Joggin' the Noggin: Towards a Physiological Understanding of Exercise-Induced Cognitive Benefits

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1 Background

There is considerable evidence that physical exercise has beneficial effects on multiple cognitive domains, particularly executive functions (Babaei et al. 2013; Best et al. 2014; Chang et al. 2012; Colcombe and Kramer 2003; Davis et al. 2011; Dupuy et al. 2015; Hillman et al. 2008; Lee et al. 2014; Predovan et al. 2012). Furthermore, exercise may be protective against the cognitive decline and neurodegeneration observed in normal ageing (Barnes et al. 2004; Colcombe et al. 2004; Dupuy et al. 2015; Erickson et al. 2011; Hill et al. 1993; Holzschneider et al. 2012; Prakash et al. 2015). Themanson and Hillman (2006) suggest that such effects may be driven by exercise-related improvements in cardiorespiratory fitness. Cardiovascular fitness, a subset of cardiorespiratory fitness, is positively associated with cognitive functioning in several domains (Brown et al. 2010; Colcombe et al. 2004; Dupuy et al. 2015; Hötting et al. 2012; Hyodo et al. 2015; Kawagoe et al. 2017; Voelcker-Rehage et al. 2010; but compare Etnier et al. 2006; Young et al. 2015). Exercise that causes an increase in cardiovascular fitness (e.g. whole body aerobic exercise such as running, cycling, or walking) generally has more significant effects on cognition and brain structure than exercise focussed on enhancing strength, such as resistance training (Colcombe et al. 2004; Colcombe et al. 2006; Dustman et al. 1984; Erickson et al. 2011; Kramer et al. 1999; Leckie et al. 2014; Struthers et al. 2017).

Thus, it appears plausible that a physiological mechanism unique to exercise yielding cardiovascular fitness improvements exists that can also yield selective neurocognitive benefits. Although not capturing all aspects of fitness, fitness is often determined by measuring pre- and post- intervention changes in maximal oxygen consumption (VO_2max) reached during a graded exercise test. This review will provide an overview of research in this field and assess four claims comprising a possible causal pathway for cognitive benefits induced by aerobic exercise: a) cardiovascular fitness promotes cerebral angiogenesis and circulation; b) improved cerebral circulation is related to

increased neurotrophin delivery and neurogenesis; c) this neurotrophin delivery contributes to the functional enhancement of neurons; and d) these enhanced neurons are sensitive to domain-specific cognitive training. While previous reviews and meta-analyses have examined the individual effects of exercise on angiogenesis, cerebral blood volume, upregulation of neurotrophins, neurogenesis, and cognition (e.g. Colcombe and Kramer 2003; Hillman et al. 2008; Smith et al. 2011; Voss et al. 2013), here we describe how these mechanisms might interact with each other and the approximate time scale of each mechanism. We also draw attention to the apparent necessity of angiogenesis and domain-specific cognitive training in this process for yielding optimal cognitive benefits from exercise interventions.

2 Cardiovascular Fitness Promotes Cerebral Angiogenesis and Circulation

Cerebral angiogenesis has been associated with cerebral blood volume (CBV) (Maia et al. 2005). Pereira et al. (2007) demonstrated that three months of aerobic exercise causes increased neurogenesis and CBV in the dentate gyrus (DG) of the human hippocampus, and the increased CBV was correlated with improved VO_2max and verbal recall. They suggested angiogenesis as a possible intermediary between exercise-induced increases in CBV and neurogenesis. Maass et al. (2015) also observed increased CBV in the hippocampus following a three-month aerobic exercise intervention, and this increase was associated with improved performance on recognition and spatial memory tasks. Further demonstrating that exercise-induced angiogenesis occurs in the brain and not just skeletal muscle, exercise has been found to induce angiogenesis in the rat frontoparietal cortex (Ding et al. 2006), motor cortex (Ding et al. 2006; Kleim et al. 2002; Swain et al. 2003), striatum (Ding et al. 2006), cerebellum (Black et al. 1990; Isaacs et al. 1992), and the mouse hippocampus (Morland et al. 2017). Exercise also promotes endothelial cell proliferation in the rat hippocampus (Ekstrand et al. 2008). Overall, it appears that

cardiovascular fitness promotes angiogenesis in the brain, and this yields improved cerebral circulation. The mechanisms for this may be related to an upregulation of gene expression for the chemokine CXCL12 (also known as SDF-1). This is observed after three weeks of exercise in mouse models of Alzheimer's disease (Parachikova et al. 2008); CXCL12 participates in angiogenesis by acting as a chemical attractor for endothelial cells (Salcedo et al. 1999). Exercise has been shown to promote both endothelial progenitor cells (EPCs) and the endothelial nitric oxide synthase (eNOS) enzyme in mice (Gertz et al. 2006). eNOS-produced nitric oxide has antioxidant effects (Fukai et al. 2000) and is important for maintenance of the vascular endothelium (Förstermann and Münzel 2006). Exercise-induced eNOS upregulation also promotes angiogenesis (Gertz et al. 2006); taken together, it seems likely that eNOS also serves to enhance the neurogenic niche. Similarly, the expression of forkhead box transcription factors that inhibit angiogenesis (FOXO1 and FOXO3a) is repressed by chronic exercise (Slopack et al. 2014; see Sanchez 2015 for review).

Following the notion that cognitive benefits of cardiovascular health could be attributed to improved cerebral oxygenation, Dupuy et al. (2015) found VO_2max-associated improvements in executive functions for young (ages 19 – 34 years old) and older (ages 55 – 72 years old) women. In particular they found that those with higher VO_2max measurements demonstrated greater changes in cerebral blood oxygenation during testing. That individuals who are less fit and who engage in less exercise did not see such circulatory changes, would indicate that aerobic exercise, which generally leads to higher cardiovascular fitness, contributes to circulation and its apparent effect on task performance. Dupuy et al. (2015) also acknowledge the possibility that individuals with lower cardiovascular fitness may have a larger stress response to cognitively demanding tasks, and that the associated sympathetic nervous system activation could negatively affect cerebral oxygenation, hence resulting in poorer cognitive performance. It could be expected that in some cases this poorer performance will amplify the stress response, forming a negative feedback loop. Of course, intense exercise also elicits a stress

response; the difference between a harmful and a beneficial stress response may lie in the regulation of certain hormones and neurotrophins (see below). In any case, though research is still in its early stages, there is thus far a general consensus that cerebral blood perfusion improves with cardiovascular fitness (likely via angiogenesis and endothelial support) and this positively affects cognitive task performance.

3 Exercise-induced Upregulation of Neurotrophins

Several neurotrophins seem to be particularly affected by physical activity. Brain-derived neurotrophic factor (BDNF), a neurotrophin critically involved in memory that supports neuronal development (Bekinschtein et al. 2008; Huang and Reichardt 2001), appears upregulated by short- and long-term exercise in the rat hippocampus, caudal neocortex, and spinal cord (Aguiar et al. 2011; Berchtold et al. 2005; Gómez-Pinilla et al. 2002; Neeper et al. 1995; Soya et al. 2007; Vaynman et al. 2004), and also in the mouse hippocampus and striatum (Aguiar et al. 2008; Johnson et al. 2003; Lafenêtre et al. 2010; Marlatt et al. 2012). BDNF is released from synaptic structures in the brain (Hartmann et al. 2001; Kojima et al. 2001; see Leßmann and Brigadski 2009 for review), and stored within platelets in the blood system (Fujimura et al. 2002). Physiological stress from acute bouts of exercise may also induce BDNF expression in immune system blood cells (Brunelli et al. 2012). In humans, transient elevations of serum BDNF levels have been found following acute and chronic exercise (Babaei et al. 2013; Ferris et al. 2007; Griffin et al. 2011; Håkansson et al. 2017; Leckie et al. 2014; Marquez et al. 2015; Rasmussen et al. 2009; Ruscheweyh et al. 2011; Schmolesky et al. 2013; Seifert et al. 2010; Szuhany et al. 2015; but compare Goda et al. 2013). Basal (resting) BDNF levels may also be increased slightly by chronic aerobic exercise in young adults (Szuhany et al. 2015; Zoladz et al. 2008) though this was not found in a five-week intervention by Griffin et al (2011) (see also Afzalpour 2015; Marquez et al. 2015). Crucially, exercise-associated improvements in spatial reasoning and memory do not occur in rats when a BDNF antagonist is administered (Vaynman et al. 2004). This strongly suggests BDNF is necessary for the production of cognitive benefits from exercise. A systematic review by

Huang et al. (2014) examines in more detail the effects of acute and chronic exercise on BDNF specifically, indicating that aerobic but not strength/resistance training generally increases peripheral BDNF concentrations.

In addition to elevated BDNF levels, increased phosphorylation of cAMP response element-binding protein (CREB) and protein kinase B (PKB, also known as serine/threonine protein kinase or Akt) in the mouse hippocampus has been observed following 5 weeks of exercise (Aguiar et al. 2011; Chae and Kim 2009; Chen and Russo-Neustadt 2005, 2009). CREB is known to have a role in synaptic plasticity, particularly in long-term potentiation (see Benito and Barco 2010 for review), and mouse studies have demonstrated that CREB is necessary for exercise-induced BDNF expression (Chen and Russo-Neustadt 2009; Conti et al. 2002). CREB is also necessary for the survival of new neurons in the hippocampus (Jagasia et al. 2009). PKB has many roles including cell growth and proliferation (see Brazil and Hemmings 2001 for review), and appears to reduce hippocampal apoptosis (Chae and Kim 2009).

Insulin-like growth factor-1 (IGF-1) also appears important. Exercise-induced neurogenesis in the rat hippocampus is inhibited following injection of a serum that blocks IGF-1 from leaving the bloodstream and entering the cerebrospinal fluid (Trejo et al. 2001). IGF-1 also contributes greatly to the exercise-induced effects of BDNF on recall (Ding, Vaynman et al. 2006). A critical role of IGF-1 delivery from the bloodstream for exercise-induced neurogenesis explains why increased cerebral circulation appears so important, as IGF-1 is a hormone that normally circulates throughout the bloodstream. Neuronal uptake of IGF-1 is stimulated by exercise, and these neurons then show signs of activity and increase their expression of BDNF (Carro et al. 2000).

Woods et al. (2012) describe how in the elderly, there is a well-documented chronic increase in baseline systemic inflammation, and they propose that this is at least partially

caused by immunosenescence. Systemic inflammation contributes to CNS inflammation (Perry, 2004), which reduces the efficacy of IGF-1 in promoting protein synthesis (Frost et al. 1997; Strle et al. 2004). Chronic aerobic exercise serves to reduce systemic inflammation via several mytokine and cytokine cascades (for review see Petersen and Pedersen 2005; Cotman et al. 2007, Mathur and Pederson 2008). Woods et al. (2012) observe that aerobic exercise interventions lasting at least 6 months have been found to reduce biomarkers of inflammation that contribute to this inhibition of IGF-1 signalling (e.g. Kadoglou et al. 2007; Kohut et al. 2006; Mattusch et al. 2000; Nicklas et al. 2009; Vieira et al. 2009; cf. Hammett et al. 2004). According to the review by Woods et al. (2012), the mechanisms by which aerobic exercise reduces inflammation are primarily driven by fat loss (as adipose tissue is known to release pro-inflammatory factors). In addition, they propose that independent of fat loss, exercise stimulates muscle production of anti-inflammatory factors, and also stimulates the vagus nerve, causing peripheral anti-inflammatory effects. Woods et al. (2012) thus offer that the anti-inflammatory effects of chronic exercise can serve to restore IGF-1 signalling which, as discussed above, contributes to BDNF expression and neurogenesis — particularly when neuronal IGF-1 uptake is elevated following acute bouts of aerobic exercise (Carro et al. 2000).

It has also been shown that serotonin (5-HT) is necessary for exercise-induced hippocampal neurogenesis, but not for unrelated baseline neurogenesis – which has implications for disorders involving serotonin deficiency (Klempin et al. 2013). Vascular endothelial growth factor (VEGF) also appears necessary only for exercise-induced hippocampal neurogenesis (Fabel et al. 2003), and regulates CXCL12 (Salcedo et al. 1999), which further indicates the importance of endothelial cell proliferation and angiogenesis in exercise-induced cognitive benefits. In mice, exercise induces expression of VEGF in the hippocampus (Morland et al. 2017; Tang et al. 2010) as well as the lungs and locomotor skeletal muscles, though increased expression is exclusive to the hippocampus in hypoxic conditions (Tang et al. 2010). In humans, exercise at high altitudes has been observed to increase serum VEGF levels immediately after exercise,

with elevated levels lasting up to one month after training (Asano et al. 1998; Schobersberger et al. 2000). Finally, exercise appears to increase the permeability of the human blood-brain barrier (BBB) (Bailey et al. 2011), which could also contribute to the aforementioned effects. A review by Voss et al. (2013) offers further insight into human and animal studies on upregulation of neurotrophic factors and consequent synaptic plasticity via exercise, as well as genetic considerations. Overall, we suggest that vascular adaptation from chronic fitness improvements serves to enhance the beneficial neurocognitive effects from transient elevations of these neurotrophins during and after acute exercise bouts.

4 Neurogenesis, Plasticity, and Learning

Aerobic exercise has been shown to increase neurogenesis in the rat and mouse dentate gyrus (Nokia et al. 2016; Marlatt et al. 2012; van Praag et al. 1999) and the rat hypothalamus (Niwa et al. 2016). Aerobic exercise also increases brain volume in older adults (Colcombe et al. 2006; Erickson et al. 2011). Cardiovascular fitness has been associated with sparing of age-related grey- and white- matter decline (Colcombe et al. 2003; Voss et al. 2016). BDNF has a key role in neurogenesis and supports neural stem cells through tropomyosin receptor kinase B (TrkB) activation (Bartkowska et al. 2007; Bath et al. 2012), and it also modulates synaptic efficacy (Vithlani et al. 2013), so it is reasonable to suggest that elevated BDNF (along with the other supporting neurotrophic factors discussed above) is involved in aerobic exercise-induced neurogenesis and neuroprotective effects.

Indeed, Palmer et al. (2000) demonstrated that adult neurogenesis in the subgranular zone of the hippocampal dentate gyrus (giving rise to excitatory granule cells) is concentrated in regions proximal to endothelial cells attached to the vasculature; an implication of this finding is that angiogenesis could promote neurogenesis by strengthening or expanding the cerebral vasculature, enhancing the neurogenic niche. In the subventricular zone of the lateral ventricles, another site of adult neurogenesis (Ming

and Song, 2011), voluntary exercise stimulates neurogenesis (Chae et al. 2014) and attenuates the decrease in cell proliferation caused by corticosterone (a stress response hormone) in rats (Lee et al. 2016). In the rat dentate gyrus, exercise promotes synaptic plasticity via increased cellular proliferation and dendrite complexity, length, and spine density (Eadie et al. 2005). Restricting exercise in rats impairs neurogenesis and reduces BDNF and VEGF levels (Yasuhara et al. 2007). It has also been demonstrated that exercise can recover impaired neurogenesis levels in the mouse hippocampus, and that this recovery is associated with enhanced BDNF gene expression and performance in an object recognition task (Lafenêtre et al. 2010).

Yet promotion of neurogenesis and synaptic plasticity may not be sufficient to achieve optimal cognitive benefits from exercise as a large proportion of newborn neurons fail to integrate into hippocampal circuits and die after 1-2 weeks (Cameron and Mckay 2001; Curlik et al. 2014; Dayer et al. 2003; Gould et al. 1999). However, despite much speculation (see Vivar & van Praag, 2013 for review), it appears that the long-term survivability of these granule cells is enhanced after hippocampus-dependent (or hippocampus-activating) learning during early phases of the cells' lifespan (DiFeo and Shors 2017; Gould et al. 1999; Sisti et al. 2007). This learning-enhanced survival correlates to task performance (Leuner et al. 2004) and contributes to spatial long-term memory (Snyder et al. 2005). New granule cells are more likely than existing granule cells to be integrated into spatial memory networks (Kee et al. 2007). The new granule cells also receive preferential input from the perirhinal and lateral entorhinal cortex, areas involved in visual discrimination, object recognition, and sensory information processing (Vivar et al. 2012; see Vivar and van Praag 2013 for review).

Therefore, we propose that although aerobic exercise can promote hippocampal neurogenesis through the mechanisms discussed above, subsequent learning in hippocampus-dependent domains such as spatial reasoning and memory is likely necessary for functional integration of new neurons and the manifestation of cognitive

benefits. Practically, several studies have found that combining exercise interventions with cognitive training produces significant benefits compared to exercise or cognitive training alone (e.g. Barnes et al. 2013; Smith et al. 2013). In regions of the brain where neurogenesis is not known to occur, activation of task-dependent regions from cognitive training in other domains and consequent increased metabolic demand could result in proportionally greater oxygenation and neurotrophin delivery to those regions, enhancing plasticity. This seems likely to occur primarily in frontal regions susceptible to age-related cognitive decline (Colcombe et al. 2003; Raz et al. 2004), where sparing effects of exercise and increased grey matter volume associated with enhanced performance on memory tasks have been observed (e.g. Colcombe et al. 2003; Colcombe et al. 2006; Gordon et al. 2008; Ruscheweyh et al. 2011). Long-term (6-12 months) aerobic fitness interventions have been associated with increased white matter volume and connectivity in the prefrontal cortex (Colcombe et al. 2006; Voss et al. 2010; Voss, Heo et al. 2013), and cardiovascular fitness is also associated with white matter volume in the corpus callosum (Johnson et al. 2012). It can be speculated that these regions are more malleable and thus more sensitive to exercise-induced neuroenhancement.

5 From Exercise to Cognition: A Model

It is important to avoid causal oversimplification and consider that exercise-induced cognitive benefits likely arise from the combined effects of multiple mechanisms. Based on the findings summarised in this review, and following the suggestion of Etnier et al. (2006) that cardiovascular fitness could be the first component in a cascade of mechanisms, we propose the model shown in Figure 1 for exercise-induced cognitive enhancement.

[Figure 1]
[Table 1]

First, physical activity (primarily aerobic) improves cardiovascular fitness. This supports cerebral angiogenesis (Kleim et al. 2002; Swain et al. 2003) possibly through mechanical shear stress on blood vessel walls (Makanya et al. 2009), responses to exercise-induced hypoxemia (Patt et al. 1997), CXCL12 upregulation (Parachikova et al. 2008), and FOXO1/FOXO3a suppression (Slopack et al. 2014; Sanchez 2015). Aerobic exercise elevates serum and hippocampal VEGF (Asano et al. 1998; Morland et al. 2017; Schobersberger et al. 2000; Tang et al. 2010), and promotes EPCs and eNOS (Gertz et al. 2006), which support the maintenance of the vascular endothelium (Förstermann and Münzel 2006) and further contribute to angiogenesis (Gertz et al. 2006; Morland et al. 2017). Cerebral angiogenesis explains observed increases in cerebral circulation (Pereira et al. 2007) and cerebral oxygenation (Dupuy et al. 2015); in combination with transiently increased permeability of the BBB (Bailey et al. 2011) there will be more efficient bloodstream delivery of neurotrophins and supporting factors for brain plasticity during or following exercise. Exercise also reduces systemic inflammatory factors, which can restore inhibited IGF-1 signalling (e.g. Kadoglou et al. 2007; Kohut et al. 2006; Mattusch et al. 2000; Vieira et al. 2009). Exercise increases phosphorylation of CREB **(**Aguiar et al. 2011; Chen & Russo-Neustadt 2009)**,** and stimulates neuronal IGF-1 uptake (Carro et al. 2000). With more efficient bloodstream delivery and improved signalling efficacy, elevated levels of IGF-1 can reach more neurons, which then increase their (CREB-mediated) expression of BDNF (Carro et al. 2000; Chen and Russo-Neustadt 2010; Conti et al. 2002; Ding et al. 2006). The rise in CREB and BDNF after repeated acute bouts of exercise enhances neurogenesis (Bartkowska et al. 2007; Bath et al. 2012; Jagasia et al. 2009), and capacity for neural plasticity is increased in the hippocampus along with frontal and parietal regions of the brain (Colcombe et al. 2003; Eadie et al. 2005; Gordon et al. 2008; Marlatt et al. 2012; Voss et al. 2010) in a process that likely involves exercise-induced PKB and CREB phosphorylation (cf. Benito and Barco 2010; Brazil and Hemmings 2001; Chae and Kim 2009). The areas most susceptible to this plasticity are functionally associated with the cognitive domains that see the most exercise-induced benefits (Colcombe et al. 2003; Gordon et al. 2008), such as executive

functions (e.g., Colcombe and Kramer 2003; Davis et al. 2011; Voss et al. 2010) and memory (e.g. Babaei et al. 2013; Håkansson et al. 2017; Holzschneider et al. 2012; Ruscheweyh et al. 2011; Snyder et al. 2005; Vaynman et al. 2004). Domain-specific learning concurrent with exercise interventions may enhance these benefits by promoting the survival of immature neurons less than four weeks old (cf. DiFeo and Shors 2017; Gould et al. 1999; Sisti et al. 2007; Snyder et al. 2005), however there is still sparse evidence regarding the optimal timing between exercise bouts and cognitive training.

In summary, angiogenesis is a relatively chronic adaptation from regularly repeated exercise (over several weeks or months), which enhances the transient effects of acute bouts of exercise such as elevated levels of neurotrophins and supporting factors by improving bloodstream delivery to critical brain areas. These factors enhance neurogenesis and brain plasticity, which yields cognitive benefits most effectively when combined with domain-specific training.

This model is certainly not complete, but based on the studies mentioned in this review, it could be considered a reasonable starting point and we hope it will be expanded on in the future as more specific pathways are elucidated and its predictions are further tested. For example, one prediction of this model is that if angiogenesis could somehow be inhibited, then we would not expect to see any significant cognitive benefits after several weeks of exercise as the key stage of improved cerebral circulation would not occur. It is important to note that this model only describes one of perhaps several potential pathways for exercise-induced cognitive benefits; others may involve higher-intensity, shorter duration exercise (and high-intensity interval training), which has been studied less than aerobic exercise but appears to increase VEGF in rats (Flora et al. 2016) and serum BDNF in humans (Yarrow et al. 2010). Other methods of IGF-1 upregulation or promotion of angiogenesis might be incorporated into the model, and further research might account for non-linear interactions of the different stages, all of which could contribute individually to a range of eventual cognitive benefits. Furthermore we do not

make any claim about a consensus for the timescales listed in Figure 1, but rather we suggest that the observed times for effects to appear in the cited studies (Table 1) indicate an approximate order of events that we expect will be supported by future studies.

Although cardiovascular fitness is important in the model we have presented here, it is likely not *always* necessary for other possible mechanisms of exercise-induced cognitive benefits. This could help explain the relatively rare but notable exceptions in an otherwise large body of supporting evidence. For example, Flöel et al. (2010) found that performance in a learning and memory task improved with physical activity, but this was not associated with cardiovascular fitness. Smiley-Oyen et al. (2008) also found executive functions improved with aerobic exercise, but not with changes in cardiovascular fitness. Resistance training has occasionally been shown to improve executive functions and memory despite small or non-significant changes in cardiovascular fitness (Nagamatsu et al. 2012; Weinberg et al. 2013) for young and old adults, and a meta-analysis by Smith et al. (2011) reported that the benefits of aerobic exercise on some (but not all) cognitive domains were increased when combined with anaerobic exercise. In addition to other variables such as environmental enrichment or the specific type, duration, frequency, and intensity of exercise, the emergence of cognitive benefits could also be affected by age. For some domains such as executive functions or memory, these benefits could be of a more neuroprotective nature in middle-aged adults such that objective improvements in cognition do not become apparent until old age (during natural cognitive decline) and are also more noticeable in children (during natural cognitive development). Exercise is cognitively beneficial at any age. Yet, cardiovascular fitness-related improvements tend to be most noticeable during childhood and old age as this is when the brain undergoes significant structural changes. Additionally, aerobic exercise contributes to the alleviation of cerebrovascular dysfunction, which is associated with age-related cognitive decline (Marshall and Lazar 2011).

To further refine the model described by Figure 1 and further investigate the role of cardiovascular fitness in cognition, future studies can be strengthened by several methodological factors. These include a control group to guard against retesting effects; a control group to guard against any potential effect of environmental enrichment (e.g. a group that starts a new social or leisure activity not involving exercise); the use of a standardised neuropsychological battery to test other cognitive domains beyond executive functions; controls for possible effects of sample population characteristics such as socioeconomic status, intelligence quotient, mental well-being/stress, baseline fitness and prior physical activity levels; controls for possible effects of diet/nutrition; measures of baseline cortisol levels which could affect memory performance (e.g. Maass et al. 2015); the inclusion of multiple age groups; multiple assessments of cardiovascular fitness (e.g., VO_2max, VO_2peak, CBV, and lactate threshold, to test for any difference between the measures); testing for gender differences, as the Colcombe and Kramer (2003) meta-analysis found that cognitive benefits were slightly greater for females than males and a meta-analysis by Szuhany et al (2015) suggests exercise-induced BDNF upregulation may be slightly greater for males; incorporating multiple exercise types (anaerobic and aerobic); varying exercise intensities and intervention durations to assess dose-response relationships as suggested by Etnier et al. (2006); and making use of increasingly accessible methods for analysing brain activity and oxygenation such as near-infrared spectroscopy (e.g. as used by Fabiani et al. 2014). Genetic influences should also be considered; for example, Erickson et al. (2013) found that carriers of a specific BDNF gene polymorphism perform poorly on a working memory assessment compared to non-carriers, but this impairment was offset by physical activity. See Denham et al. (2014) for a general review of exercise-related epigenetic modifications.

6 Summary

The mechanism by which physical activity results in cognitive benefits is complicated and it is likely that multiple pathways exist. Improvement in cardiovascular fitness is not strictly necessary in this process – it could indeed be bypassed in other pathways (e.g.

those involving anaerobic exercise). But contemporary literature seems to support the idea that greater cardiovascular fitness can contribute to many improvements in cognition via multiple mechanisms that share in common upregulation of neurotrophins including BDNF, made more available by long-term improvements of cerebral circulation, yielding greater neurogenesis and improved capacity for adaptive brain plasticity. Future research will reveal more on how specific stages in this pathway arise and may be altered (e.g., by changing exercise parameters, the influence of external factors such as diet, and integrating different forms of cognitive training). Despite the remaining questions about the precise mechanisms involved, improving cardiovascular fitness emerges as even more appealing to those wishing for greater overall health – both physical and mental.

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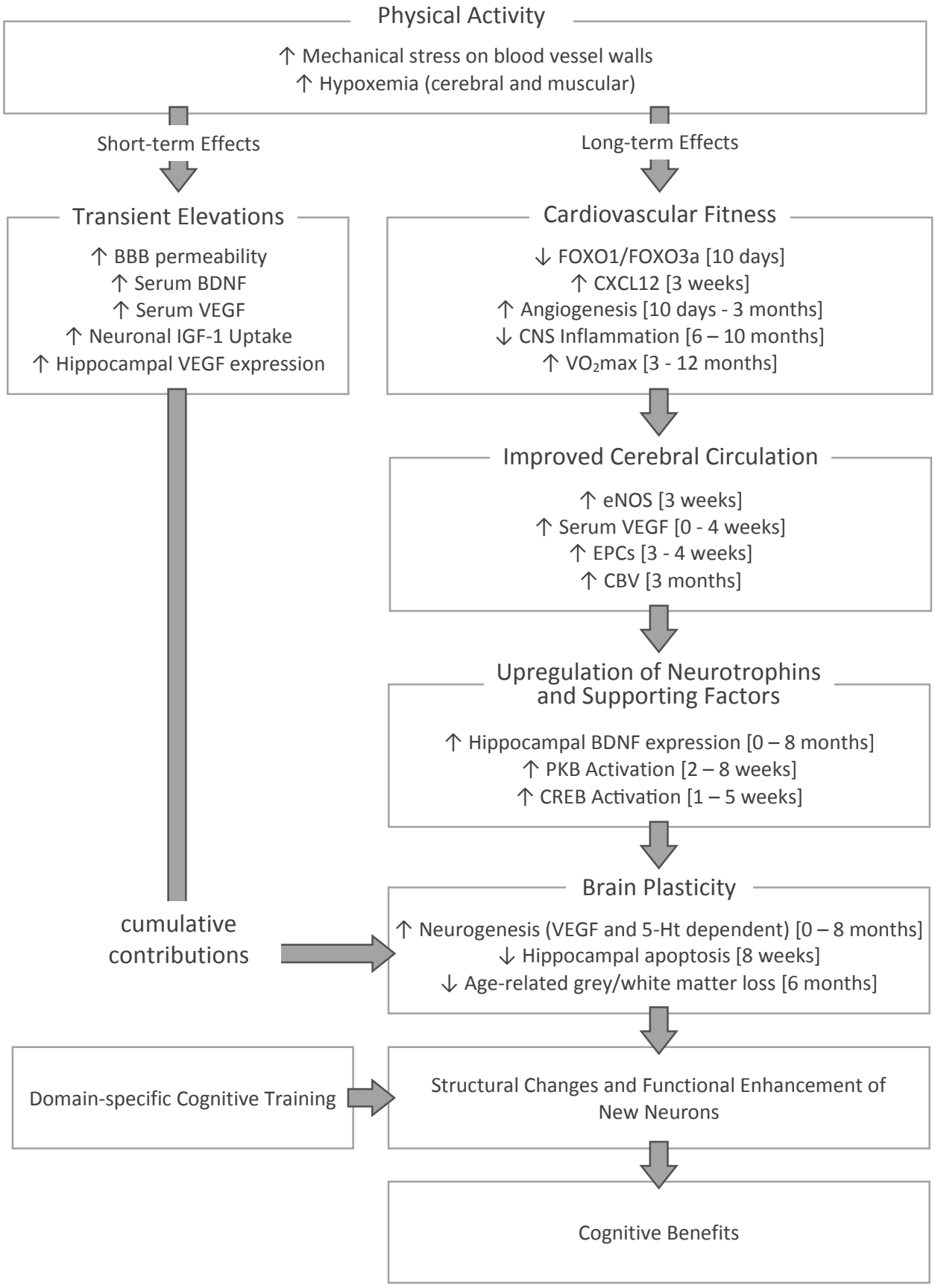
Figure Legend

Figure 1. A model for the effects of physical activity on cognition. Key stages are highlighted with their contributing factors listed underneath. Times for long-term effects to appear from regular repeated exercise in [brackets] are estimates taken from the longitudinal studies cited in this review and may vary with different methodologies. Short-term effects take place during or immediately after acute bouts of exercise; BBB = blood-brain barrier. BDNF = brain-derived neurotrophic factor. CBV = cerebral blood volume. CREB = cAMP response element-binding protein. CXCL12 = C-X-C motif chemokine 12. DG = dentate gyrus. eNOS = endothelial nitric oxide synthase. EPC = endothelial progenitor cells. FOXO1/FOXO3a = forkhead box proteins O1 and O3a. IGF-1 = insulin-like growth factor-1. PKB = protein kinase B. VEGF = vascular endothelial growth factor.

Table Caption

Table 1. Studies cited in this review that contribute to the outcomes included in Figure 1. Subject ages are given as a range, mean, or mean ± SD as specified in each study. Times refer to the point at which outcomes were measured after the start of the exercise intervention, if applicable. [†]"Time of Outcome" refers to the only time at which the outcome was measured (e.g. following sacrifice in animal studies); actual effects possibly occurred earlier. [††]Review article. BBB = blood-brain barrier. BDNF = brain-derived neurotrophic factor. CBV = cerebral blood volume. CREB = cAMP response element-binding protein. CXCL12 = C-X-C motif chemokine 12. DG = dentate gyrus. eNOS = endothelial nitric oxide synthase. EPC = endothelial progenitor cells. FOXO1/FOXO3a = forkhead box proteins O1 and O3a. IGF-1 = insulin-like growth factor-1. PKB = protein kinase B. VEGF = vascular endothelial growth factor.


Physical Activity
↑ Mechanical stress on blood vessel walls
↑ Hypoxemia (cerebral and muscular)
Short-term Effects
Long-term Effects
Transient Elevations
↑ BBB permeability
↑ Serum BDNF
↑ Serum VEGF
↑ Neuronal IGF-1 Uptake
↑ Hippocampal VEGF expression
Cardiovascular Fitness
↓ FOXO1/FOXO3a [10 days]
↑ CXCL12 [3 weeks]
↑ Angiogenesis [10 days - 3 months]
↓ CNS Inflammation [6 – 10 months]
↑ VO_2max [3 - 12 months]
Improved Cerebral Circulation
↑ eNOS [3 weeks]
↑ Serum VEGF [0 - 4 weeks]
↑ EPCs [3 - 4 weeks]
↑ CBV [3 months]
Upregulation of Neurotrophins and Supporting Factors
↑ Hippocampal BDNF expression [0 – 8 months]
↑ PKB Activation [2 – 8 weeks]
↑ CREB Activation [1 – 5 weeks]
cumulative contributions
Brain Plasticity
↑ Neurogenesis (VEGF and 5-Ht dependent) [0 – 8 months]
↓ Hippocampal apoptosis [8 weeks]
↓ Age-related grey/white matter loss [6 months]
Domain-specific Cognitive Training
Structural Changes and Functional Enhancement of New Neurons
Cognitive Benefits

Outcome	Reference	Species	Sex	Sample Size	Age of Subjects	Time of Outcome Measurement
Physical Activity						
↑ Mechanical stress on blood vessel walls	Makanya et al. 2009††	N/A	N/A	N/A	N/A	N/A
↑ Hypoxemia [contributing to angiogenesis]	Patt et al. 1997	Rat	Male	60	220 Days	130 Days†
Cardiovascular Fitness						
↓ FOXO1/FOXO3a	Slopack et al. 2014	Mouse	Female	13	9 Weeks	10 Days
↑ CXCL12	Parachikova et al. 2008	Mouse	N/A	12	15 - 19 Months	3 Weeks†
↑ Angiogenesis	Morland et al. 2017	Mouse	Both	35	7 - 9 weeks	7 Weeks†
	Slopack et al. 2014	Mouse	Female	13	9 Weeks	10 Days
	Ding et al. 2006	Rat	Female	16	22 Months	3 Weeks†
	Swain et al. 2003	Rat	Female	45	5 Months	30 Days†
	Kleim et al. 2002	Rat	Male	16	5 Months	30 Days†
	Isaacs et al. 1992	Rat	Female	38	10 Months	1 Month†
	Black et al. 1990	Rat	Female	38	10 Months	30 Days†
↓ CNot Specified Inflammation [or inflammatory biomarkers]	Vieira et al. 2009	Human	Both	127	Mean = 70 Years	10 Months†
	Kadoglou et al. 2007	Human	Both	60	Mean = 61.64 ± 4.9 Years	6 Months†
	Kohut et al. 2006	Human	Both	87	64 - 87 Years	10 Months†
	Mattusch et al. 2000	Human	Male	22	Mean = 34 Years	9 Months†
↑ VO2max	Dupuy et al. 2015	Human	Female	58	Means = 24.6 ± 3.6 and 62.9 ± 5.4 Years	N/A
	Voss, Heo et al. 2013	Human	Both	70	Mean = 64.87 ± 4.46 Years	1 Year†
	Pereira et al. 2007	Human	Both	11	Mean = 33 Years	3 Months†
Improved Cerebral Circulation						
↑ eNos	Gertz et al. 2006	Mouse	Male	16	N/A	3 Weeks†
↑ serum VEGF	Schobersberger et al. 2000	Human	Male	13	Mean = 36.3 Years	0 - 5 Days
	Asano et al. 1998	Human	Both	8	Mean = 20.4 ± 0.9 Years	10 - 29 Days
↑ EPCs	Gertz et al. 2006	Mouse	Male	16	N/A	23 - 31 Days
↑ CBV	Maass et al. 2015	Human	Both	40	Mean = 68.4 ± 4.3 Years	3 Months†
	Pereira et al. 2007	Human	Both	11	Mean = 33 Years	3 Months†
Upregulation of Neurotrophins and Supporting Factors						
↑ Hippocampal BDNF Expression	Marlatt et al. 2012	Mouse	Female	19	9 Months	8 Months†

	Aguiar et al. 2011	Rat	Female	35	24 Months	5 Weeks†
	Lafenêtre et al. 2010	Mouse	Female	38	2 - 3 Months	13 Days†
	Chen and Russo-Neustadt 2009	Mouse	Both	123	3 Months	6 Hours†
	Rasmussen et al. 2009	Mouse	Male	40	N/A	2 - 6 Hours
	Aguiar et al. 2008	Mouse	Male	24	6 Weeks	8 Weeks†
	Soya et al. 2007	Rat	Male	12	11 Weeks	10 Days†
	Berchtold et al. 2005	Rat	Male	~70	7 - 8 Weeks	14 - 90 Days
	Vaynman et al. 2004	Rat	Male	28	3 Months	1 Week†
	Johnson et al. 2003	Mouse	Male	24	~8 Weeks	1 Week
	Carro et al. 2000	Rat	N/A	18	N/A	1 Hour†
	Neeper et al. 1995	Rat	N/A	N/A	N/A	2 - 7 Days
↑ PKB Activation	Aguiar et al. 2011	Rat	Female	35	24 Months	5 Weeks†
	Chae and Kim 2009	Rat	Male	45	6 Weeks	8 Weeks†
	Chen and Russo-Neustadt 2005	Rat	Male	28	3 Months	2 Weeks†
↑ CREB Activation	Aguiar et al. 2011	Rat	Female	35	24 Months	5 Weeks†
	Chen and Russo-Neustadt 2005	Rat	Male	28	3 Months	2 Weeks†
	Vaynman et al. 2004	Rat	Male	28	3 Months	1 Week†
Brain Plasticity						
↑ Neurogenesis (VEGF and 5-HT dependent)	Nokia et al. 2016	Rat	Male	28	~6 Months	7 Weeks†
	Chae et al. 2014	Rat	Male	96	24 Weeks	2 Days - 6 Months
	Klempin et al. 2013	Mouse	Female	60	6 Weeks - 1 Year	7 Days†
	Marlatt et al. 2012	Mouse	Female	19	9 Months	8 Months†
	van Praag et al. 1999	Mouse	Female	70	3 Months	12 Days - 4 Weeks
↓ Hippocampal Apoptosis	Chae and Kim 2009	Rat	Male	45	6 Weeks	8 Weeks†
↓ Age-related white/grey matter loss	Voss, Heo et al. 2013	Human	Both	70	Mean = 64.87 ± 4.46 Years	1 Year†
	Johnson et al. 2012	Human	Both	26	Mean = 64.8 ± 2.8 Years	N/A
	Ruscheweyh et al. 2011	Human	Both	62	Mean = 60.2 ± 6.6 Years	6 Months†
	Voss et al. 2010	Human	Both	152	Means = 24.1 ± 5.1 and 66.5 ± 5.7 Years	N/A
	Gordon et al. 2008	Human	Both	60	Means = 22.5 ± 2.1 and 71.5 ± 4.7 Years	N/A
	Colcombe et al. 2006	Human	Both	59	Mean = 66.5 Years	6 Months†
Transient Elevations						
↑ BBB permeability	Bailey et al. 2011	Human	Male	8	35 ± 7 years	1 - 20 Minutes

↑ Serum BDNF	Håkansson et al. 2017	Human	Both	19	Mean = 70.8 ± 0.8 Years	35 - 95 Minutes
	Marquez et al. 2015	Human	Male	8	Mean = 28 ± 5 Years	10 - 19 Minutes
	Schmolesky et al. 2013	Human	Male	45	18 - 25 Years	20 - 40 Minutes
	Brunelli et al. 2012	Human	Male	10	Mean = 22.0 ± 0.6 Years	35 - 90 Minutes
	Griffin et al. 2011	Human	Male	47	Mean = 22 ± 2 Years	60 Minutes
	Chen and Russo-Neustadt 2009	Mouse	Both	123	3 Months	6 Hours†
	Rasmussen et al. 2009	Human	Male	8	22 - 40 Years	4 Hours
	Ferris et al. 2007	Human	Both	15	Mean = 25.4 ± 1.01 Years	30 Minutes†
	Ding, Vaynman et al. 2006	Rat	Male	32	N/A	5 Days†
↑ Neuronal IGF-1 Uptake	Carro et al. 2000	Rat	N/A	18	N/A	1 Hour†
↑ Serum VEGF	Schobersberger et al. 2000	Human	Male	13	Mean = 36.3 Years	0 - 5 Days
↑ Hippocampal VEGF expression	Morland et al. 2017	Mouse	Both	35	7 - 9 weeks	7 Weeks†
	Tang et al. 2010	Mouse	N/A	12	6 - 8 weeks	1 - 2 Hours