A new perspective of the hippocampus in the origin of exercise–brain interactions

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Abstract
Exercising regularly is a highly effective strategy for maintaining cognitive health throughout the lifespan. Over the last 20 years, many molecular, physiological and structural changes have been documented in response to aerobic exercise training in humans and animals, particularly in the hippocampus. However, how exercise produces such neurological changes remains elusive. A recent line of investigation has suggested that muscle-derived circulating factors cross into the brain and may be the key agents driving enhancement in synaptic plasticity and hippocampal neurogenesis from aerobic exercise. Alternatively, or concurrently, the signals might originate from within the brain itself. Physical activity also produces instantaneous and robust neuronal activation of the hippocampal formation and the generation of theta oscillations which are closely correlated with the force of movements. The repeated acute activation of the hippocampus during physical movement is likely critical for inducing the long-term neuroadaptations from exercise. Here we review the evidence which establishes the association between physical movement and hippocampal neuronal activation and discuss implications for long-term benefits of physical activity on brain function.

Keywords Exercise · Hippocampus · Theta rhythm · Learning · Memory · Physical activity · Neurogenesis · Movement · Spatial learning · Plasticity · Neuronal activation · Muscle · Myokines

Introduction
Over the past 20 years, it has become established that engaging in regular aerobic exercise is crucial for maintaining cognitive health throughout the lifespan (Kramer et al. 2004). Given the fact that cognitive decline is one of the most devastating aspects of aging, understanding how exercise supports cognitive performance could have extremely broad implications for quality of life. Many studies have documented long-term neurological changes that occur as a result of engaging in physical activity and which are believed to underlie the reported cognitive improvements. There have been several comprehensive reviews summarizing this literature (Cotman and Berchtold 2002; Hillman et al. 2008; Kramer et al. 2006; Cotman et al. 2007; Voss et al. 2013; Vivar et al. 2013). However, the underlying origins of such long-term brain adaptations to exercise remain intangible. Understanding the exact origins of this phenomenon and how exercise-associated signals are sensed by the brain could be transformative when thinking forward about how to design strategies to protect the central nervous system (CNS) from decline.

Of all the brain regions and neurological changes documented in response to exercise, arguably the most impressive and robust long-term changes occur in the hippocampus, a structure which plays a critical role in integrating sensory information during learning and consolidation of memories (Squire 1992; Cohen 2015). Human randomized controlled clinical trials have consistently shown increases in volume of gray matter and blood flow in the hippocampus and more specifically the dentate gyrus of the hippocampus.
Rodent models have further established that exercise increases the total number of neurons in the hippocampus by increasing adult neurogenesis by two- to sixfold, depending on the amount of exercise displayed by the strain of mouse (van Praag et al. 1999b; Mustroph et al. 2012; Clark et al. 2011b; Rhodes et al. 2003b). Exercise-induced adult hippocampal neurogenesis has received a great deal of attention as a contributing agent in the pro-cognitive effects of exercise, probably because of the robustness of the phenomenon (van Praag et al. 1999b; Clark et al. 2011b; Rhodes et al. 2003b), and the underlying premise that new neurons in a brain region important for learning and memory could enhance function of the region [but see Snyder et al. (2017), Groves et al. (2013), Mustroph et al. (2015)]. A recent study reported that hippocampal neurogenesis drops sharply in human children and is virtually absent in adults and, therefore, may not be as important as we thought for cognitive health in adulthood (Sorrells et al. 2018). However, the fact that neurogenesis rates decline precipitously with age was already well known in rodents (Kuhn et al. 1996; Nada et al. 2010). Nonetheless, even in old age, when levels are low, exercise results in a proportional enhancement of neurogenesis (van Praag et al. 2005). The functional significance of adult neurogenesis remains debatable, but the cumulative evidence suggests it persists until death, and remains highly moldable by exercise throughout life. In addition to increasing adult neurogenesis, rodent studies have established that aerobic exercise increases vascular density (Ding et al. 2006b; Clark et al. 2009), increases the concentration of a multitude of neuroprotective peptides and trophic factors including BDNF, IGF1, FGF2 and VEGF (Vaynman and Gomez-Pinilla 2005; Neeper et al. 1995; Dinoff et al. 2016; Farmer et al. 2004; Rothman et al. 2012; Vaynman et al. 2004b; Chieffi et al. 2017; Phillips et al. 2014), modifies the morphological (Wang et al. 2000; Stranahan et al. 2007; Redila and Christie 2006; Eadie et al. 2005) and electrophysiological properties of neurons (Vasuta et al. 2007; van Praag et al. 1999a; Liu et al. 2011), decreases proliferation of microglia and shifts the microglia phenotype to protective in the hippocampus (Kohman et al. 2013, 2012; Kohman and Rhodes 2013), modifies NMDA receptor subunits on neurons (Vasuta et al. 2007), and alters their activation and inhibition (Schoenfeld et al. 2013). These and other molecular and morphological modifications in the hippocampus are believed to underpin improvements in hippocampal-dependent memory, learning and cognitive function that occur as a result of regular physical activity. However, why the hippocampus is so heavily impacted by exercise is not well understood. In particular, whether the signals which support the increased neurogenesis and other neurological changes in the hippocampus from exercise are generated from within the hippocampus itself, or are derived from circulating factors released from distal tissues such as muscle, which are engaged during exercise is not known.

A recent line of investigation has presented muscle-released circulating factors produced during physical activity (e.g., irisin, cathepsin) as potential causal agents driving long-term changes in hippocampal plasticity, neurogenesis and cognitive function (Wrann 2015; Bostrom et al. 2013; Pedersen and Febbraio 2012). Indeed, it seems reasonable to consider the circulatory milieu as playing a part in the beneficial effects of physical exercise in the CNS, especially given recent evidence showing that changes in blood circulating factors in aging can regulate brain function (Castellano et al. 2015; Villeda et al. 2014; Katsimpardi et al. 2014). However, to what extent each one of these individual circulating factors, together or in isolation, can recapitulate the totality and sustainability of the benefits of exercise in regard to brain health is still a matter of debate.

Concurrently or alternatively, events originating within the CNS itself are also likely to contribute to increased hippocampal plasticity and associated cognitive improvements. In that regard, running also produces an immediate, acute and consistent electrical activation of the hippocampus which coincides with the time window of movement (Kuo et al. 2011; Kay 2005; Clark et al. 2011a). Specifically, the hippocampal formation has been shown to instantaneously engage at the onset and duration of strenuous physical movements, displaying a rhythmic synchronous activity of large numbers of neurons, which is proportional to the speed (or force) of the movement and persists for as long as physical activity persists (Buzsaki 2002; Li et al. 2012; Bland and Oddie 2001). Such repeated activation of the hippocampus associated with acute bouts of physical activity is likely to be a critical component in driving the beneficial long-term adaptations to exercise in the hippocampus and perhaps even more broadly throughout the CNS. However, the significance and specific contribution of acute neuronal activation and/or generation of hippocampal theta oscillations during physical exertion in exercise-induced hippocampal neurogenesis and improvements in cognitive status have received little attention in the literature. The multiple reviews to date on the topic of exercise–brain interactions fail to mention this crucial connection between acute hippocampal activation from physical activity and the long-term adaptations that take place in this region in response to exercise training.

In the present review, we first describe the most recent line of investigation looking at the impact of muscle-derived factors on brain function during exercise. Most importantly, we further present the different lines of evidence that illustrate the close and more novel link between hippocampal neuronal activation and physical movement and further discuss the implications that such phenomenon might have in what is currently known about the long-term benefits of physical activity on brain function.
Peripheral origins of exercise–brain interactions: the muscle hypothesis

Many organs in the body release factors into the blood in response to physical activity which could reach the brain and affect behavior such as the liver (Hansen et al. 2011), bones (Qi et al. 2016) and fat (You and Nicklas 2008). In this regard, a recent line of investigation has drawn attention to the importance of the muscle–brain axis in understanding the beneficial effects of exercise in the brain (Wrann 2015; Febbraio 2017). The skeletal muscle is the largest organ in the human body and it is heavily recruited during exercise. This combined with recent evidence showing that metabolites released from one organ might affect metabolic responses in other organs, warrants further investigation into the crosstalk between tissues during physical activity (Castellano et al. 2015; Katsimpardi et al. 2014; Villeda et al. 2014; Pedersen and Febbraio 2012; Bostrom et al. 2013). As such, the generation of paracrine factors by the skeletal muscle has been recently explored as a potential mechanism underlying the effects of physical exercise in brain plasticity, neurogenesis and cognitive performance (Kobilo and van Praag 2012; Trejo et al. 2001; Jin et al. 2003; Vaynman et al. 2004a). Several molecules, such as growth factors, enzymes, peptides and metabolites have been identified as being of potential relevance (Ding et al. 2006a; Wrann et al. 2013; Agudelo et al. 2014). For example, early studies suggested that serum insulin-like growth factor-1 (IGF) and vascular endothelial growth factor (VEGF) play an important role in exercise-induced neurogenesis, as the peripheral blockade of these systemic neurotrophic factors were shown to abolish running-induced enhancement of hippocampal neurogenesis (Trejo et al. 2001; Fabel et al. 2003).

Increases in hippocampal BDNF following exercise have also been linked to increases in muscle-derived metabolic mediators, in particular peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) (Bostrom et al. 2012; Wrann et al. 2013). PGC-1α is a transcriptional coactivator produced in skeletal muscle, and FNDC5, one of its downstream proteins, is known to be cleaved and secreted from the muscle (as irisin) in the CNS, the authors demonstrate that in CTSB knockout mice, running no longer produces the expected increases in hippocampal CTSB gene expression. In support of a causal link between CTSB and exercise-induced benefits in the CNS, the authors demonstrate that in CTSB knockout mice, running no longer produces the expected increases in neurogenesis and improvements in spatial memory (Moon et al. 2016). Elevations in running-induced CTSB plasma levels in mice were further accompanied by increases in hippocampal CTSB gene expression. In support of a causal link between CTSB and exercise-induced benefits in the CNS, the authors demonstrate that in CTSB knockout mice, running no longer produces the expected increases in neurogenesis and improvements in spatial memory (Moon et al. 2016). Although this suggests a role for this myokine in the beneficial effects of exercise in the brain, it is not clear at this point whether muscle-derived CTSB is necessary or whether hippocampal and muscle CTSB are simply expressed concomitantly in response to physical activity.

The therapeutic implications of muscle-derived circulating factors to brain health can be extremely impactful if the delivery of a peptide can be developed into a drug that may be able to confer neuroprotective effects in the brain. However, to what extent each one of these individual circulating factors, together or in isolation, can recapitulate the totality and sustainability of the benefits of running in regard to brain health is still a matter of debate. The few studies available to date do provide valuable evidence attempting to link causally circulating myokines to exercise-like effects in the CNS, but this area of research is still in its infancy.
Central origins of exercise–brain interactions: the significance of hippocampal neuronal activation

The circulating myokine hypothesis described in the preceding section states that the pro-cognitive signals originate from the muscles and cross into the brain from the blood to exert their pro-cognitive influence. However, an alternative possibility, not mutually exclusive, is that the signals originate within the brain itself. There is an extensive literature describing the brain regions involved in producing motor commands (e.g., motor cortex) (Brümmer et al. 2011; Picard and Strick 1996) and coordinating complex movements (e.g., basal ganglia, cerebellum) (Middleton and Strick 2000) which could release factors within the brain to directly or indirectly affect regions (e.g., hippocampus) involved in the range of cognitive processes that are improved following exercise (Colcombe and Kramer 2003). Most of the human studies that we are aware of that have explored acute effects of exercise on brain activation and cognitive performance have done so soon after the physical activity has completed (Basso and Suzuki 2017). To the best of our knowledge, no study has connected the immediate, acute activation of motor regions of the brain with the long-term cognitive benefits of exercise. This is probably because, it is not immediately clear how changes in motor regions involved in contracting large muscle masses would affect cognitive processes seemingly unrelated to muscle function (e.g., spatial learning and memory, pattern separation, attention, associative learning).

On the other hand, if it was observed that the hippocampus becomes acutely activated during bouts of exercise, then that might account for some of the observed changes in the region in response to exercise (e.g., synaptogenesis, neurotrophic factors, hippocampal neurogenesis) which have been hypothesized to support enhanced learning and memory. Neuronal activity-dependent changes in synaptic and structural plasticity is one of the most well-studied adaptive processes in the brain, and describes modifications in both the number of synapses and the strength (efficacy of transmission) of synapses within a neuronal circuitry (Ganguly and Poo 2013; Hebb 1949; Caporale and Dan 2008). Repeated, coincident high levels of neuronal activation is expected to change the number and composition of membrane receptors, levels of neurotrophic factors (e.g., BDNF), number and shape of dendritic spines and even dynamic modulation blood vessels structure (Engert and Bonhoeffer 1999; Barriónuevo et al. 1980; Guo et al. 2014; Lacoste and Gu 2015).

Additionally, there is strong evidence to suggest that neuronal activity within the hippocampus is a powerful modulator of neurogenesis in the SGZ of the dentate gyrus. In a very detailed study, Deisseroth et al. (2004) showed for the first time that adult neural stem/progenitor cells (NPCs) can sense excitatory neural activity and as a result undergo activity-dependent neurogenic responses. Specifically, in vitro application of depolarizing levels of KCl, to induce and mimic increased neural activity, resulted in increased neuronal production from adult hippocampal neural progenitor cells (Deisseroth et al. 2004). The authors further provide evidence that increased neuronal activity not only increases the fraction of NPCs that become neurons but also that those neurons are more likely to survive, as demonstrated by measurement of immature new neurons 4 weeks following the neuronal stimulation procedures (Deisseroth et al. 2004). Mechanistically, it seems that such excitatory stimuli are sensed directly by hippocampal proliferating neuronal progenitor cells, via L-type Ca$^{2+}$ channels and NMDA receptors present on the proliferating precursors rather than indirectly through, for example, depolarization-induced release of growth factors from neighboring mature hippocampal neurons. This was elegantly demonstrated by showing increases in neuron phenotypes in living cultures of pure NPCs (no other living cells were present) that were stimulated with calcium channel agonists (FPL64176) or NMDA receptor agonists, clearly indicating that both Ca$^{2+}$ channel activation or NMDA activation is sufficient to promote differentiation of the proliferating NPCs into neurons. This study further shows that neuronal excitation leads to long-lasting changes in gene expression in the proliferating neurons which the authors propose is the likely mechanism by which coupling between neuronal activation and neurogenesis occurs (Deisseroth et al. 2004).

In addition to affecting differentiation of neurons and neuronal survival, neuronal excitation appears to affect the pool of latent stem cells in the adult hippocampus, triggering these cells into the active proliferative state. More specifically, Walker et al. (2008) showed that depolarizing levels of KCl in vitro and pilocarpine-induced neuronal activation in vivo both resulted in increases in the number of neurospheres generated in the adult mouse hippocampus. Interestingly, this mechanism seems to be specific to the hippocampus, since under the same conditions, the other neurogenic region in the brain, the subventricular zone, does not respond to neuronal activity in the same way (resulting in the opposite effect, a decrease in neurosphere number) (Walker et al. 2008). Indeed, other in vivo manipulations or brain alterations that influence electrical activity/neuronal activation have been shown to affect mainly hippocampal neurogenesis (Cameron et al. 1995; Gould et al. 1999; Malberg et al. 2000; Arvidsson et al. 2001). For example, ischemia and seizures, which cause increased local excitation, are known to result in transient increases in neuronal proliferation in the dentate...
Hippocampal neuronal activation in response to acute physical activity

A robust correlation between neuronal activity and average running speed has been repeatedly observed using the IEG method of measuring neuronal activity (Fig. 1b). For example, we and others have found using the technique of immunohistochemical detection of c-Fos, Zif268, and Arc, that the number of IEG-positive granule neurons in the DG and other regions of the hippocampus are strongly positively correlated with average running speed within the 90 min period leading up to euthanasia (Rhodes et al. 2003a; Oladéhin and Waters 2001). In one particular study, mice voluntarily running 2000 m displayed approximately three times the number of c-Fos-positive cells in comparison to mice that ran 200 m (Rhodes et al. 2003a). Similarly, Lee et al. (2003) showed that rodents running at higher speeds in the treadmill display the highest levels of hippocampal activation (DG, CA1 and CA3) (Lee et al. 2003).

Importantly, the strong correlation between IEG activation of the hippocampus and intensity of physical exercise seems to be specific to the hippocampal formation. Acute changes in number of c-Fos-positive cells measured in 25 different regions of the brain after wheel running showed that only hippocampal regions (DG, CA2/CA3) and entorhinal cortex displayed c-Fos levels which were significantly correlated with the average running speed (Rhodes et al. 2003a). The specificity is further supported by the observation that, contrary to the hippocampus, c-Fos levels in mesencephalic locomotor regions in the brain (e.g., lateral periaqueductal gray; cuneiform nucleus, pedunculopontine tegmental nucleus, pontine nucleus), were not correlated with average running speed (Rhodes et al. 2003a). It is not clear why the locomotor regions of the brain do not reflect intensity of physical activity using the c-Fos IEG method. It could be a limitation of the IEG method since not all neurons display IEGs after neuronal activity (Clayton 2000). Alternatively, it could be that intensity of physical activity is not encoded by numbers of activated neurons in these regions, but rather the frequency with which the neurons display action potentials, which would not be detectable using the IEG method (Brümmer et al. 2011).

IEGs have been termed the genomic action potential (Clayton 2000), because they reflect the extent to which a cellular activation event results in increased gene expression and subsequent cellular remodeling. In that way, the presence of IEGs in the nucleus of a neuron indicates that the neuron has undergone some form of cellular learning, defined as a relatively long-lasting (transcription involving) change induced by neuronal stimulation. Because of their function in learning, IEGs are well known to become induced in neurons throughout the brain when an animal is exploring a novel environment (Nestler et al. 2001; Handa et al. 1993; Clayton 2000). It is, therefore, prudent to consider the possibility that the IEG response found in response to running is a result of the novelty of running or the learning that takes place as the animal becomes acquainted with their wheel. However, evidence suggests the contrary. The association between acute hippocampal IEG neuronal activation and voluntary running levels seems to be maintained throughout chronic periods of running and not just associated with the novelty of the experience. In that regard, Clark et al. (2010) showed acute running induced c-Fos in DG neurons even after 50 days of continuous running (Clark et al. 2010). Similarly, Oladéhin and Waters (2001) showed significant increases in number of activated neurons in the DG (granule and polymorphic cell layers), CA1 and CA3 regions of the hippocampus after treadmill running in animals that were previously trained to run on a treadmill, in
comparison to mice that were trained but did not run before brain sampling (Oladehin and Waters 2001). This highlights that regardless of the history of running, engaging in physical activity produces the same acute physiological response in the hippocampus every time the animal engages in a high level of physical activity.

One interesting question that arises from considering these results collectively is whether there is a physiological upper limit for the number of cells that can be activated by increasing running speed. In that regard, in mice selectively bred for high wheel running (which can run up to 2.5 times faster than control mice) the correlation between distance run (within 90 min) and hippocampal activation is lost (Rhodes et al. 2003a). Perhaps, not surprisingly, this strongly suggests a ceiling effect for the magnitude of neuronal activation induced by physical activity. On the other hand, there might also be a minimum running speed needed to trigger such neuronal activation in the hippocampus. For example, IEG (Arc, c-Fos and Zif268) induction from wheel running is attenuated during periods of relative inactivity (for example, during the light cycle), and levels of IEG expression are not correlated with distance traveled in such cases (Fig. 1b). Previous work in our lab also suggests that such magnitude of IEG expression is not induced by locomotion alone in the home cage unless the mice move at an average speed of more than 0.3 km/h (Clark et al. 2011a; Majdak et al. 2014) (Fig. 1b). Thus, a certain threshold velocity of physical movement might be needed to induce hippocampal activation in a speed-dependent manner but this remains to be demonstrated. Taken together, the IEG data demonstrate that the hippocampus becomes acutely

![Fig. 1](image-url)
activated during relatively high-intensity aerobic exercise, and that the number of neurons that are activated is directly proportional to the average running speed. However, because IEGs are detected over the timescale of 5–90 min, depending on the IEG, time for transcription and translation, it is not possible to decipher the patterns of electrical activation that must have occurred to produce the observed IEG responses.

Electrophysiology approaches looking in more detail at instantaneous speed of locomotion and neuronal activation in the hippocampus demonstrate a robust positive correlation between hippocampal neuronal firing rates and running velocity. Several independent studies in rodent models have demonstrated such correlations in CA3 and CA1 pyramidal cells and interneurons (Czurko et al. 1999; Hirase et al. 1999; Diba and Buzsaki 2008). In one study, it was estimated that voluntary wheel running activates approximately 12% of CA1 pyramidal cells, with the discharge frequency of both pyramidal cells and interneurons increasing linearly with running velocity (specifically a tenfold increase from 10 to 100 cm/s). The authors specifically suggest that in voluntary wheel running, the speed of running seems to be a critical variable dictating the frequency of activated pyramidal cells (Czurko et al. 1999; Hirase et al. 1999). More recently, similar relationships were reported in spontaneous locomotion paradigms in which animals move at lower speed ranges, for example, in spherical or linear treadmills (up to 60 cm/s) (Fuhrmann et al. 2015) and mazes (ranging from 15 to 25 cm/s) (Geisler et al. 2007). In such cases, a clear correlation between speed of movement and firing rate of hippocampal pyramidal cells and interneurons was reported.

Collectively, both molecular biology and electrophysiology experiments establish that physical activity acutely engages a large number of hippocampal neurons by increasing the probability they are activated in a given moment and also the frequency with which they fire action potentials. This relationship remains true for both voluntary and forced running, with the levels of neuronal activation being independent of the running history. Most importantly, the data suggest that the relationship is governed to a certain extend by the velocity of movement itself, with more cells being activated and firing with higher frequency as speed of movement increases (Fig. 1b). Given the strength of the relationship between acute physical exercise and neuronal activity in the hippocampus, it is important to consider what might be the implications of this response to the long-term adaptations of physical activity in the brain, and the hippocampus in particular (Table 1).

**Hippocampal theta oscillations in response to acute physical activity**

The hippocampal theta rhythm is an electrical oscillation (ranging from 4 to 8 Hz) that reflects synchronized patterns of action potentials of populations of neurons distributed throughout the hippocampus and interconnecting regions. The dense populations of different layers of cell bodies within the hippocampus, including dentate gyrus and CA1-3 fields, are all interconnected and all participate in the propagation of the electrical currents. The strongest theta rhythms are generated by the CA1 layer from direct entorhinal inputs. Another strong generator is the CA3 to CA1 projection. The dentate gyrus also generates theta rhythms, which are weaker and more difficult to separate from CA1 theta. Within each region, theta is typically characterized by frequency and amplitude, with frequency of theta overall reflecting how often neuronal cells fire in synchrony within a certain time period, whilst the amplitude is associated with how many neuronal cells fire in synchrony within a theta cycle (Burgess and O’Keefe 2005). The hippocampal theta oscillation has been originally associated with movement and exploratory behavior in rodents (Bland 1986; Kramis et al. 1975; Vanderwolf 1969) but has also been studied in the context of spatial learning (O’Keefe and Recce 1993; Kahana et al. 2001), attention and arousal (Bennett et al. 1973). Earlier work on hippocampal theta activity and movement showed a consistent relationship between generation of theta rhythm and ongoing walking, running, jumping, and swimming (referred in the literature as Type I behaviors) (Oddie and Bland 1998).

Although hippocampal theta oscillations have been known for some time to be associated with ongoing physical movement, the specific modulation of frequency and amplitude of theta during physical movement took longer to establish. Pioneering work by Bland and Vanderwolf suggested for the first time that the frequency of hippocampal theta was associated with the speed with which movement was initiated (Vanderwolf 1969; Bland and Vanderwolf 1972). An early study by Morris and Hagen (1983) and later confirmed by Bland et al. (2006b) showed that rats jumping from different heights exhibited theta frequency which was dependent on the speed with which the movement was initiated. Specifically, theta frequency was highest for the highest jump (or highest speed) (Bland et al. 2006b). Other studies demonstrated a positive relationship between velocity of ongoing movement and theta frequency in both voluntary (Slawinska and Kasicki 1998; Geisler et al. 2007; Maurer et al. 2012; Sinclair et al. 1982) and forced movement (Rivas et al. 1996; McFarland et al. 1975; Oddie et al. 1996), whilst few studies fail to find a correlation (Bouwman et al. 2005; Czurko et al. 1999). Moreover, a decline in theta frequency is consistently observed during cessation of movement (Foster et al. 1989; Sinnamon 2005). More interestingly, during movement preparation, for example immediately before a jump or spontaneous wheel running, theta frequency was shown to increase in proportion to the speed of initiation of movement (Bland et al. 2006b; Li et al. 2012), suggesting...
Table 1  Summary of rodent studies describing acute neuronal activation of the hippocampal formation during physical activity

<table>
<thead>
<tr>
<th>References</th>
<th>Rodent model</th>
<th>Type of movement</th>
<th>Running schedule</th>
<th>Speed (m/min)</th>
<th>Brain activity</th>
<th>Brain regions</th>
<th>Neuronal activation (% in relation to control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhodes et al. (2003a) Hsd:ICR mice</td>
<td>Voluntary wheel running/prevented from running</td>
<td>4.20 km/day</td>
<td>10 m/min&lt;sup&gt;a&lt;/sup&gt;</td>
<td>c-Fos Hipp (DG, CA3)</td>
<td>DG: 23%; CA3: 57%</td>
<td></td>
<td></td>
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<tr>
<td>Hsd:ICR mice selectively bred for high wheel running</td>
<td>Voluntary wheel running/prevented from running</td>
<td>12.3 km/day</td>
<td>25 m/min&lt;sup&gt;a&lt;/sup&gt;</td>
<td>c-Fos Hipp (DG, CA3); EC</td>
<td>DG: 19%; CA3: 42%; EC: 160%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2003) Sprague Dawley male rats</td>
<td>Treadmill running</td>
<td>3 days, 30 min per day (all groups)</td>
<td>Peak speed: (1) 8 m/min; (2) 14 m/min; (3) 22 m/min</td>
<td>c-Fos Hipp</td>
<td>DG: (1) 290%, (2) 310%, (3) 700%. Hilus: (1) 69%, (2) 92%, (3) 223%, CA1: (1) 180%, (2) 240%, (3) 280%, CA3: (1) 116%, (2) 166%, (3) 233%</td>
<td></td>
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</tr>
<tr>
<td>Clark et al. (2010) C57BL/6J male mice</td>
<td>Voluntary wheel running</td>
<td>Onset: 2.8 km/day, Plateau (20 days): 4.5 km/day</td>
<td>–</td>
<td>c-Fos DG</td>
<td>At all days tested (6, 26, 30, 50) showed a strong correlation between c-Fos and distance run</td>
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<tr>
<td>Clark et al. (2011a) C57BL/6J male mice</td>
<td>Voluntary wheel running</td>
<td>Average distance: 6.1 km/day over 31 days</td>
<td>–</td>
<td>c-fos, Arc, zif268 DG</td>
<td>c-Fos: ↑ 56 to 525%; zif268: ↑ 100 to 300%; Arc: ↑ up to 580%</td>
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<tr>
<td></td>
<td>Voluntary cage locomotion</td>
<td>Average distance: 0.44 km/day over 31 days</td>
<td>–</td>
<td>c-fos, Arc, zif268 DG</td>
<td>No effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clark et al. (2012) C57BL/6J female mice</td>
<td>Acute voluntary wheel running (in sedentary and running mice)</td>
<td>30 days of access to wheels in running mice</td>
<td>–</td>
<td>zif268 DG</td>
<td>Sedentary: ↑ 587%; Running: ↑ 542%</td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup>Estimated based on 20 min sampling at peak of their activity

EC entorhinal cortex, DG dentate gyrus, Hipp hippocampus
a predictive nature of theta frequency in regards to speed of movement initiation. Furthermore, physical movement at lower velocities (e.g., constant velocity of approx. 2 cm/s) showed an increase in frequency at the initiation of movement but, contrary to wheel running, frequency remained only slightly elevated over baseline during the entire running period, which seems to be reflective of the lower ongoing velocity (Kuo et al. 2011). Overall, this suggests that the frequency’s component of the theta oscillation is associated with either the ongoing animal’s speed of movement (Rivas et al. 1996; Slawinska and Kasicki 1998) and/or the velocity with which voluntary movement is initiated (Li et al. 2012; Fuhrmann et al. 2015). In support of the speed hypothesis, studies which have measured the frequency of action potentials of individual hippocampal neurons during spontaneous wheel running, showed that speed is a critical variable dictating the frequency of action potential firing of pyramidal cells with a linear velocity–frequency relationship observed for running up to 50 cm/s (Czurko et al. 1999; Hirase et al. 1999).

In addition to the frequency of theta, the amplitude of theta is also strongly correlated with running speed on treadmills or voluntary running wheels (Richard et al. 2013; Geisler et al. 2007; Rivas et al. 1996; Li et al. 2012; McFarland et al. 1975), but see (Whishaw and Vanderwolf 1973; Oddie et al. 1996) which failed to find a relationship between activation of the hippocampus and speed of movement, visual and local cues) apart from the actual physical movement (Song et al. 2005). The study showed that the spatial firing patterns across the two modes of navigation were very distinct, despite the fact that the spatial information was identical in both cases. Accordingly, movement in space, without actual physical locomotion does not seem to be sufficient to update the hippocampal firing pattern, suggesting that physical movement is a critical factor in determining place-specific firing of hippocampal neurons (Song et al. 2005). Terrazas et al. (2005) further compares the ‘active movement’ and ‘passive movement’ conditions (described in Song et al. 2005) with a ‘virtual movement’ condition, in which the animal is static and navigates through the same virtual environment, in a similar manner to what is commonly used in clinical research in humans (Terrazas et al. 2005). The theta rhythm in the ‘passive’ and ‘virtual’ conditions was much reduced in comparison to the ‘active movement’, despite the fact that both optic flow in the virtual environment and passive movement were matched for velocity (Terrazas et al. 2005). Most interestingly, whilst in the active movement condition, the theta rhythm responded to changes in speed, once the ambulatory input was removed (in the virtual and passive conditions) this functional relationship was substantially reduced (appearing as if the rodent was moving at a slower speed). Overall, it seems that changing the relationship between the animal and the surrounding spatial cues played a smaller role in updating the hippocampal activity pattern and theta rhythm, in comparison to self-motion signals.

More recently, hippocampal spatial selectivity has been studied in more sophisticated virtual reality head fixed apparatuses where mice can freely move on a rotating ball while the optic flow of the virtual set up mimics the speed of movement (Dombeck et al. 2010; Harvey et al. 2009). This system seems to be a better approximation of real world movement and also more similar to the wheel running paradigms (animals are moving in place), typically used in exercise research. Chen et al. (2013), addressed systematically the selective impact of movement (air-cushioned rotating ball) and visual input on hippocampal neuronal activation during navigation in a virtual environment in head-fixed mice (Chen et al. 2013). Accordingly, when movement was removed (by turning off the rotating ball) and only visual input was maintained, 75% of CA1 cells show a significant change in firing pattern and overall there was a significant reduction in neuronal firing rates. The theta rhythm was still present but at a reduced amplitude. Furthermore, when virtual speed (visual source) conflicted with real speed (motor source), cells that responded mostly to self-motion

**Contribution of physical movement to hippocampal neuronal activity in spatial navigation**

The data reviewed above demonstrate a robust correlation between activation of the hippocampus and speed of movement; however, they do not identify the cause of the relationship, particularly, whether such robust neuronal activation is a result of spatial or other sensory information produced during the movement or directly related to the movement itself. The research field studying spatial navigation and space processing within the hippocampus has generated some very interesting experimental data addressing this question, more specifically related to the contributions of visual stimuli during physical movement (reviewed in Buzsaki and Moser 2013). An interesting paradigm published over 10 years ago, allowed for a direct comparison of hippocampal firing patterns during active movement (rodents running freely in a circular track) and passive movement (rodents riding a motorized cart in the same circular track), while all other variables remained identical (trajectory, velocity, head direction, visual and local cues) apart from the actual physical movement (Song et al. 2005). The study showed that the spatial firing patterns across the two modes of navigation were very distinct, despite the fact that the spatial information was identical in both cases. Accordingly, movement in space, without actual physical locomotion does not seem to be sufficient to update the hippocampal firing pattern, suggesting that physical movement is a critical factor in determining place-specific firing of hippocampal neurons (Song et al. 2005). Terrazas et al. (2005) further compares the ‘active movement’ and ‘passive movement’ conditions (described in Song et al. 2005) with a ‘virtual movement’ condition, in which the animal is static and navigates through the same virtual environment, in a similar manner to what is commonly used in clinical research in humans (Terrazas et al. 2005). The theta rhythm in the ‘passive’ and ‘virtual’ conditions was much reduced in comparison to the ‘active movement’, despite the fact that both optic flow in the virtual environment and passive movement were matched for velocity (Terrazas et al. 2005). Most interestingly, whilst in the active movement condition, the theta rhythm responded to changes in speed, once the ambulatory input was removed (in the virtual and passive conditions) this functional relationship was substantially reduced (appearing as if the rodent was moving at a slower speed). Overall, it seems that changing the relationship between the animal and the surrounding spatial cues played a smaller role in updating the hippocampal activity pattern and theta rhythm, in comparison to self-motion signals.

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<table>
<thead>
<tr>
<th>References</th>
<th>Animal model</th>
<th>Type of movement</th>
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<th>Brain activity</th>
<th>Brain region</th>
<th>Relationship with velocity of movement</th>
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<tr>
<td>Slawinska and Kasicki (1998)</td>
<td>Rats</td>
<td>Spontaneous walking in horizontal runaway</td>
<td>Average = 3 steps/sec (1 to 5 steps/sec)</td>
<td>Theta (measured EEG activity)</td>
<td>Hipp: CA1</td>
<td>↑ theta frequency with speed</td>
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<td>Rats</td>
<td>Induced locomotion by electrical stimulation of SLR and PH</td>
<td>Average = 1.5 steps/sec</td>
<td>Theta (measured EEG activity)</td>
<td>Hipp: CA1</td>
<td>No correlation with theta frequency</td>
</tr>
<tr>
<td>Rivas et al. (1996)</td>
<td>Guinea pigs</td>
<td>Forced walking in conveyor belt</td>
<td>–</td>
<td>Theta frequency and amplitude</td>
<td>Hipp: CA1</td>
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<td>↑ amplitude and frequency during initiation of running; Frequency decreases (close to baseline levels) during running, while amplitude stays high. Both frequency and amplitude were correlated with movement effort (cpm) during running</td>
</tr>
<tr>
<td>McFarland et al. (1975)</td>
<td>Rats</td>
<td>Treadmill walking</td>
<td>–</td>
<td>Theta frequency and amplitude</td>
<td>Hipp: CA1</td>
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<tr>
<td>Foster et al. (1989)</td>
<td>Rats</td>
<td>Voluntary walking</td>
<td>–</td>
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<td>↑ amplitude and frequency with movement</td>
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<td>Geisler et al. (2007)</td>
<td>Rats</td>
<td>Spontaneous walking in maze settings</td>
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<td>Hipp: CA1</td>
<td>↑ oscillation frequency of pyramidal cells and interneurons with speed</td>
</tr>
<tr>
<td>Bouwman et al. (2005)</td>
<td>Rats</td>
<td>Spontaneous walking</td>
<td>up to 35 cm/s</td>
<td>Theta frequency (EEG)</td>
<td>Hipp: CA1</td>
<td>Weak positive correlation between speed and theta frequency</td>
</tr>
<tr>
<td>Li et al. (2012)</td>
<td>Rats</td>
<td>Voluntary wheel running</td>
<td>up to 35 cm/s</td>
<td>Theta frequency and amplitude</td>
<td>Hipp: CA1</td>
<td>↑ frequency with speed during preparation and initiation of running; ↑ Amplitude (of middle frequency) with speed during whole period of running</td>
</tr>
<tr>
<td>Maurer et al. (2012)</td>
<td>Rats</td>
<td>Voluntary walking</td>
<td>up to 70 cm/s</td>
<td>Cell assemblies within the Theta cycle</td>
<td>Hipp: CA1</td>
<td>More cell assemblies within a theta cycle with increasing speed; Theta cycle duration decreased with increasing speed (↑ Frequency)</td>
</tr>
<tr>
<td>Fuhrmann et al. (2015)</td>
<td>Mice</td>
<td>Spontaneous linear or spherical treadmill</td>
<td>up to 60 cm/s</td>
<td>CA1 pyramidal Theta frequency and amplitude</td>
<td>Hipp: CA1</td>
<td>↑ Frequency of theta with speed; Increase in Frequency of theta just before initiation of movement; ↑ pyramidal cells firing with speed</td>
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<td>Czurko et al. (1999)</td>
<td>Rats</td>
<td>Voluntary wheel running</td>
<td>up to 100 cm/s</td>
<td>Theta frequency</td>
<td>Hipp: CA1</td>
<td>No correlation with theta frequency</td>
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<td>↑ discharge frequency of pyramidal and interneurons with speed</td>
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<tr>
<td>Hirase et al. (1999)</td>
<td>Rats</td>
<td>Voluntary wheel running</td>
<td>15–100 cm/s</td>
<td>CA1 pyramidal and interneurons discharge frequency</td>
<td>Hipp: CA1</td>
<td>↑ oscillation frequency of pyramidal cells with speed (threefold)</td>
</tr>
<tr>
<td>Oddie et al. (1996)</td>
<td>Rats</td>
<td>Induced wheel running by electrical stimulation of PH</td>
<td>197–539 cm/s</td>
<td>Theta frequency and amplitude</td>
<td>Hipp: CA1</td>
<td>↑ frequency of theta with speed, but no relationship with amplitude</td>
</tr>
<tr>
<td>Richard et al. (2013)</td>
<td>Rats (control)</td>
<td>Alternation task (voluntary walking)</td>
<td>10 to 100 cm/s</td>
<td>Theta frequency, amplitude and power</td>
<td>Hipp: CA1</td>
<td>Significant positive correlation between speed and theta frequency and power. Speed-frequency relationship correlated with performance on the alternation task</td>
</tr>
</tbody>
</table>

SLR subthalamic locomotor region, PH posterior hypothalamus
information were not affected, suggesting that self-motion input prevails (Chen et al. 2013). Observations from these studies also suggest that at lower speeds of physical motion, the velocity-dependence changes in theta rhythm are disrupted and the hippocampus becomes less engaged/recruited (Ravassard et al. 2013).

In summary, and perhaps not surprisingly, evidence within the field of spatial learning establishes the importance of physical movement on the patterns of neuronal activation in the hippocampus and the characteristics of the theta rhythm generated during spatial navigation. On a broader scale, the implications that such observations might have in explaining the beneficial effects of physical exercise on hippocampal plasticity, neurogenesis and cognitive function need to be explored. In addition, to what extent a certain minimum speed of movement is necessary to engage the hippocampus and how exceeding this minimum physical activity might be important for generating the long-term beneficial effects of physical exercise on mental health demands further attention.

**Origins of movement-induced synchronous hippocampal neuronal activation**

Specific circuits in the brain have been identified which mediate the tight ‘communication’ between physical movement and the hippocampus. The medial septum (MS) and nucleus of diagonal band of Broca (DBB) inputs to the hippocampus are believed to play a major role in synchronizing hippocampal neuronal activity during theta oscillations, in particular both the cholinergic and GABA-ergic septohippocampal projections have been well documented (Frotscher and Leranth 1985; Misgeld and Frotscher 1986). Lesions of MS–DBB have been shown to eliminate the hippocampal theta rhythm (Oddie et al. 1996; Winson 1978) and reduce the amount of spontaneous-occurring locomotor activity (Lawson and Bland 1993; Mizumori et al. 1989). On the other hand, electrical stimulation of MS–DBB (Gray and Ball 1970) (Bland et al. 2006a) or addition of muscarinic agonists to MS–DBB increases the activity of hippocampal theta (Markowska et al. 1995), but fails to induce wheel running behavior (Bland et al. 2006a). Furthermore, electrical stimulation of the posterior hypothalamic nucleus (PH) was shown to influence theta-related activity in the hippocampus and induce locomotion in a MS–DBB-dependent manner (Smythe et al. 1991, 1992; Slawinska and Kasiccki 1998; Oddie et al. 1996), whilst PH lesions reduced the occurrence of voluntary behaviors (Robinson and Whishaw 1974). More specifically, increased stimulation of PH resulted in increased wheel-running speed and hippocampus theta frequency but did not impact amplitude of hippocampal theta (Oddie et al. 1996; Bland et al. 2006a). Multiple regression analysis further confirmed that the frequency, but not the amplitude of the PH stimulation, accounted for a significant proportion of the variance in the running speed (Oddie and Bland 1998; Oddie et al. 1996). Interestingly, when both PH and MS–DBB were stimulated simultaneously, the frequency of hippocampal theta generated always matched the frequency of theta elicited by MS–DBB and resulted in increased amplitude of hippocampal theta (reviewed in Bland and Oddie 2001).

Collectively, these studies established that the PH nucleus exerts its influence on hippocampal theta rhythm and locomotor activity via activation of the hypothalamo-septal pathway, with the degree of PH stimulation dictating the speed of running and the frequency of the theta rhythm. These experiments show that manipulations of PH which induce the generation of hippocampal theta also increase the speed of locomotion (Bland et al. 2006a).

More recently, Fuhrmann et al. (2015) identified a glutamatergic medial septal circuit that seems to be involved in the initiation and velocity of locomotion, specifically mediating the pre-motor initiation of theta oscillations in the hippocampus and the relation between locomotor speed and hippocampal neuronal firing rates (Fuhrmann et al. 2015). The authors show that vesicular glutamate transporter-2-positive glutamatergic neurons (VGlut2 neurons), which are an important source of synaptic excitation within the MS and the MSDB, are part of the mechanistic link coupling hippocampal firing rates and theta oscillations to velocity of movement. Firing MSDB VGlut2 neurons resulted in a reliable initiation of physical movement and the firing rate and number of activated VGlut2 neurons dictated the speed of movement. Furthermore, the activity of these neurons before the initiation of movement predicted accurately the speed of the upcoming locomotor event and was accompanied by an entrainment of theta oscillations (Fuhrmann et al. 2015). Adding to the causal evidence, the authors further show that inhibition of glutamatergic transmission in MSDB resulted in a reduction in theta amplitude and abolished the correlation of theta with locomotion speed. This is the first evidence linking mechanistically locomotion, theta oscillations and speed-associated activation of CA1 pyramidal neurons (Fuhrmann et al. 2015).

A specific population of cells has also been recently discovered in the medial entorhinal cortex (MEC) (approximately 15% across all layers) that responds linearly to speed of movement and also exhibits a strong theta modulation (Kropff et al. 2015). The firing patterns of speed cells in MEC is also prospective or highly correlated with future speed, which suggests that the speed signal in MEC anticipates running speed. Remarkably, when firing rate data recorded from these MEC speed cells (2–6 cells) were processed by a computerized linear decoder, the decoder
was able to predict successfully the animal’s actual running speed (Kropff et al. 2015).

The relative contribution of the medial septal nucleus and entorhinal cortex to the overall hippocampal theta pattern have been dissected using a combination of lesion and pharmacological manipulations [reviewed in Buzsaki (2002), Bland and Oddie (2001)]. Lesions of the entorhinal cortex as well as NMDA receptor blockers (ketamine) both eliminate movement-related theta, suggesting that the glutamatergic afferents from the entorhinal cortex to the distal dendrites of CA1 and CA3 are responsible for movement-induced theta (Buzsaki et al. 2002; Kramis et al. 1975). On the other hand, inactivating inputs from medial septum reduced theta oscillations and the firing rates of grid cells and hippocampal cells (Koenig et al. 2011). One possible explanation for these findings is that movement-induced theta oscillations might depend on fibers that pass through or synapse in the medial septum on their way to the entorhinal cortex with onward connection to the hippocampus. Taken together, these data suggest that the activation of the hippocampus may be involved in the motivation or preparation for intense movements that occur during exercise. To the best of our knowledge, no previous review or commentary has pointed out the likely connection between hippocampal activation involved in movement intensity with the neuroadaptations from exercise.

Conclusions

The central hypothesis put forward in this article is that pro-cognitive effects of exercise, in particular within the hippocampus, may be driven not only by the influence of peripheral tissues but also and foremost by neuronal activity generated within the hippocampus itself. Extensive evidence was reviewed illustrating the close relationship between movement speed and electrical activation of the hippocampal formation. Overall, it seems that the hippocampus is unique among brain regions as displaying the strongest correlation between frequency and amplitude of neuronal firing and speed of running. We further found evidence to suggest that the synchronous firing of large numbers of hippocampal neurons during physical activity is unlike that seen in any other context and five to ten times higher than any typical pattern of neuronal activity displayed during learning a task (Clark et al. 2012) (Fig. 1a). Most importantly, repeated synchronous firing of large numbers of neurons would be expected to produce many of the neuroadaptations discovered in the hippocampus in response to exercise such as increased neurogenesis, angiogenesis, gliogenesis, synaptogenesis, increases in neurotrophic and growth factors as well as cerebral blood flow.

Although the role of electrical activation of the hippocampus during physical exertion remains debated, the close correlation with speed and force parameters suggests the phenomenon is tightly regulated and purposeful (Oddie and Bland 1998). This is, for example, in contrast with the synchronous activation of large number of neurons during an epileptic seizure, which induce some of the same neuroadaptations (Parent et al. 1997a, 2006; Binder et al. 2001; Isackson et al. 1991; Scott et al. 2000), but in an uncontrolled way that results in cell death, and does not benefit cognitive function. The difference is likely related to the fact that hippocampal activation during exercise is involved in some aspect of the sensory–motor feedback involved in the high-intensity physical movements (Oddie and Bland 1998). The contribution of physical movement to the patterns of neuronal activation in the hippocampus and to the characteristics of theta rhythms have been well described in the spatial navigation/-learning literature (Bonnevie et al. 2013; Buzsaki and Moser 2013). Given that spatial learning and path integration are heavily dependent on the hippocampus and rely on this structure for updating an individual’s position in the environment, it is reasonable to assume that the hippocampus would respond to speed of physical locomotion. One leading hypothesis is that higher speeds of locomotion would entail that the integration time-window in which sensory cue-related information can be associated with spatial position is substantially narrower than at slower speeds, so increasing neuronal sensitivity to sensory input during locomotion would be a plausible biological strategy to deal with speed of movement (Buzsaki and Moser 2013).

Beyond understanding the underlying reasons why the hippocampus is heavily engaged during physical movement, it seems absolutely critical to further focus on the implications of this phenomenon in explaining the well-established long-term neurogenic, neuronal plasticity and cognitive adaptations to chronic physical activity. In that regard, most literature investigating the beneficial effects of exercise on brain function has mainly concentrated in documenting long-term adaptations, but has paid little attention to the more immediate and acute brain responses and how those repeated over and over again can contribute to chronic benefits. It is well established that repeated synchronous firing of hippocampal neurons (as it occurs during a learning task) can drive changes in various aspects of synaptic plasticity (e.g., increases in neurotrophic factors, spine density, etc.) (Barrionuevo et al. 1980; Guo et al. 2014) and also hippocampal neurogenesis (Deisseroth et al. 2004). In fact, neuronal-activity-induced increases in neurogenesis seem to be specific to the hippocampus, since under similar neuronal activity conditions the other neurogenic region of the brain, the subventricular zone (SVZ), does not result in increased neurogenesis (Walker et al. 2008). It is also well established that exercise increases neurogenesis only in the
hippocampus and not the SVZ (Brown et al. 2003). Together, these data are consistent with the idea that exercise-induced neuronal activity within the hippocampus might explain mechanistically the increases in hippocampal neurogenesis induced by exercise. In addition to increases in neurogenesis, the typical up-regulation of neurotrophins, such as BDNF or other hippocampal synaptic plasticity biomarkers, which are consistently observed following chronic running interventions, can all theoretically be explained by the repeated synchronous activation of hippocampal neurons (Lamprecht and LeDoux 2004; Butz et al. 2009; Kramis et al. 1975).

Conversely, recent evidence seems to indicate a potential link between muscle-derived myokines produced during running (e.g., cathepsin B, irisin/FNDC5) and improved hippocampal physiology, suggesting that brain neuroadaptations to exercise are complex and likely to be the result of multiple phenomena (Wrann 2015). Presumably, both peripheral (muscle) and central (brain) mechanisms contribute to long-term brain adaptations. However, one would expect the direct acute effect of neuronal activity within the hippocampus to be sensed by the brain first, since it has been widely shown to be an immediate concurrent response during, and even immediately preceding physical activity (e.g., Song et al. 2005; Fuhrmann et al. 2015). Exposure to the muscle secretome (by myokines crossing the blood–brain barrier) would be expected at a later stage. For instance, levels of cathepsin B were only raised in the circulation after 7 days of running (Moon et al. 2016) and increases in plasma levels of irisin following exercise in rodent studies show an up-regulation after 1–4 weeks of running (Tiano et al. 2015; Wrann et al. 2013; Eaton et al. 2017). As such, we predict that the subsequent appearance of muscle-derived myokines within brain tissue is likely to enhance neuroadaptations by creating a more favorable circulatory milieu rather than by initiating and driving such synaptic and neurogenic adaptations (Fig. 2). For example, it is possible that the presence of myokines within the circulation even after the exercise routine has terminated provide a favorable environment for changes to endure within the brain. While the peripheral components may be necessary, they do not appear to be sufficient in isolation, to trigger and sustain long-term cognitive benefits from physical activity. In that regard, studies delivering myokines peripherally (e.g., FNDC5, AICAR) only showed positive effects on hippocampus neuroplasticity up to 7 days of treatment (Wrann et al. 2013) and in some cases prolonged administration (14 days) resulted in a complete loss of beneficial effects (Guerrieri and van Praag 2015). This is perhaps indicative that in the absence of the direct physiological impact of physical activity within the brain, the neurological benefits may not be sustainable. For example, modulation of hippocampal PGC1-α/FNDC5 was shown to underpin increases in hippocampal BDNF during

**Fig. 2** Proposed mechanistic timeline for the impact of physical activity on hippocampus physiology. The central nervous system (CNS) initially communicates with the peripheral skeletal muscle to initiate movement (1), which will generate skeletal muscle contractions and neuronal activation of the hippocampal formation within the same time frame (2). Repeated neuronal activity within the hippocampus during bouts of exercise increases neurotrophic and growth factors (e.g., BDNF, VEGF, IGF-1). Similarly, the repeated contraction of skeletal muscle during physical activity will further produce myokines (e.g., irisin, cathepsin B) that may be able to reach the brain via the circulatory system by crossing the blood–brain barrier (BBB) (4). Both processes are likely to play a role in the long-term neurogenic effects of exercise (5); however, the relative contribution of each component remains debatable.
exercise and it has been proposed that the origin of FNDC5 might be the exercising muscle (Wrann et al. 2013). However, PGC1-α as well as BDNF is known to be produced in the brain in response to sustained neuronal activity (Liang et al. 2010; Castren et al. 1998), though perhaps at lower concentrations than in muscles. Therefore, given the levels of activity occurring within the hippocampal formation during exercise, it is most probable that the main source of PGC1-α and BDNF is the brain itself. This would explain why identical muscle-borne molecular factors might affect hippocampal physiology (when crossing the BBB), but it does not imply necessarily that the origin of these effects is the skeletal muscle.

Future studies should consider strategies that systematically address the relative contribution of both peripheral and central origins of the effects of physical exercise in the hippocampus, by isolating muscle and acute neuronal influences. The outcome of such studies is crucial to provide a basis for understanding whether muscle secretome or/and acute physiology within the brain are necessary and sufficient for recapitulating pro-cognitive effects of exercise. The therapeutic implications of unveiling these mechanisms can be extremely impactful in future scientific research aimed at the attention component of discrimination learning. Behav Biol 8(2):173–181


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