Understanding the Neurophysiological and Molecular Mechanisms of Exercise-Induced Neuroplasticity in Cortical and Descending Motor Pathways: Where Do We Stand?

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Abstract—Exercise is a promising, cost-effective intervention to augment successful aging and neurorehabilitation. Decline of gray and white matter accompanies physiological aging and contributes to motor deficits in older adults. Exercise is believed to reduce atrophy within the motor system and induce neuroplasticity which, in turn, helps preserve motor function during aging and promote re-learning of motor skills, for example after stroke. To fully exploit the benefits of exercise, it is crucial to gain a greater understanding of the neurophysiological and molecular mechanisms underlying exercise-induced brain changes that prime neuroplasticity and thus contribute to postponing, slowing, and ameliorating age- and disease-related impairments in motor function. This knowledge will allow us to develop more effective, personalized exercise protocols that meet individual needs, thereby increasing the utility of exercise strategies in clinical and non-clinical settings. Here, we review findings from studies that investigated neurophysiological and molecular changes associated with acute or long-term exercise in healthy, young adults and in healthy, postmenopausal women. © 2021 The Authors. Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: TMS, corticospinal excitability, SICI, BDNF, osteocalcin, aging.

INTRODUCTION

Aging leads to a decline in motor control and function (Winter et al., 1990; Buckles, 1993; Maki and McIlroy, 1996; Kluger et al., 1997; Seidler et al., 2010; Rosso et al., 2013; Sorond et al., 2015). The physiological decline in motor performance with age is associated with reduced balance and strength, impaired gait (i.e., decreased gait speed, altered pace, and rhythm), rigidity, and slow movements, which increase the risk of falling (Overstall et al., 1977; Tinetti et al., 1988; Winter et al., 1990; Baumann, 1994; Hausdorff et al., 2001; Deandrea et al., 2010; Tinetti and Kumar, 2010; Osoba et al., 2019). Approximately one in three normally aging individuals over 65 years of age experiences a fall each year (Tinetti et al., 1988; O’Loughlin et al., 1993; Canada Public Health Agency of Canada, 2014; Pearson et al., 2014; Do et al., 2015; Bergen et al., 2016; Peng et al., 2019), and, in particular, women are at a greater risk of falls and fall-related injuries than men (Peel et al., 2002; Stevens and Sogolow, 2005; Schiller et al., 2007; Hartholt et al., 2011; Canada Public Health Agency of Canada, 2014; Do et al., 2015; Johansson et al., 2016).

Fall-related injuries, which include fractures (approximately half to the hip (Cali and Kiel, 1995; Peel et al., 2002)), joint dislocation, sprains, and traumatic brain injuries (Sattin et al., 1990; Nevitt et al., 1991; Cali and Kiel, 1995; Tinetti et al., 1995; Berry and Miller, 2008; Wolinsky et al., 2009), result in increased disability, morbidity, loss of independence, and mortality (Sterling et al., 2001; Todd and Skelton, 2004; Ioannidis et al., 2009). Even non-injurious falls can cause a decline in social and physical activities, function, and health due to increased fear, diminished self-confidence, and depression, and ultimately lead to future falls with more serious outcomes (Tinetti and Williams, 1998; Stel et al., 2004; Tinetti and Kumar, 2010). Being associated with hospitalization and long-term admission to nursing homes (Tinetti and Williams, 1997; Gill et al., 2013; Canada Public Health Agency of Canada, 2014), fall-related injuries in seniors represent a significant economic burden for the healthcare system (Alexander et al., 1992; Scuffham et al., 2003; Stevens et al., 2006; SMARTRISK, 2009; Hartholt et al., 2012; Burns et al., 2016; Phelan and Ritchey, 2018; Peng et al., 2019). There is a critical need to identify interventions that can maintain and improve motor function, and thus reduce falls, and ultimately morbidity and mortality (Winter et al., 1990; Buckles, 1993; Maki and McIlroy, 1996; Kluger et al., 1997; Cauraugh et al., 2000; Berardelli et al., 2001; Krakauer, 2005;
Cameron et al., 2012; Rosso et al., 2013; Balla et al., 2011; Van Impe et al., 2012; Vidoni et al., 2012; Khedr et al., 2011; Pennisi et al., 2011; Suppa et al., 2008; Taniwaki et al., 2007; Yu et al., 2007; Obeso et al., 2006; Ota et al., 2006; Rosano et al., 2007b; Albers et al., 2015; Erro and Stamelou, 2017). Physical activity and exercise interventions have been linked to improved motor function, including better gait speed, balance, and coordination, and, consequently, to prolonged independence in older adults (Rikli and Edwards, 1991; Lacroix et al., 1993; Buckwalter, 1997; Visser et al., 2002; Brach et al., 2003; Means et al., 2005; Buchman et al., 2007; Pahor et al., 2014; Verma et al., 2016). Stroke (Cauraugh et al., 2000; Krakauer, 2005; Raghavan, 2007, 2015) and neurodegenerative diseases such as Alzheimer's (Pettersson et al., 2005; Aggarwal et al., 2006; Buracchio et al., 2010; Buchman and Bennett, 2011; Albers et al., 2015) and Parkinson's (Berardelli et al., 2001; Jankovic, 2008; Klucken et al., 2013; Erro and Stamelou, 2017) also result in motor impairments, and exercise can favor motor recovery in these clinical populations (Stein, 2004; Chen et al., 2005; Rovio et al., 2005; Crizzle and Newhouse, 2006; Herman et al., 2007; Gobbi et al., 2009; Xu et al., 2010; Foster et al., 2011; Vreugdenhil et al., 2012; Pitkalä et al., 2013; Duchesne et al., 2015; Sobol et al., 2016; Linder et al., 2019; Rosenfeldt et al., 2019). Despite the promising, positive effects of exercise in preventing, slowing, attenuating, and reversing physiological and disease-induced motor dysfunctions, the impact of the exercise "dose" remains unclear. That is, the optimal parameters of the exercise stimulus (e.g., duration, frequency, intensity) and the neurobiological mechanisms determining the extent to which exercise interventions are effective remain to be established.

Age- and disease-related motor impairments are caused by changes in motor cortical areas, basal ganglia, cerebellum, and corpus callosum (Gaspar et al., 1991; Rascol et al., 1992; Suvá et al., 1999; Blandini et al., 2000; Alagona et al., 2001; Liepert et al., 2001; Sullivan et al., 2002; Good et al., 2001; Jernigan et al., 2001; MacDonald and Halliday, 2002; Mattay et al., 2002; Hutchinson et al., 2002; Zemke et al., 2003; Lazzaro et al., 2004; Salat et al., 2004, 2005; Lefaucheur, 2005; Raz et al., 2005; Naccarato et al., 2006; Ota et al., 2006; Rosano et al., 2007b, 2008; Taniwaki et al., 2007; Yus et al., 2007; Oses et al., 2008; Harada et al., 2009; Seidler et al., 2010; Khedr et al., 2011; Pennisi et al., 2011; Suppa et al., 2011; Van Impe et al., 2012; Vidoni et al., 2012; Cameron et al., 2012; Rosso et al., 2013; Balla et al., 2014; Albers et al., 2015) (Fig. 1). Changes in prefrontal and parietal cortical regions, which are mainly involved in cognitive processes but increasingly contribute to motor control with age (Lindenberger et al., 2000; Li and Lindenberger, 2002; Heuninckx et al., 2005, 2008; Huxhold et al., 2006), are also implicated in the age-associated decline in motor function (Raz et al., 1997, 2004, 2005; Good et al., 2001; Sullivan et al., 2001; Jernigan et al., 2001; Resnick et al., 2003; Salat et al., 2004, 2005; Kennedy and Raz, 2005; Rosano et al., 2007b; Harada et al., 2009; Seidler et al., 2010; Srikanth et al., 2010; Rosso et al., 2013). Brain alterations associated with motor deficits include reduced gray matter volume and thickness in the prefrontal, parietal, and motor cortices (Good et al., 2001; Jernigan et al., 2001; Resnick et al., 2003; Salat et al., 2004; Kennedy and Raz, 2005; Rosano et al., 2007a), decreased white matter integrity, particularly of the prefronto-subcortical bundles and corpus callosum (Sullivan et al., 2002; Ota et al., 2006; Zahr et al., 2009; Srikanth et al., 2010; Van Impe et al., 2012, BC et al., 2019), and lower dopaminergic neurotransmission due to a decline in dopamine levels and in the availability of its receptors and transporters (Carlsson and Winblad, 1976; Suhara et al., 1991; Rinne et al., 1993; Volkow et al., 1996, 1998; Wang et al., 1998; Kaasinen et al., 2000, 2002; Inoue et al., 2001; Cham et al., 2007, 2008; Bohnen et al., 2009; Ishibashi et al., 2009). Exercise can delay and ameliorate age- and disease-induced brain changes by reducing the progression of white matter lesions and decline of gray and white matter volume, and by stimulating neuroplasticity which, in turn, promotes motor learning or re-learning during rehabilitation (Vaynman and Gomez-Pinilla, 2005; Colcombe et al., 2006; Forrester et al., 2008; Quaney et al., 2009; Petzinger et al., 2010, 2013; Ruscheweyh et al., 2011; Erickson et al., 2011; Mang et al., 2013; Bolandzadeh et al., 2015; Hirsch et al., 2016; Nepveu et al., 2017; Steib et al., 2018) (Fig. 1).

Exercise, physical activity, and fitness are often used interchangeably but describe different concepts (Caspersen et al., 1985; Hayes et al., 2013). Physical activity is defined as any movement of the body via skeletal muscles expanding energy and includes various activities encompassing leisure (e.g., walking, running, swimming, playing a sport), occupational (e.g., lifting heavy loads, climbing stairs, heavy construction, farming), domestic (e.g., gardening, cleaning, home repair), and transportation (e.g., walking or biking to and from work) (Caspersen et al., 1985). Physical activity is positively correlated to fitness, such that larger amounts of physical activity are associated with greater physical fitness (Caspersen et al., 1985). Exercise differs from physical activity in that the bodily movement generated by skeletal muscles and leading to energy expenditure is planned, structured, repetitive, and aimed to improve or maintain physical fitness (Caspersen et al., 1985). In other words, playing a sport for an hour or two, once every three weeks, is considered physical activity, while playing a sport for two hours, three times per week, for several months in order to improve fitness is considered exercise. Like physical activity, exercise is also positively correlated to fitness (Caspersen et al., 1985). Exercise protocols include moderate-intensity, continuous exercise (endurance-type) and more intense, intermittent exercise. The latter consists of brief bouts of intense exercise (for a total duration of less than 10 min) interspersed with intervals of low-intensity exercise or rest (Gillen and Gibala, 2014). Both exercise protocols enhance aerobic capacity, promote skeletal muscle adaptations, and reduce markers of disease risks, but intense, intermittent exercise involves a significantly shorter time commitment and lower total exercise volume (Donnelly et al., 2000; Gibala et al., 2006, 2012; Perry et al., 2008; Trapp
et al., 2008; Gibala and McGee, 2008; Little et al., 2010, 2011b, 2011a; Hood et al., 2011; Metcalfe et al., 2012; Hottenrott et al., 2012; Currie et al., 2013; Gillen et al., 2013; Iellamo et al., 2013; Cochran et al., 2014; Phillips et al., 2017). Contrary to physical activity and exercise, fitness does not refer to a movement of the body that expands energy, but to health- (i.e., cardiorespiratory endurance, muscular endurance and strength, body composition and flexibility) and skill-related (i.e., agility, balance, coordination, speed, power, reaction time) components, which people achieve and can be measured with specific tests (Caspersen et al., 1985). Cardiorespiratory fitness is of particular interest as it is associated with reduced risk of obesity, type-II diabetes, and cardiovascular diseases (Wei et al., 2000; Carnethon et al., 2003; LaMonte and Blair, 2006; Sui et al., 2008; Myers et al., 2015; Harber et al., 2017; Oktay et al., 2017) as well as increased brain health (Churchill et al., 2002; Barnes et al., 2003; Prakash et al., 2007, 2011; Burns et al., 2008; Honea et al., 2009; Johnson et al., 2012; Scheewe et al., 2013; Hayes et al., 2015). The gold standard for the assessment of cardiorespiratory fitness is graded maximal exercise tests on a treadmill or cycle ergometer which provide measures of oxygen utilization, such as the highest volume of oxygen consumed (VO$_2$ peak) or the value at which the consumed volume of oxygen plateaus or increases minimally (VO$_2$ max) (Day et al., 2003; Hayes et al., 2013; Beltz et al., 2016). Alternatively, estimates of the maximal oxygen consumption (VO$_2$max) can be obtained using sub-maximal tests, such as the Astrand-Ryhming nomogram or Rockport one-mile walk test, which provide an indirect index of cardiorespiratory fitness (Astrand and Ryhming, 1954; Cink and Thomas, 1981; Siconolfi et al., 1982; Kline et al., 1987; Fensel and Jones, 1992; Dolgener et al., 1994; Madsen, 2001; Pober et al., 2002).

To date, it has been demonstrated that exercise creates an optimal environment for neuroplasticity in the primary motor cortex and other brain regions involved in motor control and that exercise-induced neuroplasticity promotes motor learning and function (Ziemann et al., 2006; Kleim and Jones, 2008; Dayan and Cohen, 2011; Rajji et al., 2011; Lehmann et al., 2020; Wanner et al., 2020). The evidence that exercise boosts neuroplasticity is corroborated by reports of enhanced neuroplasticity in response to non-invasive brain stimulation paradigms when the latter are preceded by exercise (Mellow et al., 2020). The ability of exercise-induced plasticity to facilitate motor learning could be valuable in maintaining motor function during aging and enhancing relearning of motor skills post-stroke or in Parkinson’s patients who have deficits in motor skill acquisition and retention (Daley and Spinks, 2000; Seidler et al., 2010; Warraich and Kleim, 2010; Mang et al., 2013; Petzinger et al., 2013). However, knowledge gaps remain to be filled (Fig. 2).

First, the neurobiological and motor behavioural effects of exercise have been predominantly investigated in healthy participants, thus it currently needs to be confirmed whether findings extend to older adults and clinical populations. Promisingly, some studies have shown that exercise can promote re-
Fig. 2. What we know and what we are missing. BDNF: brain-derived neurotrophic factor; CSE: corticospinal excitability; GM: gray matter; SICI: short-interval intracortical inhibition; WM: white matter; ?: knowledge gaps.

learning of motor skills after stroke (Forrester et al., 2008; Quaney et al., 2009; Mang et al., 2013) and improve motor learning and performance in Parkinson’s patients (Fisher et al., 2008; Petzinger et al., 2013; Steib et al., 2018). Further, increases in peripheral brain-derived neurotrophic factor (BDNF) and corticospinal excitability have been found in 6-month poststroke patients following high-intensity interval exercise along with a negative correlation between exercise-induced changes in BDNF and intracortical inhibition (Boyne et al., 2019). Taken together, these findings highlight the potential for exercise protocols as intervention strategies in rehabilitation and the importance of obtaining more evidence to confirm and maximize exercise benefits for aged and diseased populations. Second, the biological mediators of exercise effects and exercise-induced motor behavioural gains have been investigated in separate studies, thereby hindering the identification of the mechanistic links between exercise-driven motor benefits and exercise-driven systemic (i.e., structural and functional brain changes), cellular, and molecular changes. Indeed, there is evidence from neuroimaging, TMS, and molecular studies for exercise increasing functional connectivity in somatosensory areas (Rajab et al., 2014), positively impacting gray matter density and white matter microstructure (Erickson et al., 2011; Voss et al., 2013b; Herting et al., 2014; Schlaffke et al., 2014; Svatkova et al., 2015), modulating corticospinal excitability and intracortical motor circuits (Yamaguchi et al., 2012; McDonnell et al., 2013; Singh et al., 2014; Smith et al., 2014; Mooney et al., 2016; Lulic et al., 2017; Stavinos and Coxon, 2017; Roeh et al., 2018; El-Sayes et al., 2019; MacDonald et al., 2019; Opie and Semmler, 2019; Nicolini et al., 2020), and upregulating molecular markers such as BDNF (Rasmussen et al., 2009; Knaepen et al., 2010; Huang et al., 2014; Skriver et al., 2014; Dinoff et al., 2017; Nicolini et al., 2020). There is also evidence for exercise improving formation and consolidation of motor memories as well as motor performance (Anshel and Novak, 1989; Roig et al., 2016, 2012, 2013; Snigdha et al., 2014; Mang et al., 2014, 2016; Statton et al., 2015; Taubert et al., 2015; Snow et al., 2016; Thomas et al., 2016a, 2016b; Ostadan et al., 2016; Baird et al., 2018; Hübner et al., 2018; Opie and Semmler, 2019; Wanner et al., 2020; Lehmann et al., 2020). However, there is little evidence for how exercise is mechanistically linked to gains in motor learning and performance. It has been shown that greater improvements in motor skill retention are accompanied by larger reductions in neural activity within sensorimotor areas (Dal Maso et al., 2018) and by larger increases in corticospinal excitability (Ostadan et al., 2016) when exercise is performed immediately following motor task practice. Further, Lehmann et al. (2020) found a relationship between enhanced learning of a new motor task and changes in frontotemporal white matter microstructure following two weeks of exercise, while Skriver et al. (2014) reported an association between increases in BDNF and improvements in motor skill acquisition and retention after a single bout of exercise. However, Mang et al. (2014) failed to find a relationship between BDNF increases and both neurophysiological (i.e., enhanced experimentally-induced long-term potentiation-like plasticity) and behavioural (i.e., motor learning) gains observed following acute exercise. It follows that future studies need to obtain a greater understanding of the mechanistic link between exercise and motor improvements, especially in clinical settings. That is to say that exercise-induced, systemic, cellular, and molecular changes (e.g., increases in gray matter density, functional connectivity, corticospinal excitability, BDNF) need to be linked to exercise-induced, motor behavioural changes. Of note, as Stillman et al. (2016) pointed out, socioemotional mechanisms, such as exercise-induced changes in mood, stress levels, and sleep, might also contribute to modulating the beneficial effects of exercise on motor learning and performance, and the extent of their contribution should be further assessed in future research. Lastly, exercise parameters including intensity, type, duration, and frequency are believed to impact exercise efficiency and contribute to interindividual variability in exercise-related systemic, cellular, molecular, and behavioural outcomes (Herold et al., 2019). While optimal duration, type, and frequency of exercise to maximize motor benefits remain to be found, there is evidence supporting that high-intensity exercise leads to the greatest increases in corticospinal excitability, BDNF, and motor...
learning in both healthy individuals and stroke patients (Ferris et al., 2007; Winter et al., 2007; Schmolesky et al., 2013; Skriver et al., 2014; Thomas et al., 2016b; Nepveu et al., 2017; Boyne et al., 2019; Andrews et al., 2020; Nicolini et al., 2020). Identifying exercise mediators of motor behavioural improvements is key to developing personalized exercise interventions that more strongly and efficiently prime neuroplasticity and thus maximize motor benefits in both healthy and clinical populations. Here, we review studies that investigated the effects of different exercise protocols on corticospinal excitability, intracortical motor circuits, and peripheral molecular markers in physically active or sedentary, healthy, young adults. We also summarize the findings from a study where we examined the relationships between cardiorespiratory fitness and measures of corticospinal excitability, intracortical motor circuits, primary motor cortex (M1) concentrations of γ-aminobutyric acid (GABA) and glutamate, cortical thickness, and white matter microstructure integrity of sensorimotor and frontal areas in healthy, post-menopausal women.

EFFECTS OF ACUTE EXERCISE

Corticospinal Excitability

Several studies have investigated whether an acute bout of exercise modulates corticospinal excitability using single-pulse transcranial magnetic stimulation (TMS) to M1 (McDonnell et al., 2013; Singh et al., 2014; Smith et al., 2014; Neva et al., 2017; Stavrinos and Coxon, 2017; MacDonald et al., 2019; Opie and Semmler, 2019; Andrews et al., 2020). Findings are mixed. No changes in cortico-motor output have been repeatedly reported in moderately-to-low physically active participants after different exercise protocols, including low-(57% of age-predicted maximal heart rate, HRmax (McDonnell et al., 2013); 40% of heart rate reserve, HRR (Smith et al., 2014)) and moderate-intensity (77% HRmax (McDonnell et al., 2013); 65–70% HRmax (Singh et al., 2014; Neva et al., 2017)). 50% HRR (Andrews et al., 2020)), 80% HRR (Smith et al., 2014)), continuous as well as high-intensity (90% HRR), interval exercise (Stavrinos and Coxon, 2017; Andrews et al., 2020). However, increases in cortico-motor excitability have been shown in moderately-to-highly physically active, healthy, young subjects after 20 min of moderate-intensity (40% and 50% HRR), but not low-intensity (30% HRR), continuous cycling (MacDonald et al., 2019). Also, similar results have been observed in individuals, whose fitness levels were not reported, after 30 min of both high-intensity (77% HRR), interval and low-intensity (50% HRR), continuous exercise, although the increase was smaller after the latter (Opie and Semmler, 2019). Consistently, our findings demonstrate that a single bout of moderate-intensity (50–70% HRmax), continuous exercise enhances corticospinal output in highly, but not low, physically active individuals (Lulic et al., 2017) (Table 1). Interestingly, the increase in corticomotor excitability following acute exercise seen in highly fit, young adults appears to be independent of either biological sex or menstrual cycle phase (El-Sayes et al., 2020) (Table 1). Further, our work suggests that the relative intensity of the exercise stimulus is an important determinant for exercise-induced modulation of corticospinal pathway plasticity in a sedentary population. Namely, we have shown that a single session of intense, interval exercise potentiates cortico-motor excitability in sedentary individuals at a workload of 105–125% peak power ($W_\text{peak}$, determined during a peak oxygen uptake, VO2peak, test) (Nicolini et al., 2020), but not ~69% $W_\text{peak}$ (El-Sayes et al., 2020) (Table 1). To summarize, while acute, continuous exercise performed at low to moderate intensities (~40–80% HRmax or HRR) elicits no changes in cortico-motor output in moderately-to-low physically active participants, it increases cortico-motor output in more trained individuals with higher fitness. A strong exercise stimulus intensity ($\geq 105–125\% W_{\text{peak}}$) is necessary to enhance corticospinal excitability acutely in a sedentary population.

Intracortical Circuits

Paired-pulse transcranial magnetic stimulation (TMS) paradigms have been used to noninvasively assess whether a single session of exercise induces neuroplasticity within M1 glutamatergic and GABAergic circuits including short-interval intracortical facilitation (SICF), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI) and intracortical facilitation (ICF). Decreased GABAergic-mediated inhibition (i.e., short-interval intracortical inhibition) has been found in individuals of unknown fitness levels after intense, interval (77% HRR), but not low-intensity (50% HRR), continuous exercise (Opie and Semmler, 2019). Similarly, reduced short-interval intracortical inhibition has been observed in moderately-to-low physically active participants 30 min after moderate-intensity (65–70% HRmax), continuous exercise, 10 min after intense, interval exercise (90% HRR) (Stavrinos and Coxon, 2017), immediately and 15 min after moderate-high-intensity (80% HRR), continuous exercise (Smith et al., 2014), and 15 min after low-moderate-intensity (40% HRR), continuous exercise (Smith et al., 2014). Despite these reports of an acute exercise-induced reduction in inhibition, Andrews et al. (2020) failed to observe a significant decrease in short-interval intracortical inhibition in subjects with moderate levels of physical activity 10 min following intense, interval (90% HRR) and moderate-intensity (50% HRR), continuous exercise. Mooney et al. (2016) also reported no changes in short-interval intracortical inhibition between 10 and 50 min after 30 min of moderate-intensity (73% HRR), continuous cycling in highly-to-low physically active, young adults. These authors, however, showed a decrease in GABAergic-mediated inhibition (i.e., long-interval intracortical inhibition) up to 20 min after exercise (Mooney et al., 2016). The reduction in long-interval intracortical inhibition has not been confirmed in moderately physically active individuals either after moderate-intensity (65–70 HRmax (Singh et al., 2014); 50% HRR (Andrews et al., 2020)), continuous exercise, or intense, interval exercise (90% HRR) (Stavrinos and Coxon, 2017; Andrews et al., 2020). Findings from studies examining the effects of acute exercise on glutamatergic, intracortical circuits
show increased intracortical facilitation after 20 min of moderate-intensity (65–70 HRmax) cycling in moderately physically active young adults (Singh et al., 2014; Neva et al., 2017) as well as after 30 min of light (48% HRR) cycling in similarly aged participants whose physical activity levels are not reported (Morris et al., 2020). However, no significant changes in intracortical facilitation have been observed in individuals aged 21–64 years and with moderate levels of physical activity following either intense, interval (90% HRR) or moderate-intensity (50% HRR), continuous exercise (Andrews et al., 2020). We found reduced intracortical facilitation and GABA_A-mediated inhibition as well as unchanged short-interval intracortical facilitation in both highly and low physically active subjects 10 min after a 20-min session of moderate-intensity (50–70% HRmax) exercise (Lulic et al., 2017). A similar exercise protocol also resulted in decreased short-interval intracortical inhibition in both females and males with high cardiorespiratory fitness levels determined during a peak oxygen uptake (VO2peak) test (El-Sayes et al., 2019), while an acute bout of intense, interval exercise (105–125% Wpeak) had no effect on short-interval intracortical inhibition and intracortical facilitation in sedentary males (Nicolini et al., 2020) (Table 1). In summary, while a number of studies have reported that acute exercise, performed at moderate to high intensities (65–90% HRmax or HRR), reduces GABA_A-mediated inhibition in highly to low physically active subjects, this is not always the case, especially in older adults with lower physical activity levels. Further research is needed to better understand the effects of exercise on intracortical plasticity across different age groups and activity levels.

Table 1. Effects of Acute Exercise.

| Reference | Participants | Exercise Protocol | Findings |
|-----------|--------------|-------------------|----------|
| Lulic et al. (2017) | highly physically active (HIGH): IPAQ: 7631 ± 6120 MET-min/wk n = 14, 9 females, 22 ± 3 years; low physically active (LOW): IPAQ: 1305 ± 773 MET-min/wk n = 14, 8 females, 21 ± 1 years | 5-min warmup; 20-min moderate-intensity, continuous cycling at 50–70% HRmax; 5-min cooldown | HIGH: ↑ MEPrest RC amplitudes, ↓AURrest; HIGH and LOW: ∆MEPactive RC amplitudes, ∆AURactive; ↓SICI, ↓ICF, ∆SICF1.2ms, ∆SICF2.5ms |
| El-Sayes et al. (2019) | fair to high CRF: VO2peak females: 43 ± 6 ml/kg/min; VO2peak males: 50 ± 5 ml/kg/min n = 34, 17 females, 21 ± 2 years | 5-min warmup; 20-min moderate-intensity, continuous cycling at 65–70% HRmax; 5-min cooldown | Females and males: ↑AURrest, ↓SICI |
| El-Sayes et al. (2020) | low CRF: VO2peak: 34 ± 4 ml/kg/min n = 19, 7 females, 22 ± 3 years | 3-min warmup; 10 1-min cycling bouts at 60–79% (moderate-intensity) or 80–100% (high-intensity) HRmax interspersed with 1-min recovery intervals at 50 W; 2-min cooldown | ∆AURrest |
| Nicolini et al. (2020) | sedentary: ≤60 min of structured PA/wk Exercise: n = 21, males, 23 ± 3 years; No Exercise: n = 19, males, 25 ± 4 years | 3-min warmup; 5 1-min cycling bouts at 105–125% Wpeak interspersed by 1.5-min recovery intervals at 30% Wpeak; 2-min cooldown | Exercise: ↑AURrest, ↑BDNF, ↑unOCN/tOCN, ↑OCN, ↑OCN, positive relationships between BDNF and either unOCN/tOCN or irisin, negative relationship between BDNF and cOCN. No Exercise: ∆AURrest, ∆BDNF, ∆unOCN/tOCN, ∆OCN, ∆OCN. Both Exercise and No Exercise: ∆AURactive, ∆ICF, ∆SICI, ∆IGF-1, ∆tCTSB, ∆proCTSB, ∆irisin |

AURactive: area under the recruitment curve for first dorsal interosseous (FDI) during tonic contraction; AURrest: area under the recruitment curve for FDI at rest; BDNF: brain-derived neurotrophic factor; cOCN: carboxylated osteocalcin; CRF: cardiorespiratory fitness determined during a peak oxygen uptake test; HRmax: age-predicted maximal heart rate; ICF: intracortical facilitation; IGF-1: insulin-like growth factor; IPAQ: International Physical Activity Questionnaire score; MEP: motor-evoked potential; MET: metabolic equivalent; PA: physical activity; pro-CTSB: precursor cathepsin B; RC: recruitment curve; SICI: short-interval intracortical inhibition; ICTSB: total cathepsin B; tOCN: total osteocalcin; unOCN: uncarboxylated osteocalcin; VO2peak: peak oxygen uptake; W: watt; wk: week; Wpeak: peak power output.
active participants, others have shown that similar exercise protocols do not elicit a change in short-interval intracortical inhibition in this population. Contrasting results have also been reported for GABA<sub>E</sub>-mediated inhibition (i.e., long-interval intracortical inhibition) and glutamatergic intracortical circuits (i.e., short-interval intracortical facilitation and intracortical facilitation). Thus, it is currently unclear whether acute exercise influences GABA<sub>E</sub>-glutamatergic circuits within the primary motor cortex. Lastly, acute, intense, intermittent exercise does not elicit changes in either GABA<sub>E</sub>-mediated inhibition (i.e., short-interval intracortical inhibition) or intracortical facilitation in the sedentary, male population.

**Molecular Markers**

The molecular mechanisms mediating exercise-induced increases in peripheral BDNF and changes in TMS-probed intracortical and corticospinal motor networks has yet to be elucidated. The neurotrophin brain-derived neurotrophic factor (BDNF), known to promote the positive effects of exercise on learning and memory (Gómez-Pinilla et al., 2002; Cotman et al., 2007; Erickson et al., 2011; Bechara and Kelly, 2013), is a likely mediator of exercise-induced M1 plasticity. In humans, increases in peripheral BDNF have been reported after various acute exercise protocols including graded maximal exercise, continuous exercise performed at moderate to high intensities (e.g., formation of uncarboxylated osteocalcin). We also showed increased uncarboxylated OCN (Nicolini et al., 2020), suggesting that this exercise protocol increases osteocalcin decarboxylation and activation (Nicolini et al., 2020). Uncarboxylated OCN is the active form, which crosses the blood brain barrier and enhances BDNF mRNA and protein expression as well as trafficking of BDNF-containing vesicles to synapses (Khrimian et al., 2017). Mera et al. (2016) have proposed that exercise promotes the production of active osteocalcin (i.e., uncarboxylated osteocalcin) by increasing skeletal muscle secretion of interleukin-6, which, in turn, facilitates osteoblast-driven bone resorption occurring at an acidic pH, ideal for osteocalcin decarboxylation (Ferron et al., 2010). We showed increased uncarboxylated osteocalcin (expressed as a ratio to total intact osteocalcin) and decreased carboxylated osteocalcin in sedentary, healthy males following intense, intermittent exercise (Table 1) (Nicolini et al., 2020), suggesting that this exercise protocol increases osteocalcin decarboxylation and activation (i.e., formation of uncarboxylated osteocalcin). We also found that larger increases in BDNF were associated with greater increases in uncarboxylated osteocalcin and decreases in carboxylated osteocalcin (Table 1) (Nicolini et al., 2020), suggesting that uncarboxylated osteocalcin, like irisin, might contribute to BDNF release in response to exercise, and ultimately to changes in neuroplasticity.
Considerations and Gaps

To summarize, moderate-intensity, continuous exercise can increase corticospinal excitability only in moderately-to-highly physically active (Lulic et al., 2017; MacDonald et al., 2019) or fit (El-Sayes et al., 2019), young adults but not in those with moderate-to-low levels of physical activity (McDonnell et al., 2013; Singh et al., 2014; Smith et al., 2014; Andrews et al., 2020) or fitness (El-Sayes et al., 2020). Promisingly, more intense, intermittent exercise appears to enhance cortico-motor output in the latter population (Nicolini et al., 2020), although not across all studies employing a similar, but nevertheless less intense, exercise protocol (Stavrinos and Coxon, 2017; Andrews et al., 2020; El-Sayes et al., 2020). Indeed, the intensity of the exercise stimulus might have contributed to the discrepancy in outcomes among these studies and might represent a key determinant of the changes in neurophysiological and molecular markers which are thought to drive exercise-induced motor neuroplasticity. Reports of high-, rather than moderate-intensity, exercise increasing BDNF release (Ferris et al., 2007; Winter et al., 2007; Schmolesky et al., 2013; Saucedo Marquez et al., 2015), motor learning (Thomas et al., 2016b), and M1 long-term potentiation-like plasticity in response to a type of non-invasive brain stimulation (intermittent theta burst stimulation) (Andrews et al., 2020) provide support for this hypothesis. Thus, it might be important to consider exercise intensity in attempts to prime plasticity within descending and intracortical motor pathways in sedentary, healthy males. Whether this extends to sedentary, healthy females, older adults or individuals with clinical conditions needs to be assessed. Other factors that might contribute to the differences in study results include the range of ages of recruited participants and of TMS pulse intensities delivered to acquire motor-evoked potential (MEP) recruitment curves for the assessment of cortico-motor excitability. Specifically, studies that have failed to observe an increase in corticomotor output recruited individuals with a wide range of ages, i.e., 18–60 years (McDonnell et al., 2013; Smith et al., 2014; Stavrinos and Coxon, 2017; Andrews et al., 2020). It is possible that age impacts motor plasticity responses to exercise that, for example, a stronger exercise stimulus or multiple sessions might be required to observe enhanced corticospinal excitability in older adults and thus a wide age spread in a cohort of participants might impede the detection of exercise-induced changes. Further, studies that reported no changes in corticomotor output following acute exercise in sedentary and moderately active subjects used TMS pulse intensities ranging from 100% to 140% of resting motor threshold (RMT) to build stimulus–response curves (Singh et al., 2014; Smith et al., 2014; Neva et al., 2017; Stavrinos and Coxon, 2017; El-Sayes et al., 2020), while we delivered TMS pulses at intensities between 90% and 200% RMT and observed an increase in the excitability of descending motor pathways in a similar cohort (Nicolini et al., 2020). This suggests that, to detect exercise-related changes in MEP amplitude in a sedentary population, it might be necessary to extend the range of TMS pulse intensities delivered to generate MEP recruitment curves so not just to capture the ascending portion, but also the plateau of the curve at higher intensities (i.e., 140–200% RMT). Lastly, questions have been raised on interindividual and intrindividual response variability impacting the validity of TMS findings. With regard to this matter, Chipchase et al. (2012), and more recently Pellegrini et al. (2020), have highlighted the importance of increasing the homogeneity of technical and methodological factors (e.g., TMS device characteristics, coil size and orientation, TMS pulse parameters) as well as participant-specific ones. The latter includes selection criteria (e.g., sex and menstrual cycle phase, age, medical and medication history, handedness, specialized hand use such as playing an instrument (Ziemann et al., 1996; Priori et al., 1999; Smith et al., 2002; Nordstrom and Butler, 2002; Ziemann, 2004; Hammond et al., 2004; Inghilleri et al., 2004; Rosenkranz et al., 2007; Nitsche et al., 2008; Rossi et al., 2009; Fujiyama et al., 2014; Heise et al., 2014; Zoghli et al., 2015; Goodwill et al., 2015; Ansdell et al., 2019)), preparation prior to the experimental session (e.g., alcohol consumption, hours of sleep (Civardi et al., 2001; Scalise et al., 2006; Conte et al., 2008; Kreuzer et al., 2011; Nardone et al., 2012; Placidi et al., 2013)), scheduling (e.g., time of the day, days between sessions (Nitsche and Paulus, 2001; Nitsche et al., 2003, 2008; Sale et al., 2007, 2008)), and instructing of participants throughout the testing session (e.g., head and neck posture, muscle activity during the testing session, attention level (Fujiwara et al., 2009); Lazarski et al., 2002; Andersen et al., 2003; Stefan et al., 2004; Fujiwara et al., 2009; Kotan et al., 2015; Kuhn et al., 2018)). Controlling for these factors is crucial to minimize response variability and thus to use TMS to reliably evaluate changes in corticospinal excitability. Consistency and rigor in reporting methodological and participant-specific factors will also allow a more reliable interpretation and comparison of TMS findings across studies.

The molecular mechanisms mediating motor plasticity after acute exercise are still largely unknown. We have recently demonstrated that, aside from enhancing serum levels of BDNF, intense, intermittent exercise alters the carboxylation state of osteocalcin in sedentary, healthy, young males (Nicolini et al., 2020). Further, greater increases in BDNF are accompanied by larger increases in uncarboxylated osteocalcin and irisin after intense, intermittent exercise in the same cohort (Nicolini et al., 2020). These results suggest that active osteocalcin and irisin might be mediators of BDNF release induced by acute exercise which, in turn, facilitates neuroplasticity. It remains to be tested whether these findings can be extended to sedentary, healthy, female or normally aging or clinical populations. In addition, relationships between motor performance and exercise-induced neurophysiological and molecular changes remain to be established. Indeed, one of the questions that remains unanswered is whether changes in molecular markers and cortical and descending motor pathways in response to exercise are associated with improved motor performance in the aforementioned populations.
Genetic factors are believed to contribute to between-subject variability, impact individual responses to exercise interventions, and modulate their efficacy in inducing M1 plasticity and motor performance improvements in older adults and during rehabilitation. A single nucleotide polymorphism (Val66Met; rs6265) at codon 66 of the BDNF gene, causing a valine-to-methionine substitution and resulting in reduced activity-dependent BDNF secretion (Egan et al., 2003), has drawn increasing attention. The BDNF Val66Met polymorphism has been shown to attenuate M1 plasticity responses to a facilitatory repetitive TMS paradigm (i.e., intermittent theta burst stimulation) following intense interval exercise (Andrews et al., 2020), that is, Val66Met appears to reduce the priming effects of intense, interval exercise on motor plasticity. Conversely, McDonnell et al. (2013) reported that, although Met carriers had lower baseline BDNF levels than Val/Val carriers, the BDNF genotype did not influence M1 plasticity responses to continuous theta burst stimulation, an inhibitory repetitive TMS paradigm. Of note, these authors found that moderate-intensity exercise might modulate GABA A- and GABA B-mediated inhibition (Table 2) (Nicolini et al., 2019). This evidence suggests that exercise might modulate GABA A- and GABA B-mediated inhibition differently in Val/Val individuals versus Met carriers. Nonetheless, it remains unclear at present whether plasticity responses to exercise within the motor system in young, aging, or clinical populations are influenced by the Val66Met polymorphism. This should be examined in future studies, as it might hinder the assessment of exercise priming effects on motor plasticity by masking exercise-induced changes in neurophysiological, molecular, and behavioural measures. Findings from this research will indicate whether genetic variants, particularly BDNF genotype, should be considered when designing exercise strategies aimed to maximize the priming of neuroplasticity, e.g., during normal aging or rehabilitation.

Lastly, it should be acknowledged that, across studies, the intensity of the exercise stimulus is differently controlled and tailored to each participant based on age-predicted maximal heart rate (HR max, i.e., 220-age), heart rate reserve (HRR; i.e., HR max - resting heart rate) or peak workload (W peak, determined during a peak oxygen uptake test). This hinders comparison of results, and future studies should assess how controlling exercise intensity by H max, HRR or W peak affects exercise-induced motor plasticity.

### EFFECTS OF EXERCISE TRAINING

#### Corticospinal Excitability and Intracortical Circuits

While several studies (reviewed above) have examined the priming effects of acute exercise on motor plasticity using single- and paired-pulse TMS paradigms, only two investigations have, at present, considered training-induced responses, i.e., the impact of more long-term exercise interventions. One study assessed whether six weeks of high-intensity, interval training (HIIT) induced changes in corticospinal excitability, intracortical GABA A-mediated inhibition, and glutamatergic facilitation in young, healthy, sedentary males (Nicolini et al., 2019). The other investigated the relationships between cardiorespiratory fitness (determined by estimating maximal oxygen consumption, VO2max, using a sub-maximal test) and neurophysiological measures (i.e., MEP recruitment curves, short- and long-latency afferent inhibition (SAI, LAI), interhemispheric (SIHI, LIHI) inhibition, short-interval intracortical inhibition, and intracortical facilitation) in healthy, postmenopausal women (Harasym et al., 2020) (Table 2). Specifically, Nicolini et al. (2019) showed that eighteen bouts of intense, intermittent exercise over six weeks did not alter cortico-motor excitability or short-interval intracortical inhibition, but reduced intracortical facilitation (Table 2). The reduction in intracortical facilitation induced by long-term, intense, interval exercise might enhance the propensity for acute plasticity within M1 by facilitating the reduction in GABA A-mediated inhibition in response to an acute exercise bout. Interestingly, a relationship between percent change in cardiorespiratory fitness and percent change in short-interval intracortical inhibition was seen in Val homozygotes after 6-week HIIT, such that greater increases in cardiorespiratory fitness were associated with larger increases in GABA A-mediated inhibition (Table 2) (Nicolini et al., 2019). This finding is consistent with previous reports of changes in peripheral BDNF, hippocampal and temporal lobe volumes, and episodic memory only in Val/Val individuals in response to a 16-week multimodal exercise program or habitual physical activity (Brown et al., 2014; Canivet et al., 2015; Nascimento et al., 2015). It also suggests that BDNF genotype might modulate the effects of long-term exercise on GABA A-mediated inhibition in sedentary males. Lastly, fitness does not impact motor plasticity in healthy postmenopausal women, as no relationships between cardiorespiratory fitness and TMS-probed corticospinal excitability or intracortical motor circuits have been found (Table 2) (Harasym et al., 2020). It is, however, possible, and remains to be tested, that high levels of cardiorespiratory fitness prime plasticity responses to acute exercise within the motor system.

#### Molecular Markers

Acute exercise increases peripheral BDNF levels (Gold et al., 2003; Ferris et al., 2007; Goekint et al., 2008; Tang et al., 2008; Cho et al., 2012; Heyman et al., 2012; Mang et al., 2013; Skriver et al., 2014; Saucedo Marquez et al., 2015; Nicolini et al., 2020). In contrast, most studies have found no effect of exercise training...
on circulating BDNF (Schiffer et al., 2009; Erickson et al., 2011; Ruscheweyh et al., 2011; Voss et al., 2013a; Maass et al., 2016; Goldfield et al., 2018, 2019; Gourgouvelis et al., 2018), although there are exceptions. Zoladz et al. (2008) reported increased plasma BDNF following five weeks of endurance training in physically active males, whereas Leckie et al. (2014) found elevated serum BDNF only in subjects older than 65 years following one year of moderate-intensity walking. Additionally, Heisz et al. (2017), while observing no group differences in serum BDNF between participants who underwent six-weeks of HIIT and those who did not, showed that individuals with greater increases in cardiorespiratory fitness had larger increases in BDNF. Consistent with the majority of reports, we found that six weeks of HIIT had no effect on serum BDNF in sedentary males (Table 2) (Nicolini et al., 2019). We also showed that this exercise protocol did not affect serum levels of IGF-1 or cathepsin B in the same cohort (Table 2) (Nicolini et al., 2019). Two other studies have assessed the effects of long-term exercise on peripheral cathepsin B in low-active, young adults. One reported an increase after four months of supervised treadmill training (Moon et al., 2016), while the other found no changes following eight weeks of aerobic exercise (Gourgouvelis et al., 2018). Our findings together with Gourgouvelis et al. (2018) seem to indicate that cathepsin B might not be involved in mediating the effects of long-term exercise. Nonetheless, we found that increases in cardiorespiratory fitness were accompanied by decreases in total and precursor cathepsin B (Table 2) (Nicolini et al., 2019), suggesting that greater aerobic capacity might require more mature cathepsin B, which is the enzymatically active form produced from cleavage of the inactive precursor (Mach et al., 1994; Mort and Buttle, 1997; Hook et al., 2015). Therefore, despite no changes in total and precursor cathepsin B having been detected after long-term exercise in low-active, young adults, it cannot be ruled out at present that the mature, active form of cathepsin B might contribute to mediating neuroplasticity responses to long-term exercise.

### Neurotransmitter Concentrations, Cortical Thickness, and White Matter Microstructure

M1 neurotransmission can be probed using magnetic resonance spectroscopy, which allows the quantification of neurotransmitter concentrations, such as the most prevalent inhibitory (GABA) and excitatory (glutamate) neurotransmitters (Levy et al., 2002; Novotny et al., 2003; Floyer-Lea et al., 2006; Singh et al., 2009; Stagg et al., 2011; Stagg, 2014). Further, cortical thickness and integrity of white matter microstructure within the motor system can be assessed from anatomical magnetic resonance images (Fischl and Dale, 2000) and via diffusion tensor imaging (Alexander et al., 2007), respectively. To date, few studies have used these tools to assess how long-term exercise modulates motor plasticity in young, aging, or clinical populations. Recently, it has been shown that myelination within the M1 area containing the motor outputs to the legs is increased in older adults (> 65 years) after twelve weeks of cycling at 64% VO\textsubscript{2max} (Rowley et al., 2020). Further, in older adults, higher cardiorespiratory fitness has been associated with greater white matter integrity in the cingulum (Marks et al., 2011; Oberlin et al., 2016; Chen et al., 2020), cerebral peduncle (Chen et al., 2020), anterior corona radiata (Oberlin et al., 2016), anterior internal capsule (Oberlin et al., 2016), fornix (Oberlin et al., 2016), and corpus callosum (Johnson et al., 2012; Oberlin et al., 2016).

### Table 2. Effects of Exercise Training.

| Reference         | Participants | Exercise Protocol | Findings                                                                 |
|-------------------|--------------|-------------------|--------------------------------------------------------------------------|
| Nicolini et al.   | sedentary: ≤60 min of structured PA/wk | 3 times/wk/6 weeks: 3-min warmup | ØAURCREST, ØAURC ACTIVE, ØSICI, ØBDNF, ØIGF-1, ØICF, ØCTSB, Øpro-CTSB; tICF, negative relationship between VO\textsubscript{2peak}, Δ% and either tCTSB Δ% or pro-CTSB Δ% |
| et al. (2019)     | n = 18, males, 23 ± 4 years | 5 1-min cycling bouts at ~105–135\% \textit{W}\textsubscript{peak} interspersed by 1.5-min recovery intervals at 30% \textit{W}\textsubscript{peak} |                                                                                           |
| Harasym et al.    | CRF range between 22 and 70 ml/kg/min: n = 35 (TMS), postmenopausal women, 60 ± 3 years subset n = 24 (MRI), 60 ± 4 years | 2-min cooldown | No relationship between CRF level and either AURC ACTIVE, SICI, ICF, SIHI, LAI, or ICF; No relationship between CRF level and M1 GABA+ or Glu concentrations; No relationship between CRF level and MCT in S1, M1, PMD, PMV, SFG, MFG, IFG, and OFG; positive relationship between CRF level and WM microstructure in PMD, S1, and PARAHPCC |
| (2020)            |                                                                                           |                                                                                           |

AURCREST: area under the recruitment curve for first dorsal interosseous (FDI) during tonic contraction; AURC ACTIVE: area under the recruitment curve for FDI or abductor pollicis brevis (APB) at rest; BDNF: brain-derived neurotrophic factor; CRF: cardiorespiratory fitness measured by estimating maximal oxygen consumption (VO\textsubscript{2max}); GABA: \textalpha-amino butyric acid; Glu: glutamate; ICF: intracortical facilitation; IFG: inferior frontal gyrus; IGF-1: insulin-like growth factor; LAI: long-latency afferent inhibition; LIHI: long-latency interhemispheric inhibition; M1: primary motor cortex; MCT: mean cortical thickness; MEP: motor-evoked potential; MFG: middle frontal gyrus; OFG: orbital frontal gyrus; PA: physical activity; PARAHPCC: parahippocampal cingulate; PMD: dorsal premotor cortex; PMV: ventral premotor cortex; pro-CTSB: precursor cathepsin B; S1: primary somatosensory cortex; SAI: short-latency afferent inhibition; SFG: superior frontal gyrus; SICI: short-interval intracortical inhibition; SIHI: short-latency interhemispheric inhibition; tCTSB: total cathepsin B; VO\textsubscript{2peak}: peak oxygen uptake; wk: week; WM: white matter; \textit{W}\textsubscript{peak}: peak power output.
Interestingly, Johnson et al. (2012) found that the portions of the corpus callosum with greater fitness-related integrity are those connecting premotor cortex and frontal regions, which are involved in high-level motor planning. Tseng et al. (2013) further supported the notion that physical activity attenuates age-related decline in white matter integrity by showing that life-long, aerobic exercise training in older Masters athletes was associated with greater white matter microstructural integrity in the cingulum, posterior thalamic radiation, inferior and superior longitudinal fasciculi as well as in the non-dominant superior corona radiata, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus. In line with these findings, we found that higher cardiorespiratory fitness levels were linked to greater white matter microstructural integrity in dorsal pre-motor cortex, primary somatosensory cortex, and cingulum (Table 2) (Harasym et al., 2020) in postmenopausal women, a population that is at a greater risk of age-related injuries than men (Peel et al., 2002; Stevens and Sogolow, 2005; Schiller et al., 2007; Hartholt et al., 2011; Canada Public Health Agency of Canada, 2014; Do et al., 2015; Johansson et al., 2016). These results suggest that high levels of cardiorespiratory fitness preserve white matter microstructure in these areas and thus, ultimately, maintain motor function (e.g., faster reaction times, better motor coordination, greater tactile acuity) (Kantak et al., 2012; Borich et al., 2015) and memory (Kantarci et al., 2011) in this population. In addition to being effective in counteracting white matter degradation and motor performance decline associated with aging, high cardiorespiratory fitness seems to mitigate age-related reductions in cortical thickness. Lee et al. (2016) showed a positive relationship between self-reported physical activity and cortical thickness in healthy, older adults, who longer exercise duration (≥1 h/day) was linked to greater cortical thickness, both overall and in frontal regions. Of note, subjectively measured physical activity levels do not reflect objectively quantified cardiorespiratory fitness (i.e., determined using a VO2peak test) (Tager et al., 1998). Williams et al. (2017) reported a significant positive relationship between cardiorespiratory fitness and cortical thickness in older, but not in young, adults, such that higher cardiorespiratory fitness was linked to thicker cortex, with the strongest effects in the precentral (M1), paracentral, parahippocampal, and supramarginal gyri as well as in the non-dominant orbitofrontal and middle temporal cortices. These authors also found that highly fit, older adults had greater cortical thickness than low fit, older adults in the same brain areas, which are also the most vulnerable to age-related atrophy. Additionally, cortical thickness of some brain regions did not differ in highly fit, older versus young adults, suggesting that cardiorespiratory fitness attenuates age-related cortical decline in older adults, particularly in the precentral gyrus (M1), pars triangularis, and non-dominant precuneus (Williams et al., 2017). Further, Jonasson et al. (2017) showed that cardiorespiratory fitness was linked to greater cortical thickness in the dorsolateral prefrontal cortex in older adults, while Wood et al. (2016) reported that old Masters athletes, who started competitive aerobic training early in life, sustained it for over 30 years, and had high levels of cardiorespiratory fitness, exhibited greater cortical thickness throughout a wide range of cortical areas, especially in the pre- and postcentral gyri, medial prefrontal cortex, and insula, compared to age-matched, healthy individuals (Wood et al., 2016). Contrary to these studies, we found no significant relationship between cardiorespiratory fitness and cortical thickness in sensorimotor cortex (i.e., primary somatosensory, primary motor, pre-motor cortices, and the supplementary motor area) or frontal regions (i.e., superior, middle, inferior, and orbitofrontal gyr) in postmenopausal women (Table 2) (Harasym et al., 2020). It should, however, be investigated further whether long-term exercise training is protective against age-related cortical thinning in aging women. Lastly, while there is one report of increased GABA but not glutamate-glutamine-glutathione concentration in sensorimotor cortex after a single bout of intense, interval exercise (Coxon et al., 2018), no study has assessed the effects of cardiorespiratory fitness, or long-term exercise training, on GABA and glutamate levels within M1. We were the first to report that cardiorespiratory fitness appears to have no effect on M1 GABA and glutamate levels in aging women (Table 2) (Harasym et al., 2020). In summary, long-term exercise training counteracts white matter degradation, reductions in cortical thickness, and decline in motor function associated with aging. Fitness, however, does not seem to impact M1 GABA and glutamate concentrations or to preserve cortical thickness within sensorimotor and frontal cortices in postmenopausal women.

Considerations and Gaps

No baseline changes in neurophysiological and molecular measures (aside from a reduction in intracortical facilitation) were evident at the end of a 6-week HIIT protocol. It is, however, possible that this exercise intervention might prime the motor system for acute plasticity, that is sedentary males who perform six weeks of HIIT might show changes in the tested measures immediately after a single bout of exercise as opposed to those who do not. It is also possible that longer exercise interventions are required to facilitate M1 plasticity in a sedentary population. Further, given the paucity of studies that have assessed the priming effects of long-term exercise on intracortical and descending motor networks, it is unclear and should be established in future work whether the findings collected so far can be extended to sedentary female, moderately-to-highly fit, normally aging, or clinical populations. Additionally, despite failing to observe a relationship between cardiorespiratory fitness and M1 GABA or glutamate levels in postmenopausal women, high levels of cardiorespiratory fitness might result in greater GABA and/or glutamate within M1 following acute exercise. Lastly, it should be assessed whether a long-term exercise intervention can increase M1 neurotransmission, cortical thickness, and white matter microstructural integrity in sedentary, aging women. Evidence from such studies is crucial to optimize individualized exercise programs for maximal priming of plasticity.
Exercise is a relatively low-cost intervention for maintaining or enhancing motor function during normal aging (Rikli and Edwards, 1991; Buckwalter, 1997; Visser et al., 2002; Brach et al., 2003; Means et al., 2005; Buchman et al., 2007) as well as for ameliorating motor performance deficits associated with clinical conditions (Bergen et al., 2002; Crizzle and Newhouse, 2006; Herman et al., 2007; Forrester et al., 2008; Gobbi et al., 2009; Cooke et al., 2010; Alberto et al., 2011; Vreugdenhil et al., 2012; Pitkälä et al., 2013; Coelho et al., 2013; De Andrade et al., 2013; Sobol et al., 2016; Linder et al., 2017; Rosenfeldt et al., 2019). Mechanisms at different levels (i.e., molecular, cellular, systemic, and socioemotional) modulate exercise benefits on motor learning and function (Stillman et al., 2016). Particularly important mediators of exercise positive effects on motor behaviour are increases in corticospinal excitability and BDNF, both established modulators of neuroplasticity (Ziemann et al., 2001; Siebner and Rothwell, 2003; Siebner et al., 2004; Bramham and Messaoudi, 2005; Thickbroom et al., 2006; Kleim et al., 2006; Bekinschtein et al., 2008; Yoshii and Constantine-Paton, 2010; Fritsch et al., 2010; Carson and Kennedy, 2013; Tunovic et al., 2014; Lu et al., 2014; Leal et al., 2017; Kowiarzki et al., 2018), a mechanism by which our brain learns motor behaviour (Rioult-Pedotti et al., 2000; Muellbacher et al., 2002; Doyon and Benali, 2005; Monfils et al., 2005; McNellis et al., 2009; Dayan and Cohen, 2011; Cantarero et al., 2013). Attention should also be paid to osteocalcin, a molecular marker that is likely to contribute to modulating the positive behavioural transfer effects of acute exercise by enhancing BDNF release (Mera et al., 2016; Khrimian et al., 2017; Nicolini et al., 2020). Further, exercise prescription (e.g., intensity, duration, type, frequency) is thought to influence exercise-related systemic, cellular, molecular, and behavioural outcomes. To date, there is only evidence supporting high-intensity exercise being optimal to maximize motor benefits, at least acutely. Optimal duration, type, and frequency of exercise to prime maximal neuromuscularity within intracortical and corticospinal motor networks remain to be identified. Another important knowledge gap that needs to be filled concerns the mechanistic link between exercise-induced systemic, cellular, and molecular changes and exercise-induced improvements in motor learning and function. As of now, exercise-induced changes in systemic, cellular, molecular, and behavioural outcomes have been examined in separate studies. For example, TMS findings have shown that exercise increases corticospinal excitability (Lulic et al., 2017; El-Sayes et al., 2019; MacDonald et al., 2019; Opie andSemmler, 2019; Nicolini et al., 2020), while neuroimaging ones have demonstrated that exercise positively influences functional connectivity, gray matter density, and white matter microstructure in motor areas (Erickson et al., 2011; Voss et al., 2013b; Herting et al., 2014; Rajab et al., 2014; Schlaflke et al., 2014; Svatkova et al., 2015; Rowley et al., 2020). Further, molecular studies have reported BDNF upregulation after exercise (Rasmussen et al., 2009; Knaepen et al., 2010; Huang et al., 2014; Dinoff et al., 2017; Nicolini et al., 2020), while behavioural ones have shown that exercise results in improved motor learning (Roig et al., 2012; Statton et al., 2015; Thomas et al., 2016a, 2016b; Wanner et al., 2020). Based on these findings, it is likely that increases in cortical excitability, functional connectivity, and BDNF might contribute to mediating improvements in motor behaviour following exercise as these systemic, cellular, and molecular changes have been related to motor learning independently of exercise (Rioult-Pedotti et al., 2000; Sanes and Donoghue, 2000; Donchin et al., 2002; Muellbacher et al., 2002; Doyon and Benali, 2005; Monfils et al., 2005; Kleim et al., 2006; Boyke et al., 2008; Taubert et al., 2010; Teixeira et al., 2010; McHughen et al., 2010; Dayan and Cohen, 2011; He et al., 2013; Sehm et al., 2014; Tunovic et al., 2014; Lee et al., 2014). Five studies, mentioned in the Introduction and all conducted with healthy and young adults, have assessed exercise-induced changes in neurobiological and behavioural outcomes, with four reporting a relationship (Skriver et al., 2014; Ostadan et al., 2016; Dal Maso et al., 2018; Lehmann et al., 2020) and one failing to do so (Mang et al., 2014). It is important that more studies, particularly involving aging and diseased individuals, examine exercise-linked systemic, cellular, molecular, and behavioural outcomes in the same study, in order to mechanistically establish whether exercise-induced increases in TMS-probed corticospinal excitability, in neuroimaging-assessed functional connectivity, gray matter, and white matter as well as in molecular measures, such as BDNF, are related to improvements in motor behaviour. Indeed, in order to be able to successfully utilize exercise protocols in rehabilitation and to preventively off-set motor deficits associated with physiological aging, we need to determine whether exercise-induced systemic, cellular, molecular, and behavioural changes seen in healthy adults are also found in older individuals and clinical populations. Lastly, the effects of long-term exercise on motor learning and performance need to be investigated in future research. Although some promising findings suggest that exercise training has positive transfer effects on motor learning and performance for older adults, stroke survivors, and Parkinson’s patients (Bakken et al., 2001; Miyai et al., 2002; Herman et al., 2007; Quaney et al., 2009; Wang et al., 2020), the motor benefits of long-term exercise remain largely speculative due to the paucity of month-to-year-long exercise intervention studies. Filling the remaining knowledge gaps will allow the design of exercise interventions that optimally enhance motor plasticity.

CONFLICTS OF INTEREST

All authors have no potential sources of conflict of interest to declare.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Chiara Nicolini: Writing - original draft, Writing - review & editing. Margaret Fahnestock: Funding acquisition, Writing - review & editing. Martin J. Gibala:
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