Review

Exercise-Induced Neuroplasticity: A Mechanistic Model and Prospects for Promoting Plasticity

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Abstract

Aerobic exercise improves cognitive and motor function by inducing neural changes detected using molecular, cellular, and systems level neuroscience techniques. This review unifies the knowledge gained across various neuroscience techniques to provide a comprehensive profile of the neural mechanisms that mediate exercise-induced neuroplasticity. Using a model of exercise-induced neuroplasticity, this review emphasizes the sequence of neural events that accompany exercise, and ultimately promote changes in human performance. This is achieved by differentiating between neuroplasticity induced by acute versus chronic aerobic exercise. Furthermore, this review emphasizes experimental considerations that influence the opportunity to observe exercise-induced neuroplasticity in humans. These include modifiable factors associated with the exercise intervention and nonmodifiable factors such as biological sex, ovarian hormones, genetic variations, and fitness level. To maximize the beneficial effects of exercise in health, disease, and following injury, future research should continue to explore the mechanisms that mediate exercise-induced neuroplasticity. This review identifies some fundamental gaps in knowledge that may serve to guide future research in this area.

Keywords

aerobic exercise, neurophysiology, neuroimaging, neurotrophic factors, neuroplasticity

Introduction

Aerobic exercise is an effective method of inducing neuroplasticity within the human brain and is commonly used as a rehabilitative approach for individuals who have experienced neurological injury. However, the mechanisms by which aerobic exercise induces neuroplasticity are not fully understood, making it difficult to create optimal exercise interventions for rehabilitation. Aerobic exercise induces neuroplasticity at molecular, cellular, and systems levels of analyses. Using these levels of analyses, Stillman and colleagues (2016) have proposed a model to describe the cognitive changes that accompany long-term exercise. The present review expands on this model by elaborating on the sequence of events leading from one level of scientific analyses to the next, ultimately resulting in improvements in cognition and motor performance. The purpose of this review is to provide a detailed model outlining the mechanisms of neuroplasticity induced by chronic and acute exercise. Importantly, we distinguish between neuroplasticity evoked by chronic aerobic exercise (or a history of physical activity) versus neuroplasticity induced by acute aerobic exercise (i.e., a single session). This is an important distinction since it is well known that chronic exercise alters brain structure and function, yet it remains unclear how acute exercise induces neuroplasticity. Understanding the mechanisms of how acute responses to exercise lead to long-term neuroplasticity will provide a better understanding of the sequence of events leading to long-term behavioral outcomes. This review also provides information on practical consideration and important factors that affect the propensity for exercise-induced neuroplasticity. Notably, this review is focused on neuroplasticity induced by aerobic exercise in healthy humans and not strength training (see Chang and others 2012 for review of the latter).

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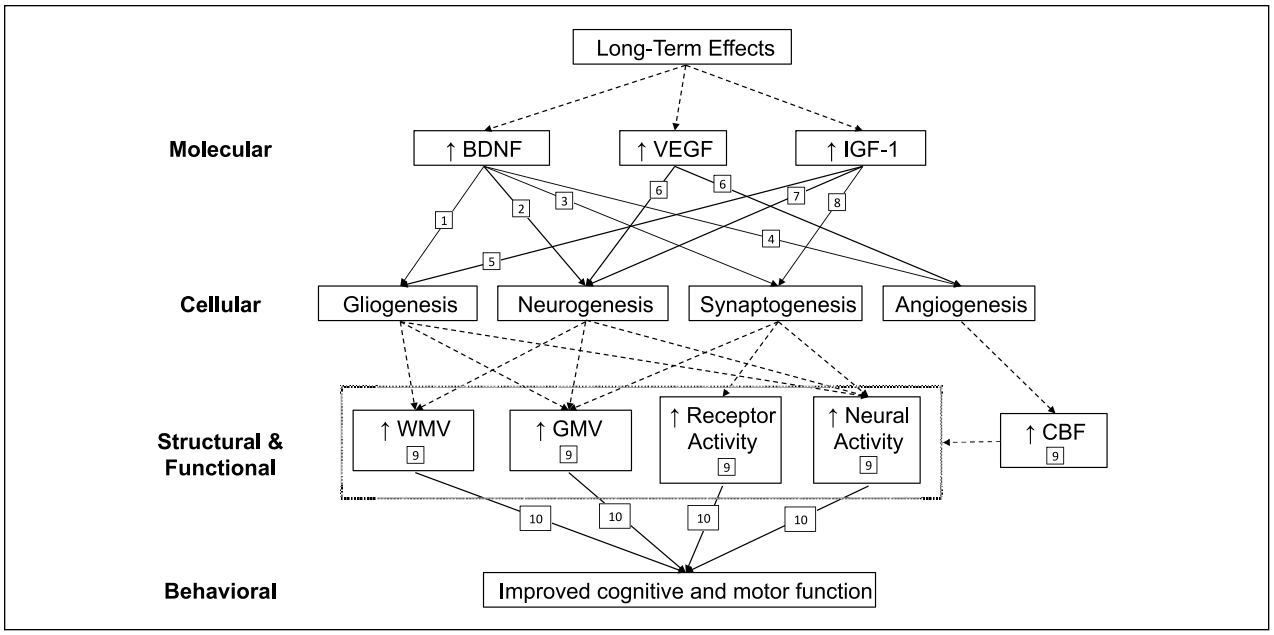


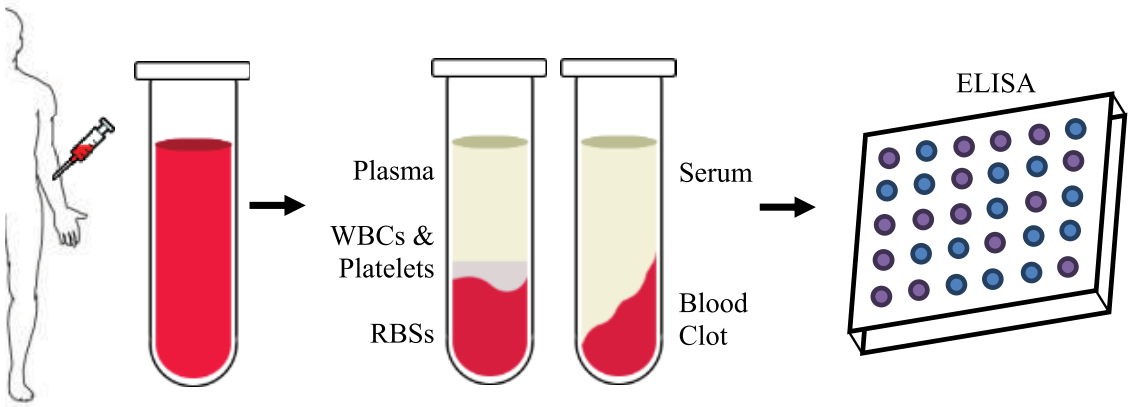
Figure 1. Model of neuroplasticity induced by chronic aerobic exercise. Chronic aerobic exercise induces greater levels of circulating BDNF, IGF-1, and VEGF. These factors promote gliogenesis, neurogenesis, synaptogenesis, and angiogenesis. Increases in neurogenesis likely mediate increases in GMV, WMV, and neural activity. Gliogenesis also likely mediates increases in GMV and WMV. Synaptogenesis may mediate increases in neural activity and receptor activity seen following repeated aerobic exercise. Finally, angiogenesis may mediate increases in CBF. Increases in GMV, WMV, neural activity, and receptor activity are associated with improvements in cognitive and motor function.
BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor 1; VEGF = vascular endothelial growth factor; WMV = white matter volume; GMV = gray matter volume; CBF = cerebellar blood flow. Dashed lines indicate speculation.
References: (1) Cheng and others 2007; (2) Benraiss and others 2001; Pencea and others 2001; Zigova and others 1998; (3) Acheson and others 1995; Binder and Scharfman 2004; (4) Lin and others 2014; (5) Carson and others 1993; Hsieh and others 2004; Ye and others 1995; (6) Fabel and others 2003; (7) Trejo and others 2001; (8) Trejo and others 2007; (9) see Table 2; (10) Hübner and Voelcker-Rehage 2017; Stillman and others 2016.

Model of Neuroplasticity Induced by Chronic Aerobic Exercise

Chronic aerobic exercise has long been shown to improve quality of life (Goodman and others 2016; Mang and others 2013). Figure 1 depicts the model of neuroplasticity induced by chronic aerobic exercise. Exercise-induced changes are measured by various approaches revealing molecular, cellular, structural, functional, and behavioral changes. The evidence for this model at each level is presented below.

At the *molecular* level, chronic aerobic exercise alters the concentration of peripheral brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) (Cotman and others 2007). BDNF promotes neuroplasticity throughout development and adulthood (Monteggia and others 2004; Poo 2001) and is commonly quantified from blood serum or plasma using an enzyme-ligand immunosuppressant assay (ELISA) (see Box 1). Chronic exercise increases the efficiency of BDNF uptake into the central nervous system (CNS) and upregulates transcription and signaling cascades (Currie and others 2009). Cross-sectional studies (i.e., studies investigating differences between fit and unfit individuals) have shown inconsistent findings regarding the relationship between fitness and BDNF levels. Some studies demonstrate lower serum and plasma BDNF levels in those with greater cardiorespiratory fitness and in those who participate in regular physical activity (see review by Huang and others 2014). Huang and colleagues (2014) speculate that the negative association between fitness and BDNF suggests increases in the efficiency of BDNF uptake into the CNS that accompany gains in fitness. However, long-term exercise interventions indicate that serum and plasma BDNF levels increase following exercise training (Leckie and others 2014; Seifert and others 2010; Zoladz and others 2008), while others report no change (Griffin and others 2011; Maass and others 2016; Schiffer and others 2009; Voss and others 2013a). These variances may relate to small samples sizes and variability in exercise parameters.

Box 1. Peripheral Neurotrophic and Growth Factors.



Collection	Pre-Processing	Analysis
Neurotrophic and growth factors are collected peripherally from blood, cerebrospinal fluid, or saliva. Fasted blood samples are most commonly used to reduce variability due to diet and circadian rhythms.	Blood is centrifuged to separate serum/plasma from other blood components. Serum/plasma is aliquoted and stored in a freezer for later analysis.	Peripheral levels of neurotrophic and growth factors are assessed via enzyme-linked immunosorbent assay (ELISA). Peripheral levels are believed to reflect central levels, although this cannot be directly tested in humans.

IGF-1 is important for normal brain development and maintenance (Nieto-Estevez and others 2016; Sonntag and others 2013), and is obtained from blood serum and plasma and quantified using an ELISA (see Box 1). The relationship between IGF-1 and chronic exercise appears to be dependent on age (Table 1). Cross-sectional studies have shown a positive correlation between physical activity and IGF-1 levels in young (Ardawi and others 2012) but not older adults (Rudman and Mattson 1994; Voskuil and others 2001). Furthermore, increases in IGF-1 following long-term exercise interventions have only been shown in young adults (Ardawi and others 2012; Manetta and others 2003; Nindl and others 2012; Schiffer and others 2009). However, reductions in IGF-1 levels in young adults have also been seen following exercise interventions (Rosendal and others 2002; Schiffer and others 2009). Therefore, IGF-1 levels are only modifiable by chronic exercise in the younger population. Further investigation through long-term exercise interventions are needed to identify when, across the lifespan, exercise has the greatest influence on IGF-1 and when such influence dissipates.

VEGF promotes proliferation of neural precursors (Jin and others 2002) and provides a vascular environment suitable for the growth of neurons (Louissaint and others 2002). Quantified similarly to BDNF and IGF-1 (see Box 1), VEGF is negatively correlated with cardiorespiratory fitness in young adults, such that individuals with higher cardiorespiratory fitness showed lower levels of peripheral VEGF (Jurimae and others 2017). As suggested with BDNF, this negative relationship may indicate greater uptake of VEGF in the CNS. However, there are no changes in VEGF levels following long-term aerobic exercise interventions in older adults (Duggan and others 2014; Maass and others 2016; Voss and others 2013a), and this has yet to be studied in young adults. Therefore, similar to IGF-1, it is possible that age is a determining factor modifying levels of VEGF.

BDNF, IGF-1, and VEGF cause *cellular* changes in the brain including gliogenesis, neurogenesis, synaptogenesis, and angiogenesis. Importantly, the evidence supporting this level of the model comes from in vitro or animal models, primarily involving rodents. Gliogenesis is the process by which astrocytes, oligodendrocytes, and microglia are formed. Chronic exercise enhances gliogenesis (Mandyam and others 2007), and may be driven by increases in BDNF and IGF-1. Research has shown that BDNF promotes neural stem cell differentiation into astrocytes (Cheng and others 2007) and IGF-1 promotes neural progenitor differentiation into oligodendrocytes (Carson and others 1993; Hsieh and others 2004; Ye and others 1995). Hence, increased levels of BDNF and IGF-1 in the CNS can provide an optimal environment for gliogenesis.

Table 1. The Effects of Chronic Aerobic Exercise on IGF-1 and VEGF.

Study	Participants	Study design	Fitness assessment/exercise intervention	Results
IGF-1				
Voskuil and others 2001	n = 50 (50.7 ± 1.6 years)	Cross-sectional	Questionnaire (active: 30 min/day cycling or sports and 30 min/day high-intensity physical activity)	No association between pIGF-1 and physical activity
Rudman and Mattson 1994	n = 26 (65.4 ± 0.92 years)	Cross-sectional	Seven Day Physical Activity Recall questionnaire (active: 3 h/week)	No correlation between sIGF-1 and physical activity
Ardawi and others 2012	Cross-sectional: n = 1235 (33.83 ± 8.41 years) Intervention: n = 58 (35.10 ± 1.06 years)	Cross-sectional and long-term intervention	Questionnaire: Group 1: <30 min/week, Group 2: 30–60 min/week, Group 3: 60–120 min/week, Group 4: ≥120 min/week	Cross-sectional: ↑ sIGF-1 in Groups 2–4
			Intervention: 2 months (2 h, 4 times/week) Walking, running and cycling	Intervention: ↑ sIGF-1
Manetta and others 2003	n = 8 (24.4 ± 1.4 years)	Long-term intervention	4 months (17 h/week) Month 1: cycling at 120–160 beats/min Months 2–4: cycling at 170 beats/min	↑ pIGF-1
Nindl and others 2012	n = 93 women (18.8 ± 0.6 years); 29 men (19.1 ± 1.3 years)	Long-term intervention	4 months Gender-integrated basic combat training	↑ sIGF-1 Percent change in sIGF-1 associated with percent change in VO_2 max in men
Vaara and others 2015	n = 52 (19.5 ± 0.6 years)	Long-term intervention	11 weeks Basic military training	∅ sIGF-1
Lange and others 2000	n = 16 (75 ± 1 years)	Long-term intervention	3 months (3 times/week) Cycling at 65% to 70% of VO_{2max}	∅ pIGF-1
Maass and others 2016	n = 21 (68.4 ± 4.3 years)	Long-term intervention	3 months (3 times/week) Walking/running starting at 65% HR_{max}, ↑ by 5% every 4 weeks	∅ sIGF-1 ↑ hippocampal volume associated with sIGF-1
Voss and others 2013a	n = 30 (67.3 ± 5.8 years)	Long-term intervention	12 months (3 times/week) Weeks 1–7: walking at 50% to 60% HR_{max} Weeks 8–1 year: walking at 60% to 70% HR_{max}	∅ sIGF-1 ↑ temporal cortex connectivity associated with sIGF-1
Rosendal and others 2002	n = 12 (20 ± 1 years)	Long-term intervention	11 weeks (daily) Military training	∅ sIGF-1 at week 11
Schiffer and others 2009	n = 9 (23 ± 1.7 years)	Long-term intervention	3 months (3 times/week) Running at 80% HR_{max}	↓ basal pIGF-1
VEGF				
Jurimae and others 2017	n = 20 (19.0 ± 2.9 years)	Cross-sectional	VO_2 max test	Negative correlation between sVEGF and VO_2max
Duggan and others 2014	n = 85 (60.7 ± 6.7 years)	Long-term intervention	12 months (45 min/5 times/week) Weeks 1–8: aerobic exercise at 60% to 75% HR_{max} Weeks 8–1 year: aerobic exercise at 75% HR_{max}	∅ sVEGF

(continued)

Table 1. (continued)

Study	Participants	Study design	Fitness assessment/exercise intervention	Results
Maass and others 2016	n = 21 (68.4 ± 4.3 years)	Long-term intervention	3 months (3 times/week) Walking/running starting at 65% HR_{max}, ↑ by 5% every 4 weeks	∅ sVEGF
Voss and others 2013a	n = 30 (67.3 ± 5.8 years)	Long-term intervention	12 months (3 times/week) Weeks 1–7: walking at 50% to 60% HR_{max} Weeks 8–1 year: walking at 60% to 70% HR_{max}	∅ sVEGF

∅ = no change; ↑ = increased; ↓ = decreased; IGF-1 = insulin-like growth factor 1; VEGF = vascular endothelial growth factor; pNF = plasma neurotrophic level; sNF = serum neurotrophic level; HRmax = maximum heart rate.

Neurogenesis is the process whereby new neurons are created. Chronic aerobic exercise increases neurogenesis (van Praag 2008), which may be a result of increased BDNF, IGF-1, and VEGF. BDNF stimulates neuronal cell proliferation and differentiation, such that BDNF infused into the adult rat cortex increases the neuronal population (Benraiss and others 2001; Pencea and others 2001; Zigova and others 1998). IGF-1 also promotes the proliferation of neurons. Specifically, IGF-1 treatment increased the number of neurons in cell cultures (Perez-Martin and others 2010; Torres-Aleman and others 1990), while blocking IGF-1 using antiserum prevented exercise-induced increases in neuronal populations (Trejo and others 2001). VEGF is also involved in neurogenesis, as blocking exercise-induced increase in peripheral VEGF via injection of Flt-1 fusion protein abolishes exercise-induced neurogenesis (Fabel and others 2003). Together, these findings implicate BDNF, IGF-1, and VEGF as important regulators of neurogenesis following chronic exercise.

Synaptogenesis is the formation of synapses between neurons and is increased as a result of chronic exercise (Lista and Sorrentino 2010). Again, these changes are likely driven by changes in BDNF and IGF-1. BDNF regulates synapse formation and growth (Acheson and others 1995; Binder and Scharfman 2004) through strengthening of glutamatergic neurotransmission (Binder and Scharfman 2004) and weakening of gamma-aminobutyric acid (GABAergic) neurotransmission (Binder and Scharfman 2004; Kowianski and others 2017). Furthermore, BDNF increases AMPA receptor expression at the synaptic cleft, while decreasing $GABA_A$ receptor expression (Kowianski and others 2017). Reductions in IGF-1 decreases the number of glutamatergic synapses, suggesting that IGF-1 is also involved in synaptogenesis (Trejo and others 2007). Therefore, exercise-induced synaptogenesis appears to be driven by changes in BDNF and IGF-1.

Angiogenesis is the formation of new blood vessels and is increased by chronic exercise (Lista and Sorrentino 2010). VEGF plays an important role in the promotion of angiogenesis, as VEGF mRNA and protein are correlated with exercise-induced increases in micro-vessel density (Ding and others 2006; Fabel and others 2003). Levels of BDNF and VEGF expression are positively correlated, as BDNF stimulates VEGF transcription (Lin and others 2014). Furthermore, BDNF plays a role in VEGF-mediated angiogenesis, as partial-knockout of BDNF reduces VEGF expression and abolishes angiogenesis (Lin and others 2014). Therefore, VEGF and BDNF likely mediate exercise-induced increases in angiogenesis.

Exercise-induced molecular and cellular changes are fundamental to inducing changes in *brain structure*. Differentiation between gray and white matter via neuroimaging identifies cortical loci modified by chronic exercise. Exercise is associated with increased gray matter volume in the hippocampus, cerebellum, basal ganglia, cingulate, frontal, parietal, occipital, temporal, and insular cortices (Table 2). Chronic exercise also increases white matter volume in the frontal, parietal, and occipital lobes (Table 2). These findings are observed in both young and older adults, although most research has focused on the latter. Changes in gray and

Table 2. The Effects of Chronic Aerobic Exercise on Various Brain Regions.

Brain region	GM volume	WM volume	Perfusion	[GABA/Glu]	Receptor activity	Neural activity (activity-related)	Neural connectivity
Hippocampus	↑*(1)		↑(11)			X(17)	↑(25)
Cingulate	↑(2)		↑(12)			X(18)	
Frontal	↑(3)	↑(10)	↑(13)			↑*(19)	↑*(26)
Prefrontal	↑(1,2)						
Primary Motor	↑(4)				↑*(16)	↑(20)	↓(26)
Parietal	↑(2)	↑(10)	↑(14)			↑*(21)	↑(26)
Occipital	↑(6)	↑(10)		X(15)		↑*(22)	↓(26)
Temporal	↑(2)					↑*(23)	
Cerebellum	↑(7)						
Insular	↑(8)					↑*(23)	
Basal ganglia	↑*(9)					↑*(24)	
Thalamus						↑(20)	

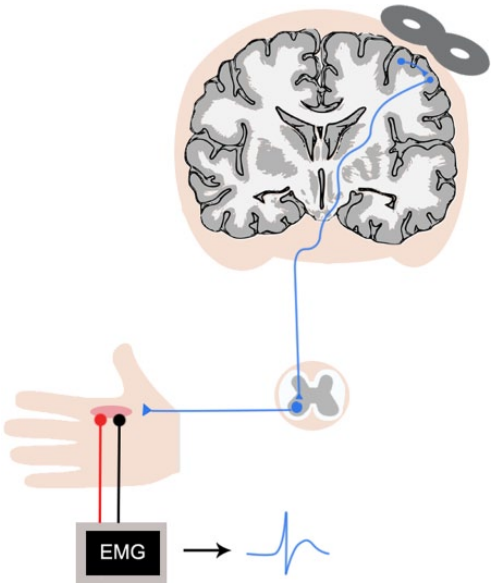
↑ = increases; ↓ = decrease; X = inconsistent findings; * = changes are associated with improved cognitive/motor function; blank boxes indicate not investigated; GM = gray matter; WM = white matter; [GABA/Glu] = gamma-aminobutyric acid and glutamate concentration; (#) = reference number.

References: (1) Erickson and others 2014; (2) Hayes and others 2013; (3) Colcombe and others 2006; Jonasson and others 2016; Ruscheweyh and others 2011; (4) Colcombe and others 2006; (5) Benedict and others 2013; Colcombe and others 2003; Floel and others 2010; Tseng and others 2013; Wood and others 2016; (6) Erickson and others 2009; (7) Fletcher and others 2016; (8) Gondoh and others 2009; (9) Fletcher and others 2016; Verstynen and others 2012; (10) Sexton and others 2016; (11) Burdette and others 2010; Chapman and others 2013; Maass and others 2015; Maass and others 2016; (12) Boraxbekk and others 2016; Chapman and others 2013; Thomas and others 2013; (13) Zimmerman and others 2014; (14) Thomas and others 2013; Zimmerman and others 2014; (15) Dennis and others 2015; Maddock and others 2016; (16) McGregor and others 2011; McGregor and others 2013; (17) ↑: Holzschneider and others 2012; ↓: Voelcker-Rehage and others 2011; (18) ↑: Holzschneider and others 2012; Wong and others 2015; ↓: Colcombe and others 2004; Voelcker-Rehage and others 2011; (19) Colcombe and others 2004; Holzschneider and others 2012; Prakash and others 2011; Rosano and others 2010; Wong and others 2015; (20) Wong and others 2015; (21) Colcombe and others 2004; Holzschneider and others 2012; Prakash and others 2011; (22) Holzschneider and others 2012; (23) Holzschneider and others 2012; Rosano and others 2010; (24) Holzschneider and others 2012; Wong and others 2015; (25) Burdette and others 2010; (26) Raichlen and others 2016.

white matter are driven by improved neuronal integrity, a marker of intact axons and myelin (Burzynska and others 2014; Voss and others 2013b) and increased density (Kleemeyer and others 2016; Tian and others 2014a; Tian and others 2014b) and myelination (Thomas and others 2016a). Changes in brain structure are likely attributed to increased gliogenesis, neurogenesis, and synaptogenesis, which are regulated by neurotrophic and growth factors. This is supported by the positive association between increased BDNF levels and increased hippocampal volume (Erickson and others 2011). Therefore, BDNF may be a precursor for exercise-induced increases in brain volume, exerting its effects via promotion of cellular processes. Future studies should investigate if changes in brain volume following long-term interventions are associated with increased IGF-1 and VEGF, confirming their contribution to exercise-induced increases in brain volume.

Exercise-induced cellular and structural changes lead to alterations in *brain function*. Brain function is characterized as receptor and neuronal activity, evaluated in the resting state or in the context of a task. Transcranial magnetic stimulation (TMS; see Box 2) can be used to noninvasively assess short- and long-term changes in cortical neurotransmitter receptor activity and transcallosal communication that occur following acute and chronic exercise, respectively. Physical activity levels do not appear to alter short-interval intracortical inhibition (SICI), a $GABA_A$-mediated circuit, or intracortical facilitation (ICF), a glutamatergic circuit in the primary motor cortex (M1) (Lulic and others 2017). Comparatively, the ipsilateral silent period (iSP) is lengthened by chronic exercise (McGregor and others 2011; McGregor and others 2013). While it is currently unknown which neurotransmitter receptors mediate iSP, these findings indicate that chronic exercise increases transcallosal inhibition. Chronic exercise improves white matter integrity in the corpus callosum (Johnson and others 2012; Oberlin and others 2016; Svatkova and others 2015; Verkooijen and others 2017), likely contributing to the increases in iSP.

Box 2. Transcranial Magnetic Stimulation.



TMS is a noninvasive method of brain stimulation in which an electrical current is generated in a wire coil (TMS coil), producing a magnetic field. This magnetic field passes painlessly through the scalp and induces an electric field perpendicular to that of the magnetic field, activating cortical neurons beneath the TMS coil. When delivered to the motor cortex, it creates a descending volley in the corticospinal tract and leads to a response in the target muscle, known as a motor-evoked potential (MEP). The size of the MEP reflects the integrity of the corticospinal tract. In paired-pulse form, TMS can be used to assess inhibitory and excitatory intracortical and interhemispheric phenomena, which reflect receptor and transcallosal activity, respectively. The first stimulus, known as the conditioning stimulus, modulates the second stimulus, known as the test stimulus. Intracortical phenomena are assessed by delivering two TMS stimuli to the same hemisphere while interhemispheric phenomena are assessed by delivering a TMS pulse to each hemisphere. Below are parameters that are typically used in TMS studies.

Intracortical phenomena	Receptor activity	Common stimulation parameters
Short-interval intracortical inhibition	$GABA_A$	ISI: 2 ms, TS: 1 mV, CS: 80% or 90% AMT
Long-interval intracortical inhibition	$GABA_B$	ISI: 100 ms, TS: 1 mV, CS: 1 mV
Intracortical facilitation	NMDA	ISI: 10 ms, TS: 1 mV, CS: 80% or 90% AMT
Ipsilateral silent period	—	TMS pulse to the ipsilateral hemisphere during isometric contraction of muscle

Receptor activity: Ziemann and others 2014; ISI = interstimulus interval; TS = test stimulus; CS = conditioning stimulus; AMT = active motor threshold.

fMRI activation in response to tasks assessing executive function demonstrate exercise-induced increases in serval areas of the brain. These include the frontal, temporal, parietal, and occipital lobes, insular and motor cortices, cingulate, thalamus, basal ganglia, and hippocampus (Table 2). Physically active individuals also have greater P3 amplitudes (Hillman and others 2004), reflecting greater attentional resources allocated to task-relevant information (Polich and Heine 1996), and shorter P3 latencies (Hillman and others 2004), thought to reflect faster processing time (Duncan-Johnson 1981). These findings suggest that physically active individuals have greater attentional processing (Hillman and others 2004) and conflict monitoring (Gajewski and Falkenstein 2015a, 2015b) compared to sedentary individuals. Exercise-induced changes in brain function may be mediated by increased neurotrophic and growth factors and cerebellar blood flow (CBF). Increased serum BDNF following aerobic exercise training is associated with increased hippocampal activation (Wagner and others 2017) and increased neural connectivity (i.e., increased communication between neurons) (Voss and others 2013a). Furthermore, increased neural activity is likely sustained by exercise-induced increases in CBF (Table 2), as increased CBF is associated with increased neural connectivity (Burdette and others 2010).

Chronic aerobic exercise results in *behavioral* changes, defined here as changes in cognitive and motor performance. Improvements in cognition are seen following chronic exercise training (see review by Stillman and others 2016) and are a result of molecular and cellular events. For instance, BDNF and IGF-1 signaling mediate cellular events, which are crucial for exercise-induced improvements in cognition (Stillman and others 2016). Furthermore, increases in gray matter volume and neural activity are associated with improved cognition (Stillman and others 2016). The effects of chronic exercise on motor performance and motor skill retention is currently unclear (see review by Hübner and Voelcker-Rehage 2017). However, several studies have consistently shown

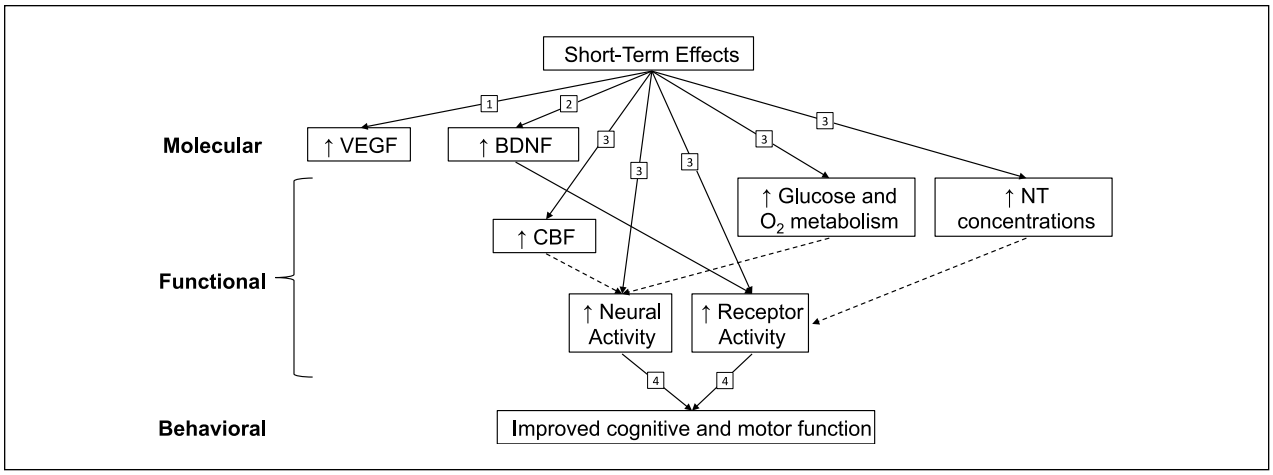


Figure 2. Model of neuroplasticity induced by acute aerobic exercise. Acute aerobic exercise induces greater levels of peripheral BDNF and VEGF, increased neurotransmitter concentration, and increased glucose and oxygen metabolism. Furthermore, acute aerobic exercise increases CBF, neural activity, and receptor activity. Increases in neural activity are likely mediated by increased CBF and glucose and oxygen availability. Increases in receptor activity are likely mediated by increases in neurotransmitter concentrations and BDNF. Over time, neuroplasticity induced by acute exercise leads to changes seen due to repeated exercise. BDNF = brain-derived neurotrophic factor; VEGF = vascular endothelial growth factor; NT = neurotransmitter; CBF = cerebellar blood flow; O_2 = oxygen. Dashed lines indicate speculation.
References: (1) see Table 3; (2) Huang and others 2014; (3) see Table 4; (4) Mang and others 2016; Nanda and others 2013; Ozyemisci-Taskiran and others 2008; Roig and others 2012; Snow and others 2016; Statton and others 2015; Weng and others 2015.

a positive association between fitness level and motor skill acquisition (Etnier and Landers 1998; Wang and others 2016). Although it has not been studied directly, improvements in motor performance are potentially mediated by the same mechanisms mediating cognitive improvements

Summary and Considerations

As the model depicted in Figure 1, increased central circulation of neurotrophic and growth factors upregulate neurogenesis, synaptogenesis, gliogenesis, and angiogenesis. Through upregulation of gliogenic and neurogenic processes, aerobic exercise increases white matter volume, while gliogenesis, neurogenesis, and synaptogenesis increase gray matter volume. These structural changes are likely driven by improved cerebrovascular function as a result of exercise (Table 2). As such, angiogenesis may mediate the structural changes in gray and white matter volume through improved cerebrovascular function and perfusion. This is crucial for neuronal growth and synapse formation as a greater blood supply is essential to providing adequate nutrients to support neuronal development. Last, exercise-induced structural changes result in increased efficiency of neural activation and communication. Ultimately, through these mechanisms, exercise leads to improved cognitive and motor function.

When utilizing long-term exercise interventions, it is important to consider the intervention length and the frequency of sessions within an intervention. No study has directly compared the effects of intervention length and frequency, making it difficult to determine the optimal parameters for neuroplasticity induction. From the studies reviewed here, it is possible to suggest probable intervention lengths that promote changes in brain structure and neural activity. For example, gray matter volume is increased following 2.5- to 12-month interventions, suggesting that 2.5 months of aerobic exercise may be sufficient to induce structural changes (Gondoh and others 2009). Increased functional connectivity is observed following 12 (Voss and others 2010; Voss and others 2013a) but not 3 months (Chirles and others 2017) of aerobic exercise, suggesting that more than 3 months of exercise is required to alter this measure. Future studies should determine the optimal intervention length to produce the greatest increases in gray matter volume and neural activity. Despite differences in intervention length, all studies showing increases in gray matter volume and neural activity used the same frequency of exercise bouts in the intervention (i.e., three exercise bouts per week). This frequency seems to be effective for inducing neuroplasticity via aerobic exercise training.

Model of Neuroplasticity Induced by Acute Aerobic Exercise

Figure 2 provides a mechanistic model to identify the neural effects that follow acute aerobic exercise (i.e., a single session of aerobic exercise). Similar to chronic exercise, acute aerobic exercise results in changes at

Table 3. The Effects of Acute Exercise on IGF-1 and VEGF.

Study	Participants	Exercise intervention	Results
IGF-1			
Schwarz and others 1996	n = 10 (28 ± 5 years)	LIE: 10 min at 80% lactate threshold HIE: 10 min at 50% of the difference between lactate threshold and VO_2max	↑ sIGF-1 following LIE and HIE
Cappon and others 1994	n = 10 (29 ± 4 years)	HIE: 10 min at 50% of the difference between lactate threshold and VO_2max	↑ sIGF-1 immediately and 20 min post-exercise
Kraemer and others 2004	n = 6 (27.7 ± 3.2 years)	Intermittent running for 10 min at 60% VO_2max, 10 min at 75% VO_2max, 5 min at 90% VO_2max, 2 min at 100% VO_2max	↑ sIGF-1
Skriver and others 2014	n = 16 males (24.1 ± 3.4 years)	20 min cycling: 3 blocks HIE interspersed by 2 blocks at 50 W	↑ pIGF-1
Griffin and others 2011	n = 47 (22 ± 2 years)	Graded maximal cycling	∅ sIGF-1
Koistinen and others 1996	n = 23 amateur runners (23–55 years)	Helsinki City Marathon	∅ sIGF-1
VEGF			
Czarkowska-Paczek and others 2006	n = 14 cyclists (18 ± 0.5 years)	Graded cycling until exhaustion	↑ sVEGF Recovery (2 h post): returned to baseline
Schobersberger and others 2000	n = 13 marathon runners (36.3 years)	Swiss Alpine Marathon of Davos	↑ sVEGF immediately and 5 days post-exercise
Kraus and others 2004	n = 8 endurance athletes (30 ± 3 years), 8 sedentary (22 ± 1 year)	1 h cycling at 50% W_{max}	↑ pVEGF in both groups
Gavin and others 2004	n = 12 sedentary (22 ± 1 years)	1 h cycling at 50% VO_2max	↑ VEGF mRNA
Wahl and others 2011	n = 12 triathletes/cyclists (24.7 ± 3.4 years)	Cycling Trial 1: four 4-min bouts at 90% to 95% PPO separated by 3-min bouts at 45% PPO Trial 2: four 4-min bouts at 90% to 95% PPO separated by 3 min of rest	↑ sVEGF post-trial 1 ↓ sVEGF 30–60 min post trial 2
Gunga and others 1999	n = 8 soldiers (21.5 ± 3.8 years)	The 6th Posta Atletica from La Serena (Chile) to San Juan (Argentina); 506.4 km divided into 12 runs of 42.4 km	↓ sVEGF

∅ = no change; ↑ = increased; ↓ = decreased; IGF-1 = insulin-like growth factor 1; IGFBP = insulin-like growth factor binding protein; VEGF = vascular endothelial growth factor; pNF = plasma neurotrophic level; sNF = serum neurotrophic level; HIE = high-intensity exercise; LIE = low-intensity exercise; HR_{max} = maximum heart rate; W_{max} = maximal wattage; PPO = peak power output.

molecular, functional, and behavioral levels. However, unlike chronic exercise, it is unlikely that acute exercise produces cellular or structural changes. Acute exercise may initiate the cellular pathways that, over time and with prolonged exercise, will induce the structural and functional changes seen due to chronic exercise. To our knowledge, no study has examined the cellular changes following acute aerobic exercise. Structural changes require activation of signaling pathways via upregulation of transcription, which needs a significantly longer period of time to take effect. Therefore, the model depicted in Figure 2 only includes mechanisms at molecular, functional, and behavioral levels.

Fewer studies have investigated the impact of acute exercise on measures of BDNF, IGF-1, and VEGF. At the *molecular* level, acute exercise modulates the concentration of peripheral BDNF, IGF-1, and VEGF (Table 3). Multiple studies have shown that a single session of aerobic exercise increases BDNF (see review by Huang and others 2014) and VEGF (Table 3). However, IGF-1 has been reported to increase (Cappon and others 1994; Kraemer and others 2004; Schwarz and others 1996; Skriver and others 2014) or not change (Banfi and others 1994; Griffin and others 2011; Jahreis and others 1989; Koistinen and others 1996) following acute exercise.

Acute exercise also increases neurotransmitter and metabolite concentrations. For example, acute exercise increases GABA (Maddock and others 2016) and glutamate concentrations (Maddock and others 2011; Maddock and others 2016) in the visual cortex, as assessed by magnetic resonance spectroscopy. Furthermore, acute aerobic exercise increases glucose metabolism in the cerebellum, sensorimotor cortex, occipital cortex, and supplementary and premotor areas (Table 4). Oxygenated hemoglobin is increased in the prefrontal cortex following acute exercise (Brugniaux and others 2014; Giles and others 2014;

Table 4. The Effects of Acute Aerobic Exercise on Various Brain Regions.

Brain region	Perfusion	[GABA/Glu]	Glucose metabolism	Oxygen metabolism	Neural activity (resting)	Neural activity (task-related)	Receptor activity	Neural connectivity
Hippocampus	↓(1)							
Cingulate						↓(15)		
Frontal					↑(11)	↓(15)		
Prefrontal				↑(10)		↑(16)		
Supplementary motor			↑(5)					
Premotor			↑(6)					
Primary motor	↑(2)		↑(7)				↑(18)	
Parietal					↑(12)	↓(17)		↑(19)
Secondary sensory								↑(19)
Occipital		↑(4)	↑(8)		↑(13)	↑(15)		
Temporal					↓(14)			
Cerebellum			↑(9)					
Insular	X(3)							

↑ = increases; ↓ = decrease; X = inconsistent findings. Blank boxes indicate not investigated. [GABA/Glu] = gamma-aminobutyric acid and glutamate concentration; (#) = reference number.

References: (1) MacIntosh and others 2014; (2) Smith and others 2010; (3) ↑: Williamson and others 1999; ↓: MacIntosh and others 2014; (4) Maddock and others 2011; Maddock and others 2016; (5) Christensen and others 2000; (6) Tashiro and others 2001; (7) Christensen and others 2000; Fukuyama and others 1997; Shimada and others 2013; Tashiro and others 2001; (8) Shimada and others 2013; Tashiro and others 2001; (9) Christensen and others 2000; Shimada and others 2013; Tashiro and others 2001; (10) Brugniaux and others 2014; Giles and others 2014; Ide and others 1999; Lefferts and others 2016; Lucas and others 2012; Yanagisawa and others 2010; (11) ↑: Bailey and others 2008; Gutmann and others 2015; Moraes and others 2007; Petruzzello and others 2001; ↓: (12) Bailey and others 2008; Gutmann and others 2015; Schneider and others 2009; (13) Schneider and others 2009; Youngstedt and others 1993; (14) Gutmann and others 2015; (15) Li and others 2014; (16) Li and others 2014; Yanagisawa and others 2010; (17) MacIntosh and others 2014; (18) Lulic and others 2017; Singh and others 2014; Smith and others 2014; Stavrinos and Coxon 2017; Yamaguchi and others 2012; (19) Rajab and others 2014.

Ide and others 1999; Lefferts and others 2016; Lucas and others 2012; Yanagisawa and others 2010) suggesting increases in oxygen metabolism.

A single session of aerobic exercise alters *brain function.* Receptor activity, assessed by TMS, is altered following acute exercise. Specifically, intracortical facilitation is increased (Singh and others 2014) or decreased (Lulic and others 2017) following acute exercise, suggesting that NMDA receptor activity is increased or decreased, respectively. SICI (Lulic and others 2017; Singh and others 2014; Smith and others 2014; Stavrinos and Coxon 2017; Yamaguchi and others 2012) and long-interval intracortical inhibition (LICI) (Mooney and others 2016; Singh and others 2014) are reduced following a single session of cycling, indicating reduced $GABA_A$ and $GABA_B$ receptor activity due to acute exercise (Ziemann and others 2014). Interestingly, reductions in SICI following acute exercise may be driven by elevated BDNF, which act to reduce $GABA_A$ receptor activity (Brunig and others 2001). A decrease in SICI is an important precursor to neuroplasticity in the motor cortex, as it indicates a cortical environment that is more susceptible to neuroplasticity induction (Amadi and others 2015).

Alpha power, assessed via neural oscillations, is increased in the parietal (Bailey and others 2008; Gutmann and others 2015; Schneider and others 2009), frontal (Bailey and others 2008; Gutmann and others 2015; Petruzzello and others 2001), occipital (Schneider and others 2009), and temporal (Gutmann and others 2015) lobes following acute exercise. Additionally, beta power is increased following exercise in the frontal (Bailey and others 2008; Moraes and others 2007; Schneider and others 2009), parietal (Bailey and others 2008; Schneider and others 2009), and occipital lobes (Schneider and others 2009; Youngstedt and others 1993). Both alpha and beta oscillations reflect inhibition, such that a decrease in power reflects reduced inhibition (Klimesch 2012; Rossiter and others 2014). Therefore, an increase in alpha and beta power that follow acute aerobic exercise may represent increased inhibition in the parietal, frontal, and occipital lobes.

Acute exercise increases communication between brain regions, as assessed via resting-state fMRI. In a study by Rajab and colleagues (2014), resting-state BOLD functional connectivity was assessed before and 20 minutes following moderate intensity cycling, and showed an exercise-induced increase in functional connectivity, specifically among the loci associated with motor function and tactile processing (Rajab and others 2014). Activity in thalamic-caudate regions, which plays a role in motor learning and reward, was also increased following exercise (Rajab and others 2014). Following

acute exercise, executive function task-related activity as assessed via fMRI is increased in the prefrontal and occipital cortices and decreased in the cingulate, frontal lobe, and parietal lobe (Table 4). Chang and colleagues (2015) investigated the effects of cycling on P3 amplitude assessed during an attention network test and observed larger P3 following exercise, reflecting greater task-relevant attentional resources following exercise. Tsai and colleagues (2016) also observed exercise-induced increases in P3 amplitude assessed during a task-switching protocol. These increases in P3 amplitude were accompanied by faster reaction time on these cognitive tasks (Chang and others 2015; Tsai and others 2016).

Acute exercise is capable of inducing *behavioral* changes, including improvements in cognitive and motor function. For example, acute exercise reduced reaction time (Ozyemisci-Taskiran and others 2008), improves memory and planning (Nanda and others 2013), and improves working memory (Weng and others 2015). Furthermore, acute exercise improves motor skill acquisition (Snow and others 2016; Statton and others 2015; Skriver and others 2014), retention (Roig and others 2012; Skriver and others 2014; Thomas and others 2016c; Thomas and others 2016d), and motor memory (Mang and others 2016; Thomas and others 2016b). Importantly, motor memory improvements due to exercise are greatest when the exercise and acquisition period are close in time (Thomas and others 2016b). These cognitive and motor improvements are likely mediated by exercise-induced increases in neural and receptor activity.

Summary and Considerations

Changes in neurotransmission, neurotrophic factors, and glucose and oxygen metabolism are likely mediators that drive changes in brain function. Exercise-induced increases in neural activity are likely sustained by increased CBF (Table 4), which provide neurons with necessary nutrients such as oxygen and glucose. Increased CBF during acute exercise also allows BDNF, IGF-1, and VEGF to cross the blood-brain barrier (Lopez-Lopez and others 2004; Mang and others 2013; Trejo and others 2001) and reach the cortex. Over repeated bouts of exercise, increased levels of neurotrophic and growth factors promote cellular processes and lead to structural, functional and behavioral changes.

It is important to consider the intensity and duration of acute exercise bouts used in exercise interventions. Although intensity and duration are related (i.e., higher intensity exercise is performed for shorter durations), separation of these factors is critical to evaluate their individual contributions to exercise-induced neuroplasticity. When holding duration constant, the *intensity* of an acute bout of exercise affects neuroplasticity induction at a molecular and behavioral level. Greater increases in BDNF (Ferris and others 2007; Nofuji and others 2012; Rojas Vega and others 2012) and IGF-1 levels (Schwarz and others 1996) have been observed following high-intensity exercise compared to lower intensities. Furthermore, greater improvements in motor skill retention are observed following high-intensity exercise compared to lower intensities (Thomas and others 2016d). When holding intensity constant, increasing the *duration* of acute exercise may not provide additional benefits, with evidence suggesting that 20 minutes of acute exercise is sufficient to induce neuroplasticity. For example, serum BDNF levels reached maximum concentration after 20 minutes of aerobic exercise, with no further increase observed following 30 minutes of exercise (Schmidt-Kassow and others 2012). Furthermore, 20 versus 40 minutes of exercise produced similar increases in serum BDNF levels (Schmolesky and others 2013). Future research should directly compare different exercise durations to determine the optimal duration to alter neurotrophic factor levels and neural and receptor activity (e.g., does 40 minutes of exercise result in greater increases in neural activity compared to 20 minutes of exercise?).

Factors That Impact Neuroplasticity Induction via Aerobic Exercise

Several factors may contribute to the direction and extent of exercise-induced neuroplasticity. Experimental consideration of these factors may reduce the variability within and between studies to better isolate the mediators of exercise-induced neuroplasticity.

Biological Sex

Neuroplasticity induced by noninvasive brain stimulation is greater in females compared to males (see review by Ridding and Ziemann 2010). For example, in females, the inhibitory effects of cathodal transcranial direct current stimulation are prolonged compared to males (Kuo and others 2006) (Fig. 3). Therefore, females appear to demonstrate a greater propensity for neuroplasticity, suggesting that biological sex may also affect exercise-induced neuroplasticity. In support of this suggestion, studies with a greater proportion of females in their participant cohort revealed greater exercise-induced improvements in cognitive function compared to studies dominated by males (Colcombe and Kramer 2003; Middleton and others 2008; Barha and others 2017a; Barha and others 2017b). As reviewed elsewhere, females may exhibit more efficient uptake of BDNF into the CNS compared to males (see review by Szuhany and others 2015). There also exist structural and functional differences between sexes,

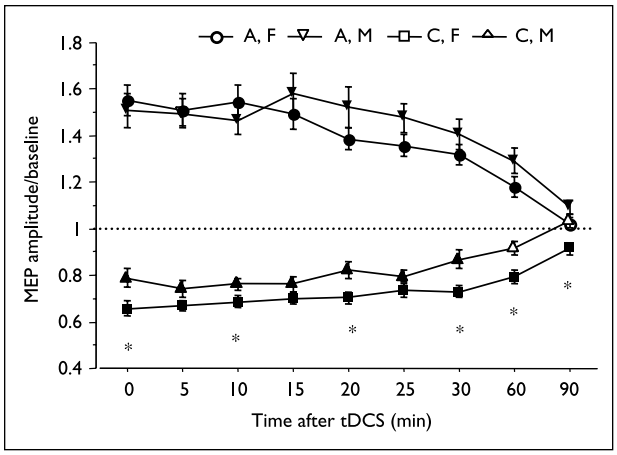


Figure 3. Impact of biological sex on neuroplasticity induction. Females show prolonged inhibitory effects of cathodal transcranial direct current stimulation (tDCS) compared to males (*indicated significance; A = anodal tDCS; C = cathodal tDCS; F = females; M = males). Figure reused from Kuo and others 2006, with permission.

which may mediate neuroplasticity induction. Females have greater gray matter volume compared to males and show greater baseline neural activity, potentially mediated by greater CBF, glucose metabolism, and neurotransmitter concentrations (see review by Cosgrove and others 2007). Taken together, these findings suggest that exercise-induced neuroplasticity is likely greater in females compared to males. Future research should directly compare the effects of exercise on the mechanisms of neuroplasticity in males and females to test this hypothesis.

Ovarian Hormones

Neuroplasticity induced by noninvasive brain stimulation is greater during ovulation, when estradiol levels are higher, compared to menstruation (Inghilleri and others 2004) (Fig. 4). This suggests that exercise-induced neuroplasticity may also be greater when estradiol levels are higher, although this is yet to be investigated. At the molecular level, animal studies have shown that estradiol increases BDNF expression and protein levels (see review by Sohrabji and Lewis 2006). At the cellular level, estradiol (Begliuomini and others 2007) and progesterone (McEwen and others 1997) upregulate synaptogenesis by increasing the number of dendritic spines and synapses. Estradiol may also reduce intracortical and interhemispheric inhibition, as the depth of SICI (Smith and others 1999; Smith and others 2002) and iSP (Hausmann and others 2006) at baseline are reduced in the follicular phase of the menstrual cycle compared to the luteal phase. Therefore, it appears that exercise-induced neuroplasticity will be greater when estradiol levels are higher. However, to date, no study has investigated the impact of ovarian hormones on exercise-induced neuroplasticity at various stages of the menstrual cycle.

Genetic Variations

A genetic variation of BDNF occurs at codon 66 whereby a valine (val) is replaced with methionine (met) (Berretta and others 2014) in ~30% to 50% of humans (Mang and others 2013). Val66met carriers show reduced neuroplasticity induction compared to noncarriers. For example, motor training did not increase corticospinal excitability or reorganize motor maps in val66met carriers, but did so in noncarriers (Kleim and others 2006) (Fig. 5). Furthermore, val66met carriers did not show exercise-induced improvements on a memory task, while noncarriers did (Hopkins and others 2012). Reduced neuroplasticity in these individuals may be driven by the effects of the BDNF val66met polymorphism on the mechanisms mediating exercise-induced neuroplasticity. Val66met carriers show reduced depolarization-induced BDNF secretion in the CNS (Egan and others 2003; Mang and others 2013). For example, long-term exercise interventions only increased circulating BDNF in those without the val66met polymorphism (Lemos and others 2016). The lack of BDNF increase may translate to reduced exercise-induced neurogenesis, as seen in mice with the val66met genotype (Ieraci and others 2016). Reductions in neurogenesis may result in reduced brain volume in humans, as individuals with val66met polymorphism showed reduced gray matter volume in the prefrontal cortex, hippocampus, temporal and occipital lobes (see review by Pearson-Fuhrhop and Cramer 2010). Furthermore, those with the BDNF val66met polymorphism performed worse on cognitive (Pearson-Fuhrhop and Cramer 2010) and motor tasks (McHughen and others 2017), although one study showed no effect of the polymorphism on motor learning (Mang and others 2017). Therefore, individuals with the BDNF val66met polymorphism appear to have a reduced propensity for exercise and nonexercise induced neuroplasticity compared to those without it.

A second genetic variation that likely affects exercise-induced neuroplasticity is the ε4 allele of the apolipo-protein (APOE ε4), occurring in ~15% of the Caucasian population (Farrer and others 1997). APOE plays a role in the growth and regeneration of CNS tissue by increasing neuronal repair (see review by Pearson-Fuhrhop and Cramer 2010). Although the influence of APOE ε4 on exercise-induced neuroplasticity has yet to be examined, it is suggested that APOE ε4 carriers display reduced neurogenesis since neurite outgrowth in human cell cultures is enhanced following the addition of nerve growth factor

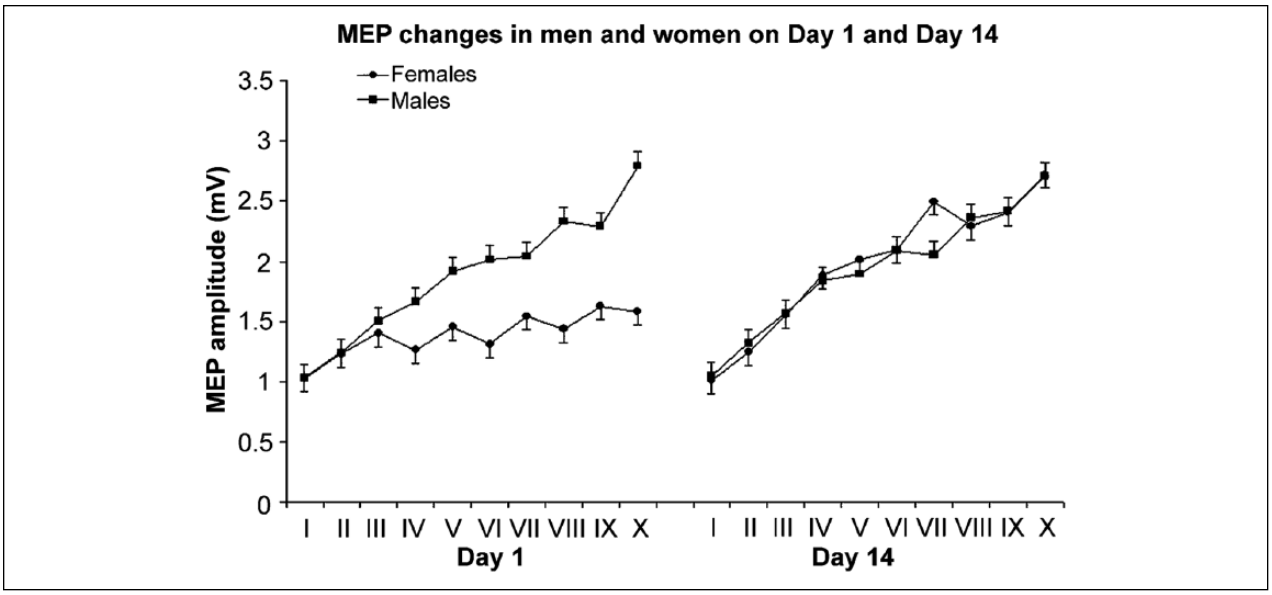


Figure 4. Impact of ovarian hormones on neuroplasticity induced by noninvasive brain stimulation. Females show greater neuroplasticity induced by repetitive TMS on day 14 (ovulation) of the menstrual cycle compared to day 1 (menstruation). Males show similar neuroplasticity induction on both testing sessions. Reprinted from Inghilleri and others 2004, with permission from Elsevier.

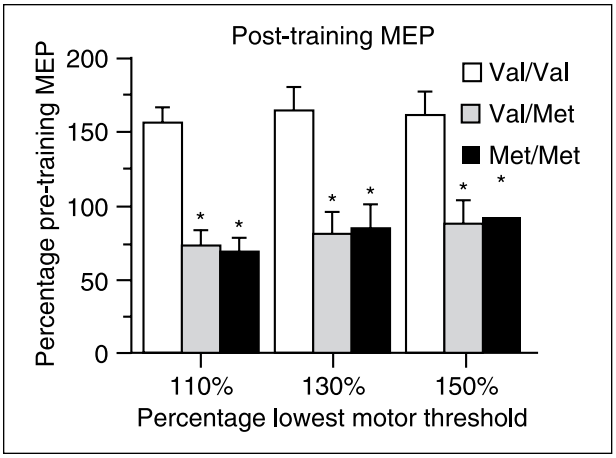


Figure 5. Impact of the BDNF val66met polymorphism on neuroplasticity induction. Individuals with val66val BDNF alleles show increased MEP amplitudes following motor training. Met allele carriers do not show MEP amplitude increases following motor training (* indicated significance; white bars = val66val individuals; grey bars = val66met individuals; black bars = met66met individuals). Reprinted from Kleim and others 2006, with permission from Macmillan.

and APOE ε3, but not APOE ε4 (Holtzman and others 1995). Furthermore, APOE ε4 carriers show decreased hippocampal volume and task-related activation compared to noncarriers (see review by Pearson-Fuhrhop and Cramer 2010). Last, APOE ε4 carriers demonstrated reduced cognitive function (Flory and others 2000). Therefore, future studies should assess the impact of APOE ε4 on neuroplasticity induced by exercise by directly comparing the effects in APOE ε4 carriers and noncarriers (Barha and others 2017b).

Fitness Level

Acute exercise increased corticospinal excitability, as assessed by TMS, in physically active but not sedentary individuals (Lulic and others 2017) (Fig. 6). The differential effect of exercise on these groups are driven by the changes seen across all levels of the model as a result of chronic exercise (described in "Model of Neuroplasticity Induced by Chronic Aerobic Exercise" above). It is important to note that these findings do not suggest that sedentary individuals do not show neuroplasticity induction. Future research may determine the optimal exercise parameters to promote neuroplasticity in sedentary individuals.

Limitations

We limited this review to the topic of aerobic exercise in healthy adults. However, many studies have investigated exercise-induced changes in children, specifically using neuroimaging techniques, indicating similar structural and functional benefits of exercise (see review by Berchicci and others 2015). However, in studies investigating neuroplasticity induction in children, it is difficult to dissociate the effects of experience-dependent neuroplasticity (i.e., that induced by exercise) and developmental neuroplasticity.

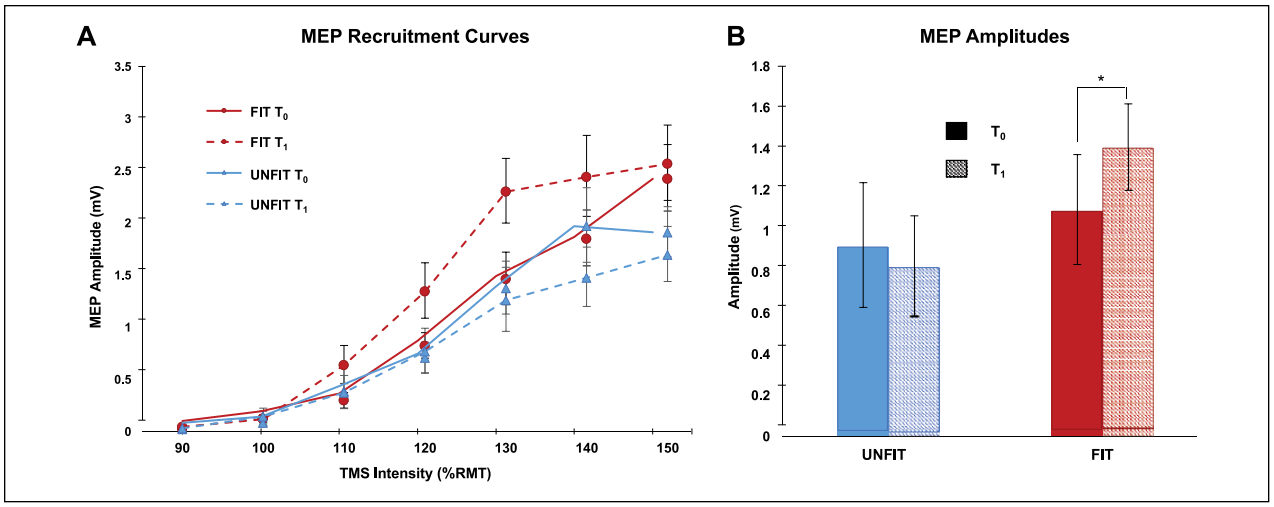


Figure 6. Impact of fitness level on exercise-induced neuroplasticity. Fit individuals show greater neuroplasticity induction compared to unfit individuals. (A) MEP recruitment curves obtained before and 10 minutes post an acute exercise intervention. (B) MEP recruitment curve amplitudes increase following acute exercise in fit but not unfit individuals (* indicated significance; blue lines/bars = unfit individuals; red lines/bars = fit individuals; solid lines/bars = pre-acute exercise; dashed lines/bars = 10 minutes post-acute exercise). Figures adapted with permission from Lulic and others (2017).

Furthermore, we only addressed findings in healthy individuals and not those with neurological disease or injury. It is important to note that clinical populations also show benefits of exercise (see reviews by Mak and others 2017; Xing and others 2018). The effects of exercise on neuroplasticity induction in clinical populations is of interest as it may provide more information on exercise protocols capable of promoting recovery or improving symptoms following injury. Finally, the papers reviewed here were limited to studies investigating only the effects of aerobic exercise. However, resistance training can also induce structural and functional changes in the brain (Voss and others 2011) and alter cortical excitability (Kidgell and Pearce 2011). Resistance exercise has less effect on neurotrophic factors compared to aerobic exercise (see review by Huang and others 2014). It is suggested that resistance and aerobic exercise induce changes via different mechanisms. Therefore, the mechanistic models provided in this review only consider changes induced by aerobic exercise and not combined training (i.e., aerobic and resistance training together).

Conclusion

This review aimed to provide an understanding of the mechanisms that mediate neuroplasticity induced by aerobic exercise. In this review, we elaborate on the model proposed by Stillman and colleagues (2016) by describing the sequence of events leading from one level to the next and distinguishing neuroplasticity evoked by chronic and acute exercise. Through this comprehensive review of the literature, it is apparent that various factors modulate the neuroplastic effects of aerobic exercise. Studies assessing exercise-induced neuroplasticity should be aware of these factors to reduce variability and future research should fully establish how these factors modulate neuroplasticity. Understanding the impact of these factors on neuroplasticity induction by aerobic exercise will allow for the optimization of exercise protocols used in future research.

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