditioning (reviewed by [188, 205]).

Clinical studies with AD patients indicate that physical and cognitive activities are associated with reduced risk of disease [206–208]. Similarly, rodent models of AD that undergo voluntary exercise display encouraging results. Using a Tg2576 mouse model, Yuede and colleagues (2009) found that voluntary runners (16 weeks of wheel running) displayed greater investigation latencies of novel objects in a recognition memory paradigm in comparison to sedentary controls, or forced exercise animals [202]. Transgenic animals containing the ε4 allele of the *APOE* gene exhibit cognitive impairment on the hippocampus-dependent radial-arm water maze task. Following 6 weeks of free access to wheel-running, ε4 mice displayed improvements in this task compared to their sedentary counterparts [209]. The TgCRND8 model of AD also benefits from voluntary exercise; 5-months of voluntary running decreased Aβ plaques in the hippocampus and enhanced hippocampal-dependent learning in the MWM [210]. Another AD model, THY-Tau22, displays progressive learning and memory alterations [211, 212]. In response to a 9-month voluntary exercise period, memory alterations were prevented in the THY-Tau22 mice as assessed by a two-trial Y-maze task in which running animals spent more time in the novel arm [213]. Cognitive deterioration as well as behavioural and psychological symptoms of dementia (BPSD)-like behaviours, such as anxiety and the startle response, were ameliorated by exercise in triple transgenic (3xTg) AD mice with access to running wheel. Of the different experimental cohorts studied, the best neuroprotection was identified in 7 month-old 3xTg-AD mice that had undergone exercise treatment for 6 months [204]. APPswe/PS1ΔE9 mice display spatial memory impairments in the MWM. In response to 10 weeks of voluntary-wheel running, this cognitive decline is significantly decreased in comparison to sedentary controls [201].

In contrast to the above-mentioned studies, TgCRND8 mice with access to running wheel for a 10 week period displayed no improvements in cognitive or neuropathological parameters in comparison to non-runner controls. Despite this, spontaneous stereotypic behaviours of TgCRND8 mice [214], such as repetitive bouts of jumping, climbing, or bar-chewing, were significantly reduced in the wheel-running transgenics [215]. Furthermore, APP23 mice that ran for 8.5 months did not show enhancements in spatial learning, or hippocampal neurogenesis. Interestingly, environmental enrichment lacking a running wheel improved MWM performance and increased hippocampal neurogenesis [216]. This is an important

distinction, as other studies report enhanced cellular plasticity in TgCRND8 [217] and improved cognition in PS1/PDAPP [218] AD models in response to "enrichment" that includes running wheels.

Summary

Although voluntary exercise is the focus of the present review, AD-related exercise research is by no means limited to this paradigm. Treadmill and forced exercise experimental designs are also commonly used in this field. Similar to the majority of voluntary running studies, they show the importance of exercise in preventing the cognitive decline associated with AD [219, 220], repressing neuronal cell death [221], enhancing neurogenesis [222], improving hippocampal LTP [219], and improving cognitive function [223–226]. Trends in current literature suggest that exercise may help to prevent the cognitive decline associated with AD and delay the onset of symptoms. Interestingly, these benefits appear to require relatively long periods of exercise. While cognitive improvements in AD studies require voluntary access to running wheels for 10 weeks up to 9 months, healthy animals or FASD model animals for example, typically undergo exercise paradigms ranging from 7 days to 2 months (see previous sections).

Parkinson's disease

PD is characterized by the progressive loss of dopamingeric neurons in the substantia nigra that projects to the striatum of the basal ganglia. Physical symptoms of this disorder including motor dysfunction such as rigidity; tremor and bradykinesina are accompanied by non-motor symptoms such as cognitive deficits and depressive disorders. Volumetric magnetic resonance imaging studies have suggested a progressive hippocampal volume loss in PD patients [227]. Intracellular accumulation of α-synuclein is the pathological feature of Parkinson's disease and mutations in the gene encoding for this protein is known to be linked to this disease [228]. Abnormalities in hippocampal plasticity have been observed in α-synuclein-related transgenic animal models [229, 230] as well as lesion models of dopamine depletion using either the 1-methyl-4-phenyl-1,2,3,6-tetrhydropyridine (MPTP) or 6-hydroxydomine (6-OHDA) [231–233], which leads to death of dopamingeric neurons and subsequent depletion of dopamine in the dorsal striatum.

PD and structural plasticity

Altered structural plasticity including cell proliferation, differentiation, and survival of adult-born neurons, as well as decreased dendritic complexity and spine formation has been related to the pathogenesis of PD (reviewed by [234]). Decreased hippocampal neurogenesis is altered in 6-OHDA and MPTP–induced animal models of PD [235, 236]. Similarly, decreased cell proliferation and neuronal survival are also found in transgenic mice expressing mutant α-synuclein [237, 238], which echo the decreased hippocampal cell proliferation observed in postmortem brain from PD patients [235].

There are currently no studies examining the effects of voluntary wheel running on structural plasticity in PD. However, in the 6-OHDA- rat model of PD, a regime of 4-weeks of treadmill exercise (30 min/day, 5 days/week) increased cell proliferation and the migration of neural stem cells towards the lesion site accompanied by up-regulated BDNF and glial cell-derived neurotrophic factor (GDNF) in the striatum [239]. Exercise training also enhances survival and integration of transplanted cells in animal model of PD (reviewed by [240]).

PD and functional plasticity

Impaired synaptic plasticity in hippocampal subregions has been reported in animal models of PD. Decreased LTP and enhanced LTD were found in the CA1 region in mice injected with MPTP [233], while decreased LTP and impairment of long-term recognition memory was found in the DG of mice with bilateral 6-hydroxydopamine (6-OHDA) lesions [231]. The impaired LTD in the DG may be linked to disrupted dopaminergic and noradrenergic transmission in the DG [232] and decreased NR2A/NR2B subunit ratio in NMDA receptors [241].

Although clinical studies have demonstrated that physical training improved motor function as well as cognitive performance in PD patients [242, 243], currently there are no studies reporting changes of hippocampal synaptic plasticity following physical training in animal models of PD. Thus, it is unclear whether exercise-induced beneficial effects on cognitive performance on PD patients are at least partly mediated by enhanced hippocampal neurogenesis or synaptic plasticity.

Studies examining the potential beneficial effects of physical exercise on PD are primarily focused on behavioral recovery on motor skill performance [244–248]. In the MPTP mouse model, improvement in motor function is likely linked to increased dopamine transmission, enhanced expression of dopamine receptors or increased glutamate receptor

expression in the dorsal striatum following exercise [249, 250].

Summary

In summary, there are very few studies examining the benefits of voluntary wheel running on structural and functional plasticity in the hippocampus. This may be due to the etiology of the disease and the difficulties in motor function that are observed. However, evidence from human studies does suggest that voluntary exercise, potentially in pre-symptomatic patients may be beneficial for hippocampal function.

Huntington's disease

HD is an autosomal dominant neurodegenerative disease caused by a characteristic cytosine-adenine-guanine (CAG) repeat expansion within the *HD* gene, which results in an expansion of poly-glutamine residues in the huntingtin protein. Under normal conditions, there are 6 – 35 CAG repeats, whereas HD patients may have up to 250 repeats [251]. As a result, mutant huntingtin aggregates into insoluble ubiquitinated neuronal intranuclear inclusions (NIIs) [252]. This mutation primarily causes neurodegeneration of medium spiny neurons in the caudate nucleus, as well as deterioration of certain populations of striatal interneurons [253] and cortical atrophy in other brain regions as the disease progresses (reviewed by [169]).

The characteristic clinical symptom of HD is progressive involuntary choreatic movements followed by later onset bradykinesia and rigidity [254]. In addition to motor disturbances, cognitive impairment and psychiatric symptoms are associated with the progression of the disease, which is invariably fatal 15 – 20 years after onset (reviewed by [242]).

HD and structural plasticity

In contrast to the contradictory results accompanying neurogenesis in AD, there is an apparent consensus that HD reduces adult hippocampal neurogenesis. Lazic and colleagues (2004) were the first to identify this using the R6/1 transgenic model of HD [256]. Additional research of R6/1 [257–259] and R6/2 mice [260–263], as well as a transgenic rat model [264] have extended upon our understanding of adult neurogenesis deficits in the hippocampus of HD rodent models.

To investigate the potential of physical exercise as therapeutic strategy in HD, various studies have analyzed the modulation of neurogenesis after voluntary running in a variety of HD models. Those that specifically investigated adult animals, show that running enhances adult hippocampal neurogenesis, but only in wildtype controls and not in R6/1 HD mice [265, 266].

HD and functional plasticity

Sedentary R6/1 HD mice develop phenotypic rear-paw clasping by 16 weeks of age. Additionally, they display abnormal rearing behavior as well as deficits in motor coordination and spatial working memory. Following 10 weeks of access to a running wheel, the rear-paw clasping onset is delayed, there are normalized levels of rearing behavior and cognitive impairments are ameliorated. Despite this, motor coordination is not rescued [267]. Voluntary exercise during a 4 week period was found to have anti-depressive effects in R6/1 transgenic mice that showed reduced immobility in forced-swim test [265].

In the current review, we focus on adult animals. However, characteristic motor dysfunction is an unavoidable confound with rodent HD models since they are known to run less than wildtype littermates. Considering the progressive nature of HD, several studies have used juvenile animals to investigate the impact of exercise prior to overt symptoms. In 5 week old R6/2 HD mice, a 4 week period of voluntary wheel-running did not rescue the observed reduction in adult hippocampal neurogenesis (60% of wildtype level) [268]. More recently, Potter and collaborators (2010) established that exercise was not beneficial in N171-82Q transgenics, and that it may in fact be detrimental to the vulnerable HD nervous system [269]. Conversely, others have reported that wheel running delays onset of motor deficits [270], improves gait, motor coordination, and slows progression of cognitive dysfunction [271] in juvenile R6/1 HD mice.

Summary

There is a paucity of data examining the effects of exercise on hippocampal plasticity in HD. Taken together, the effectiveness of exercise as an environmental therapy for HD is currently transgenic model-dependent with age-related discrepancies in the literature.

DISCUSSION AND CONCLUSIONS

There is a multitude of evidence that suggests that physical exercise can lead to significant benefits in hippocampal structure and function in rodents, which ultimately results in behavioral benefits. As highlighted in the various sections there are some gaps in the literature that need to be filled, but the majority

Table 2
Effects of voluntary running on adult hippocampal neurogenesis in animal models of neurological disorders

Disease model	Animal age/ Model	Running period	Markers examined	Effect of running	Reference
FASD	7 weeks old/ Rat	7 days	BrdU (proliferation and survival)	Rescued deficit in proliferation and survival	Redila et al., 2006
	4 weeks old/ Rat	12 days	BrdU (proliferation and survival)	Increased proliferation, no effect on survival	Helfer et al., 2009
	7 weeks old/ Rat	12 days	Ki67, BrdU, NeuroD	Increased proliferation and neuronal differentiation	Boehme et al., 2011
	4 weeks old/ Rat	12 days (followed by 30 days enrichment)	BrdU (survival)	Rescued deficit in cell survival	Hamilton et al., 2014
TBI	Not reported				
Stroke	Adult/ Mouse/ photothrombotic cortical infarct	42 days (beginning day of infarct)	BrdU (Proliferaion)	Increased proliferation relative to sedentary stroke group	Geibig et al., 2012
	Adult/ Mouse/ MCAO	42 days (beginning 7 days after MCAO)	BrdU (Proliferation)	No change in proliferation	Chun et al., 2007
	Adult/ Mouse/ MCAO	42 days (beginning 7 days after MCAO)	BrdU (Survival)	Increased survival relative to sedentary stroke	Chun et al., 2007
AD	5 months old/ Mouse/ APPswe/PS1 ΔE 9	10 weeks	Nissl staining; BrdU (proliferation and survival)	Prevented neuronal loss; Increased proliferation and neuronal differentiation	Tapia-Rojas et al., 2015
	5 months old/ Mouse/ Tg2576	16 weeks	Nissl staining	Greater hippocampal volume	Yuede et al., 2009
	6 and 18 months old / Mouse/ APP23	10 days	BrdU, DCX, NeuN	Increased proliferation and neuronal differentiation in 18 month-old mice only	Mirochnic et al., 2009
PD	Not reported				
HD	8–12 weeks old/ Mouse/ R6/1	4 weeks	BrdU (proliferation and survival)	No effect	Renoir et al., 2012
	3 months old/ Mouse/ R6/1	8 days	Ki67, BrdU, NeuN	No effect	Ransome and Hannan, 2013

Abbreviations: AD, Alzheimer's Disease; BrdU, bromodeoxyuridine; DCX, doublecortin; FASD, fetal alcohol spectrum disorder; HD, Huntington's Disease; MCAO, intraluminal middle cerebral artery occlusion; PD, Parkinson's Disease; TBI, traumatic brain injury.

of the evidence suggests that exercise can be beneficial not only in healthy adult animals (Table 1), but also in disease models, including developmental disorders, mood disorders, traumatic brain injury and neurodegeneration (Tables 2–4). How exercise leads to these substantial benefits in hippocampal function

Table 3
Effects of voluntary running on hippocampal synaptic plasticity in animal models of neurological disorders

Animal model	Animal age	Running period	Area analyzed	Effect of running	Reference
FASD	8 weeks old/ Rat	10 days	DG	Rescued deficit in LTP	Christie et al., 2005
TBI	Not reported				
Stroke	Not reported				
AD	7 months old/ Mouse/ 3xTg-AD	6 months	CA1	Rescued deficit in LTP	García-Mesa et al., 2011
PD	Not reported				
HD	Not reported				

Abbreviations: AD, Alzheimer's disease; CA, *Cornu Ammonis*; DG, dentate gyrus; FASD, fetal alcohol spectrum disorders; HD, Huntington's disease; LTP, long-term potentiation; PD, Parkinson's disease; TBI, traumatic brain injury.

Table 4
Effects of voluntary running on hippocampal dependent behaviours in animal models of neurological disorders

Animal model	Animal age/ Model	Running period	Behaviour examined	Effect of running	Reference
FASD	8 weeks old/ Rat	10 days	MWM	Deficits in reference and working memory were reversed	Christie et al., 2005
	3 weeks old/ Rat	30 days	MWM	Rescued deficits in reference memory	Thomas et al., 2008
	4 weeks old/ Rat	12 days (followed by 30 days enrichment)	Contextual fear conditioning	No effect	Schreiber et al., 2012
	4 weeks old/ Rat	12 days (followed by 30 days enrichment)	Context pre-exposure facilitation	Rescued deficits	Hamilton et al., 2014
TBI	Adult/ Rat/ Lateral FPI	7 days (starting 14 days post injury)	MWM	Reduced deficits in acquisition of spatial memory	Grace et al., 2009
	Adult/ Mouse/ Left parietal CCI	4 weeks (starting 1 or 5 weeks post injury)	MWM	Reduced impairment in acquisition of spatial memory, reference memory, reversal memory acquisition, and reversal reference memory after 5 week delay in exercise onset No change after 1-week delay in exercise onset	Piao et al., 2013
	Adult/ Rat/ Lateral FPI	7 days (starting day of injury)	MWM	Increased impairment in acquisition of spatial memory	Griesbach et al., 2004
	Adult/ Rat/ Lateral FPI	7 days (starting 14 days post injury)	MWM	Decreased impairment in acquisition of	Griesbach et al., 2004

(Continued)

Table 4
(Continued)

				spatial memory after delayed exercise initiation	
Stroke	Adult/ Mouse/ photothrombotic cortical infarct	42 days (beginning day of infarct)	MWM	Increased rate of spatial memory acquisition. No change in reference memory	Geibig et al., 2012
	Adult/ Mouse/ MCAO	42 days (beginning 7 days after MCAO)	MWM	Rescued impairment in acquisition of spatial memory	Chun et al., 2007
AD	5 months old/ Mouse/ Tg2576	16 weeks	Novel object recognition	Reduced decline in recognition memory	Yuede et al., 2009
	10–12 months old/ Mouse/ *APOE ε*4	6 weeks	Radial-arm water maze	Improved performance (less errors)	Nichol et al., 2009
	1 month old/ Mouse/ TgCRND8	5 months	MWM	Enhanced learning rate	Adlard et al., 2005
	3 months old/ Mouse/ TgCRND8	10 weeks	One-trial object recognition paradigm, Barnes maze	No effect	Richter et al., 2008
	3 months old/ Mouse/ THY-Tau22	9 months	Two-trial Y-maze	Prevented development of memory alterations	Belbarbi et al., 2011
	4 and 7 months old/ Mouse/ 3xTg-AD	1 month and 6 months	MWM; Startle Response; Dark and Light box test	Rescued retention deficiency; reduced BPSD-like behaviours	García-Mesa et al., 2011
	5 months old/ Mouse/ APPswe-PS1ΔE9	10 weeks	MWM	Prevented impairment in spatial acuity and memory acquisition	Tapia-Rojas et al., 2015
PD	Not reported				
HD	10 weeks old/ Mouse/ R6/1	10 weeks	T-maze; Y-maze	Rear-paw clasping onset delayed; rescued deficit in spatial working memory	Pang et al., 2006
	8–12 weeks old/ Mouse/ R6/1	4 weeks	Forced-swim test	Anti-depressive effects (reduced immobility)	Renoir et al., 2012

Abbreviations: AD, Alzheimer's disease; CCI, controlled cortical impact; FASD, fetal alcohol spectrum disorder; FPI, fluid percussion injury; HD, Huntington's disease; MCAO, middle cerebral artery occlusion; MWM, Morris Water Maze; PD, Parkinson's disease; TBI, traumatic brain injury.

is still under debate. Exercise increases blood vasculature and enhances angiogenesis in the brain and boosts levels of neurotrophins, including brain derived neurotrophic factor (BDNF) [272, 273]. These increases are observed with short or long periods of running, and appear to remain upregulated for a period of time after exercise has ceased [73, 82, 272, 274]. BDNF can increase the production of cell survival genes and proteins important for synaptic plasticity and neurogenesis which may explain the benefits observed in synaptic plasticity and learning and memory [275, 276]. Other factors to consider include enhancements in dendritic complexity and spine density as well as glial cell function. The many potential mechanisms through which exercise can boost hippocampal function are discussed in great detail in recent reviews [277–279].

This review focussed primarily on rodent models of disease, but it is important to note that many of the benefits of exercise found in rodents are also observed in humans. Many human studies have found significant benefits of exercise, not only in healthy individuals but also in individuals with neuropsychiatric and neurodegenerative disorders. It is difficult to assess neurogenesis and synaptic plasticity in humans, however, there is ample evidence to suggest that exercise can enhance learning and memory and other aspects of hippocampal function (reviewed by [277]). Exercise has been shown to enhance hippocampal learning and memory tasks in children [280, 281], adolescents, [282], adults [283] and the elderly [284, 285]. In fact, many studies have investigated whether exercise can reduce or prevent age-related cognitive decline. Studies have indicated that exercise can boost gray matter volume in the hippocampus of aged individuals [286] which leads to enhanced memory [284], and may delay the onset of dementia or Alzheimer's disease (reviewed by [287,288]).

In conclusion, exercise interventions can be extremely beneficial for hippocampal structure and function. The benefits of exercise on hippocampal neurogenesis, synaptic plasticity and behaviour have been extensively studied and have been summarized in this review. The mechanisms responsible for these beneficial effects appear to be vast and diverse, but many effects appear to converge on enhancing BDNF in the brain. Importantly, the benefits of physical exercise are also observed in humans, indicating that exercise interventions should be considered at any age in order to enhance hippocampal learning and memory and delay cognitive decline.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare regarding this manuscript.

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