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Review article

Functional relevance of resistance training-induced neuroplasticity in health and disease

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Running title: Neural adaptations to resistance training in health and disease

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None

Abstract

Repetitive, monotonic, and effortful voluntary muscle contractions performed for just a few weeks, i.e., resistance training, can substantially increase maximal voluntary force in the practiced task and can also increase gross motor performance. The increase in motor performance is often accompanied by neuroplastic adaptations in the central nervous system. While historical data assigned functional relevance to such adaptations induced by resistance training, this claim has not yet been systematically and critically examined in the context of motor performance across the lifespan in health and disease. A review of muscle activation, brain and peripheral nerve stimulation, and imaging data revealed that increases in motor performance and neuroplasticity tend to be uncoupled, making a mechanistic link between neuroplasticity and motor performance inconclusive. We recommend new approaches, including causal mediation analytical and hypothesis-driven models to substantiate the functional relevance of resistance training-induced neuroplasticity in the improvements of gross motor function across the lifespan in health and disease.

Keywords: Maximal voluntary contraction (MVC), Strength training, Electromyography (EMG), Transcranial magnetic brain stimulation (TMS), Electroencephalography (EEG), Functional magnetic resonance imaging (fMRI), Athletic performance, Aging, Parkinson's disease, Multiple Sclerosis, Stroke, Directed Acyclic Graphs, Causal Mediation Analysis

1. Introduction

A series of historical studies introduced the idea that structural and functional modifications in specific brain and spinal circuits (i.e., neuroplasticity) contribute to the rapid initial increase in maximal voluntary muscle (MVC) force following a period of resistance training (RT) in healthy humans (Sale and MacDougall, 1981; Sale et al., 1983; Sale et al., 1982). Broadly, neuroplasticity is ‘the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections’ (p.1592, (Cramer et al., 2011)). The gain in function, i.e., the increase in MVC force is a positive adaptation to RT as a result of modifications in the neural command to and the activation of the muscle. A figure in a review adopted by numerous textbooks depicts the relative roles of neural and muscular adaptations to RT (Fig. 11 in (Sale, 1988)). The figure conceptualizes a sharp, initial rise in the contributions by the nervous system to strength gains, which plateau after a few weeks of RT when muscle hypertrophy becomes the determinant factor of strength gains. The review states that ‘...increases in peak force and rate of force development *are associated with* increased activation of prime mover muscles’ (p. s135, (Sale, 1988)). Sale later revised this scheme and postulated that RT-induced muscle adaptations (hypertrophy) do occur already after one session of RT in untrained subjects, as evidenced by muscle fiber damage and a subsequent stimulation of protein synthesis (Fig. 11, p. 305) (Sale, 2003).

Since the publication of these seminal papers over 30 years ago, nearly 20 reviews have highlighted several structural and functional adaptations at the spinal and supraspinal level with a role in strength gains during the initial 2-12 weeks of RT (Table 1, Fig. 1) (Aagaard, 2003, 2018; Aagaard et al., 2010; Carroll et al., 2001; Carroll et al., 2011; Cormie et al., 2011a, b; Duchateau et al., 2006; Enoka, 1988; Folland and Williams, 2007; Gabriel et al., 2006; Hedayatpour and Falla, 2015; Hortobágyi and Maffiuletti, 2011; Kidgell et al., 2017; Kidgell and Pearce, 2011; Kraemer et al., 1988; Markovic and Mikulic, 2010; Mason et al., 2019; Oranchuk et al., 2019; Siddique et al., 2019). The assumption was that these adaptations increase MVC force by improving neural activation of skeletal muscle’s contractile machinery. However, much evidence of neural adaptations is indirect and the specific mechanisms remain elusive. There is also no consensus on individual mechanisms nor evidence on the relative significance of the various adaptive mechanisms.

Critically for numerous populations such as athletes, the steadily increasing number of older adults, and patients, the unaddressed and timely question is how, ‘neural adaptations’ are functionally relevant? We propose that the root cause of a lack of progress in the field is an over interpretation of and over-reliance on the data showing, for the most part, merely parallel changes in indices of neuroplasticity and measures of MVC force or multi-joint, gross motor performance. We hypothesize that the parallel changes in neural outcomes and MVC force or motor performance can occur without a meaningful or statistically significant association. We suspect that the reasons for the uncorrelated changes after RT are: 1) The task-specificity of measurements at rest is low relative to training at high forces but technically it is challenging to reliably assess neuroplasticity during MVC measurements and the interpretation of such data is complex (Lundbye-Jensen et al., 2005); 2) Selection of only one or two variables quantifying neuroplasticity none of which on its own versus a network analysis or multivariate approach would be conceptually expected to predict increases in MVC force, and 3) Changes in neuroplasticity and MVC force occur with different time courses during and after RT (Csapo et

al., 2011; Kubo et al., 2010) and at sites that have been overlooked (Baker and Perez, 2017; Choudhury et al., 2019; Fernandez-Del-Olmo et al., 2014; Glover and Baker, 2020).

If the association between RT-induced increases in MVC force and changes in markers of neuroplasticity is low, it is not surprising that such associations are nearly non-existent between changes in measures of neuroplasticity and increases in gross motor performance such as walking, jumping, and throwing. There is indeed a paucity of studies examining how newly acquired physical abilities (i.e., increase in MVC force) can be incorporated into, for example, older adults' and patients' gait, allowing them to walk safely faster (Beijersbergen et al., 2013). Neuroplasticity associated with RT would be functional if it acted as the enabling mechanism in the increases in gross motor performance in healthy adults and in patients with Parkinson's disease (PwPD), multiple sclerosis (PwMS), and stroke (PwS). A potential reason for the weak or non-existing correlations between changes in MVC force and gross motor performance is the low task specificity between single-joint RT exercises and gross motor tasks made up of multi-joint movements. Single joint RT can increase muscle size and strength but might not be as effective to increase gross motor performance as would exercises involving multi-joint movements that closely mimic the spatiotemporal structure and muscle activation patterns of walking, running, jumping, or reaching with the arms (Kraemer et al., 2002; Kraemer and Ratamess, 2004). In other words, if RT primarily includes single-joint exercises, transfer to functional movements such as walking, running, and jumping are limited which can be explained through the principle of training specificity. This principle denotes that the applied RT exercise should resemble the functional movement task to increase the likelihood of transferring RT-related strength gains to function (Reilly et al., 2009). Thus, there is a need to move to the next, i.e., more functional level in understanding the relation between neural adaptations to RT, the potential changes in gross motor function, and the underlying mechanisms.

The purpose of this review was to examine 1) if individual variations in RT-induced gains in MVC force are associated with individual variations in specific indices of neuroplasticity and 2) if such a relationship underlies improvements in MVC force and, more broadly, multi-joint, gross motor function in athletes, older adults, and patients. Clearly, correlation is not causation. However, we argue that the determination of correlative changes would fill the gap in current knowledge which is based on merely parallel changes in indices of neuroplasticity and behavioral outcomes of RT. A critical shortage in previous research is a lack of correlative analyses of changes in behavioral outcomes (MVC force, motor performance) and measures of underlying neuroplasticity.

One way to address this knowledge gap is through causal mediation analyses that aim to obtain unconfounded estimates of the direct and indirect effects of RT on motor performance (Zhang et al., 2016). In the current context, mediation is the process through which RT causes increases in motor performance. The untested hypothesis is that some or all of the total effect of RT on motor performance operates through a mediator, i.e., neuroplasticity. The direct effect is the effect of RT on the motor performance free of the mediator's effect. The indirect path is the effect of RT on the outcome operating through mediator(s). Following an increasing number of attempts using causal mediation analyses in kinesiology (Condello et al., 2019; Condello et al., 2016; Condello et al., 2017; Forte et al., 2013; Jekauc et al., 2017; Marcos-Pardo et al., 2020; Mavros et al., 2017; Tollár et al., 2019a; Tollár et al., 2020), we provide illustrative examples for this

approach to recommend a more systematic, mechanistic, and hypothesis-driven examination of the functional relevance of RT-induced neuroplasticity in improving motor performance in health and disease. First, we examine evidence for the association between the most often reported indices of neuroplasticity and increases in MVC force generated by muscles at a single joint. Next, we review exemplary evidence how neural adaptations to RT could mediate improvements in gross motor function in athletes, older adults, and selected groups of patients with mobility impairments. Concerning the inclusion of such a diverse array of population, we posit that RT for 2-12 weeks can reduce muscle weakness through induction of neuroplasticity hence an increased understanding of the functional relevance of such neural adaptations are applicable to all participants of RT interventions regardless of clinical background. We conclude with recommendations for future research and, based on experimental data extracted from individual papers listed in reviews, we propose evidence-based, mechanistic structural equation models that update Sale's classical, descriptive model (Sale, 1988, 2003). Such modeling makes it possible to causally link RT-induced changes in markers of neuroplasticity and motor performance, as reviewed in detail previously (Nuzzo et al., 2019a; Steele et al., 2020; Tollár et al., 2019a).

2. Functional relevance of RT-induced neuroplasticity to increase MVC force

Here, we examine changes induced by RT in markers of neuroplasticity underlying the increases MVC force. Markers of muscle activation include surface electromyographic activity (sEMG) and voluntary activation (VA), responses to peripheral nerve stimulation (Hoffman or H-reflex, voluntary or V-wave), responses to transcranial magnetic brain stimulation (TMS), and imaging.

2.1 Muscle activation: sEMG activity and MVC force. MVC force is the result of the strong activation of prime mover individual muscles forming the agonist muscle group, the coordinated deactivation of individual muscles forming the antagonist muscle group, and coordinated activation of remote muscle groups to stabilize posture (Rutherford, 1988; Rutherford and Jones, 1986). RT-induced plasticity in the coordination among individual agonists and the coordinative changes among stabilizers have been rarely examined. Studies instead have focused on measuring markers of neuroplasticity in representative individual muscles of agonists and coordination between agonist and antagonist muscle groups (Arnold and Bautmans, 2014; Hortobágyi et al., 2006; Remaud et al., 2007).

Concerning markers of neuroplasticity in representative individual muscles of agonist, MVC force is determined by motor unit recruitment and the rate at which motor neurons discharge action potentials (Carroll et al., 2011; Folland and Williams, 2007). The net output (spinal and supraspinal) controls motor unit recruitment and discharge rate during muscle contraction. Thus, structural and functional changes in spinal circuits or within brain areas upstream to the spinal motor neurons could be the locus of neural adaptations to RT, underlying increases in MVC force (Kidgell et al., 2017; Kidgell and Pearce, 2011; Siddique et al., 2019).

Changes in muscle size and MVC force occur in a temporally dissociated manner. sEMG activity has been used as a surrogate measure of neuroplasticity. It summates the action potentials of detectable motor neurons recruited during muscle contraction. Indeed, increases in sEMG activation of the trained muscle precede detectable changes in hypertrophy (Akima et al., 1999; Häkkinen et al., 2001a; Häkkinen et al., 2001b; Narici et al., 1989; Rutherford and Jones, 1986).

However, of the 25 individual studies analyzed in reviews, we found only 2 studies reporting very strong associations ($r \approx 0.70$) between increases in sEMG and muscle strength following RT (Häkkinen and Komi, 1986; Häkkinen et al., 1985). We classify correlation coefficients of 0.1, 0.3, 0.5, 0.7, and 0.9 as weak, moderate, strong, very strong and extremely strong correlations, respectively (Hopkins et al., 2009; Schober et al., 2018). The majority of studies either did not report or find an association between sEMG-indexed neural adaptations to RT and improvements in MVC force. Whether reduced neural drive to antagonists could explain increased MVC force remains controversial, as an equal number of studies report such reductions (Carolan and Cafarelli, 1992; Häkkinen et al., 1998; Simoneau et al., 2007) and also no changes in antagonist sEMG after RT (de Boer et al., 2007; Holtermann et al., 2005; Reeves et al., 2005), but none reported correlated changes in MVC force and antagonist sEMG. Limitations with sEMG, such as action potential cancellation biases, constrains sEMG amplitude as an index of neuroplasticity. Measuring sEMG constituents, i.e., motor unit recruitment and the rate at which motor neurons discharge action potentials could reduce this bias and there is first evidence indicating an association between these parameters and strength gains (Del Vecchio et al., 2019a). An additional complicating factor in many studies is that sEMG was often recorded in a single muscle, whereas MVC force is the result of several individual muscles making up the agonist muscle group and the coordinated de-activation of antagonist and activation of remote stabilizers, factors rarely measured (Rutherford, 1988; Rutherford and Jones, 1986). Even properly, i.e., Mmax-normalized, sEMG measures can be insensitive markers of neural adaptations to RT interventions of drastically different compositions (Duchateau et al., 2020), necessitating the use of more advanced sEMG methods (Vieira and Botter, 2021). In total, the evidence is, at best, weak for sEMG-indexed muscle activation as a measure of neuroplasticity accompanying RT. (See Recommendations 5.1, 5.4).

2.2 Muscle activation: VA and MVC force. Compared with sEMG, twitch interpolation provides greater insights to determine VA, which is a summed estimate of the number of motor neurons recruited and the rate at which they discharge action potentials (Allen et al., 1998; Nuzzo et al., 2019b; Shield and Zhou, 2004). Presumably, VA measured by twitch interpolation over the motor point reflects the neuroplasticity in a single agonist muscle. It is therefore surprising that the relevant systematic reviews of the topic did not include studies using peripheral nerve stimulation to assess VA. Instead, some studies reported only VA measured by TMS (Carroll et al., 2011; Kidgell et al., 2017; Siddique et al., 2019). Counterintuitively, MVC force was found to also increase after RT without changes in VA (Herbert et al., 1998; Tillin et al., 2011). Notwithstanding, VA and MVC force tended to increase in parallel after RT (Behrens et al., 2016; Brown et al., 2017; Giboin et al., 2018) and, in some cases, in a moderately to highly correlated manner ($r = 0.54-0.77$) (Ema et al., 2018; Toien et al., 2018), which has been attributed to low VA at baseline, especially in older adults (Arnold and Bautmans, 2014). Furthermore, the limited evidence suggest that VA might act as a mechanism enabling the incorporation of increased MVC force into gross motor performance. For example, increases in VA and gait speed correlated strongly ($r = 0.67$) after RT in mobility-limited older adults (Hvid et al., 2016). However, we note that if VA is a comprehensive measure of neural drive and reaches 100% of available motor neurons in initially sedentary healthy adults after RT, it is rather unlikely that highly-resistance trained athletes can further improve VA. Instead, it is more likely that such athletes can improve MVC force through muscle hypertrophy (Balshaw et al., 2019). One possibility is that measuring VA in one muscle does not represent adaptations in the rest of the

individual muscles making up the agonist muscle group that produces MVC force, resulting in an underestimation of VA for the whole muscle group and thus resulting in low or no correlations with motor performance (Allen et al., 1998; Nuzzo et al., 2019b; Shield and Zhou, 2004). The inconsistent data are also related to the forms of measuring VA, including single, double, and multiple peripheral electrical pulses and TMS-induced VA. (See recommendations 5.2, 5.4).

2.3 Peripheral nerve stimulation and MVC force. The H-reflex amplitude, produced by peripheral nerve stimulation at rest, can provide an estimate of the excitability of spinal motor neurons, and hence a marker of neuroplasticity after RT. A meta-analysis found no changes in H-reflex amplitude measured at rest in response to RT (Siddique et al., 2019). The V-wave is an H-reflex variant evoked during forceful muscle contractions by supramaximally stimulating a peripheral mixed nerve. Although the V-wave is influenced by all of the synaptic inputs to the motor neuron pool, during maximal contractions a large part of the motor neuron input comes from the descending neural drive and could be a marker of task-specific neural adaptations to RT (Aagaard et al., 2020; Aagaard et al., 2002). Meta-analytical evidence of five studies (n=52 subjects) suggested a consistent increase in V-wave amplitude after RT; however, only one study showed a moderate correlation ($r=0.45$) between changes in MVC force and V-wave amplitude after RT (Vila-Cha et al., 2012). The H-reflex and V-wave, like most often VA, is a single muscle measure and does not represent all of the individual muscles in the agonist group nor can these outcomes indicate changes in coordination among the synergistic muscles. (See recommendation 5.2, 5.4).

2.4 Brain stimulation and MVC force. Non-invasive brain stimulation such as single and paired pulse TMS can measure changes in the excitatory-inhibitory circuits produced by changes in corticospinal excitability (CSE) and/or changes in the efficacy of intracortical inhibitory or facilitatory interneurons after RT (Hallett, 2000). Such changes produced by RT would hypothetically increase the magnitude and efficacy of the motor command so that the motor neurons would receive a greater drive, increasing MVC force after RT. Meta analyses of TMS data support the idea that CSE increases and intracortical inhibition decreases after RT (Kidgell et al., 2017; Siddique et al., 2019). This is particularly true when the TMS measurements are done using a background contraction (i.e., not at rest). The parallel increases in MVC force and CSE, and decreases in inhibition have led to the assumption by some (Kidgell et al., 2017; Siddique et al., 2019), that these processes are mechanistically linked, but not all authors concur (Nuzzo et al., 2019a). Indeed, of the studies that measured CSE (n=22 studies), contralateral silent period (n=7 studies), and short-interval intracortical inhibition (n=8 studies) after RT, only two reported significant but moderate associations between decreases in silent period (a measure of cortical inhibition) and increases in MVC force ($r\sim-0.50$) (Hendy and Kidgell, 2013; Kidgell and Pearce, 2010). A lack of correlation could in part be due to the dissimilarity between the test and training tasks (i.e., rest vs. contraction, intensity and type of contraction). This task-specificity effect seems to be weaker in RT than in balance training (Mouthon and Taube, 2019). For example, even within the same study only externally but not internally paced RT produced changes in CSE and cortical inhibition measured during contraction, implying that the adaptations in CSE and cortical inhibition did not contribute to strength gains (Leung et al., 2017). Neuroplastic changes were also absent after RT when responses to TMS were measured during muscle contraction in an arm muscle (Lundbye-Jensen et al., 2005). In sum, most studies did not seem to have computed, reported, or found functionally relevant associations between

changes in TMS-derived indices of neuroplasticity and improvements in MVC force after RT. The evidence for a functional link between strength gains and increases in CSE or decreases in cortical inhibition in healthy adults is modest, questioning the functional role of these neural adaptations in increasing MVC force. (See recommendations 5.2, 5.4).

2.5 Imaging data and MVC force. Neuroplasticity accompanying RT has been rarely examined by brain imaging. Data from 18 brain imaging studies suggested that RT can increase gray matter thickness and volume, and improve functional and resting-state connectivity in several brain areas (Herold et al., 2019). However, these studies were designed to determine the relationship between brain plasticity and cognitive function rather than increases in motor performance. Understandably, these studies did not describe association between changes in motor performance and brain plasticity.

Short term, 2-12 weeks of RT produced inconsistent brain adaptations as measured by magnetic resonance imaging (MRI). Twelve weeks of RT increased gray matter density in the posterior and anterior lobe of the cerebellum, the superior frontal gyrus in the frontal lobe, and in the anterior cingulate cortex of the limbic lobe in healthy older adults. However, the authors did not assess the relation between these brain changes and motor performance (Fontes et al., 2017). Sixteen sessions of 36 right-unilateral isometric plantarflexions improved MVC force in the trained (40%) and untrained (30%) leg and decreased mean diffusivity of the left corticospinal track (effect size = 1.4) and decreased putamen volumes (Palmer et al., 2013). The 40% increase in MVC force correlated moderately, $r=-0.55$, with the observed $\sim 2\%$ changes in mean diffusivity, reflecting, according to the authors, improved myelination. The changes in putamen volume might be related to improved motor learning. The diffusivity data could reflect the strength element of the training adaptations. However, the 30% increase in the untrained contralateral side (cross-education) occurred without any changes in brain structure.

Right-unilateral ulnar deviation RT ($n=24$ sessions) improved each hand's MVC force by $\sim 46\%$ (Farthing et al., 2007). When subjects contracted the right-trained hand in the magnet after RT, the activation in left primary motor and somatosensory cortex, dorsal premotor cortex, and other areas increased compared with the activation before RT ($n=4$ subjects). When subjects contracted the left-untrained hand after RT, activation in the right sensorimotor cortex and left temporal lobe increased compared to before RT. Unilateral handgrip RT spared the opposite immobilized limb from MVC force loss ($+0.8\%$). The force-sparing correlated with increased left motor cortex volume of activation. In the non-training controls, MVC grip force of the immobilized limb decreased by 11% without changes in the contralateral motor cortex activation (Farthing et al., 2011). However, there were no further correlation analyses performed between measures of neural adaptations and changes in MVC force.

The activity of the cerebral cortex measured with the mean frequency of the electroencephalogram (EEG) increased independent of intervention type in PwPD (Carvalho et al., 2015), suggesting a fitness component in the exercise effects on improved brain flow (Tollár et al., 2019a). EEG-derived corticomuscular coherence measured at different MVC forces was also independent of training history in RT and aerobically trained athletes (Dal Maso et al., 2017). The effects of short-term RT on the amplitude of the movement related cortical potentials (MRCPs) in healthy untrained subjects are inconsistent. Three weeks of unilateral explosive RT

increased MVC force, rate of tension development, and sEMG. These changes were accompanied by *decreases* in the amplitude of the MRCPs. The authors did not report if the changes in force and EEG measures correlated with each other. The interpretation was that RT improved neural economy, as submaximal force generation was achieved by reduced cortical drive (Falvo et al., 2010). However, four weeks of eccentric vs. concentric leg RT increased MVC outcomes and also *increased* MRCP amplitudes recorded during submaximal muscle contraction in healthy older adults (Kang et al., 2016). Motor imagery of forceful elbow flexion for 30 minutes at rest increased MVC force and also MRCP amplitude by 20-22% at C3 and Cz electrodes (Yao et al., 2013). Accordingly, the increase in descending command would recruit previously inactive motor units and/or have higher discharge rate of active motor units, thereby increasing MVC force. RT might have also lowered inhibition to the motor neuron pool of the muscles, increasing net motor neuron output (Yao et al., 2013). These data were interpreted as evidence for neuroplasticity in motor cortex, cerebellum, supplementary motor area, and dorsal premotor cortex; however, the authors did not report correlations between EEG, sEMG, and MVC force (see also (Liu et al., 2019). Collectively, there is evidence that RT produced favorable changes in brain structure and function, but there is little evidence for such changes to correlate with increased MVC force. Additionally, there has been no attempt to relate brain imaging data to sEMG, TMS, or peripheral stimulation data following RT; consequently, current imaging data provide little mechanistic evidence for how changes in putative brain areas and networks after RT could increase motor performance. (See recommendations 5.3, 5.4).

3. Functional relevance of neural adaptations to RT in aging and neurological conditions

In light that aging, especially in combination with a disease, reduces the responsiveness of skeletal muscle to mechanical stimuli (Drummond et al., 2008; Kumar et al., 2009), a clearer understanding of how neuroplasticity could mediate increases in motor performance after RT would improve the specificity of exercise prescription for older adults and patients. In particular, patients with neurological and neurodegenerative conditions would benefit, as RT could exploit well-functioning areas of the central nervous system to stimulate neuroplasticity and activities of daily living. (See for this section Recommendation 5.5).

3.1 RT-induced neuroplasticity for improving older adults' walking speed. Gait speed in late mid-life predicts health, medical, and cognitive conditions later in life, including mortality/survival and morbidity (Beijersbergen et al., 2013). Understanding the biomechanical and neural mechanisms of minimizing age-related loss of gait speed is thus an important element of designing and prescribing exercise for older adults. In such studies, lower extremity RT improved MVC force of muscles involved in force generation in the stance phase of gait (Hortobágyi et al., 2015). However, increases in gait speed and MVC force of muscles involved in the propulsion thrust correlated weakly (Beijersbergen et al., 2017; Uematsu et al., 2018; Uematsu et al., 2014). The assumption is that RT-induced neuroplasticity underlies increases in gait speed. Indeed, changes in sEMG after RT suggested that older adults used a fraction of the training-induced increases in muscle activation-capacity during walking. Moreover, after RT, the changes in inter-joint coordination assessed through gait kinematics, poorly predicted the increases in gait speed (Beijersbergen et al., 2013). That is, muscle activation measured during gait by sEMG after RT had no or only limited functional relevance for increasing gait speed. We speculate each subject adapted differently, 'choosing a different solution', precluding the emergence of a common neural adaptive pattern. When the functional priority is to increase gait

speed, the stand-alone administration of a RT program has low effectiveness, which can be increased by combining RT with gait re-training protocols in the elderly (Gillespie et al., 2012). Such approaches are designed so that RT-induced neuroplasticity could facilitate the incorporation of newly acquired muscle strength into gait kinetics. However, the functional role of RT-induced neuroplasticity in improving older adults' walking speed remains unclear.

3.2 RT-induced neuroplasticity and motor function in PwPD. Most PwPD have lower strength levels and display lower rates of force development compared to healthy age-matched control subjects (Inkster et al., 2003; Paasuke et al., 2004; Paasuke et al., 2002). Notwithstanding its effects on MVC, Parkinson's disease can impair the neural drive to the muscle and thereby cause a lower VA (Huang et al., 2017) and a higher unsteadiness of voluntary force (Skinner et al., 2019).

While MVC force has been shown to correlate strongly ($r=0.68-0.80$) with chair rise and timed-up-and-go performance in a few studies (Inkster et al., 2003; Schilling et al., 2009), systematic reviews concluded that RT-induced increases in MVC force might not translate into functional improvements in PwPD (Cherup et al., 2019; Falvo et al., 2008; Ramazzina et al., 2017; Roeder et al., 2015; Tillman et al., 2015). The only hint for RT-induced neuroplasticity to correlate with motor function emerged when RT-induced increases in MVC force and EMG muscle activation predicted upper limb bradykinesia after 24 months of RT (David et al., 2016). In sum, PwPD respond to RT but the neuroplastic and strength adaptations are uncorrelated and have limited or no effects on activities of daily living. This may be related to the low specificity of RT exercise to the muscle activation patterns present in activities of daily living. It remains unclear how and if the RT-induced neuroplasticity could act as enabling mechanisms for PwPD to improve activities of daily living through the increased MVC force.

3.3 RT-induced neuroplasticity and motor function in PwMS. PwMS often have low MVC force in limb muscles, affecting functional capacity (Kjohlhede et al., 2015b). MVC force of the knee flexor ($r \sim 0.5-0.7$) was found to correlate more strongly than knee extensor ($r \sim 0.1-0.4$) with walking capacity in PwMS (Broekmans et al., 2013). The clinical interpretation was that PwMS would benefit from RT to improve walking ability (Manca et al., 2019). Indeed, RT increased MVC force by up to 36% in PwMS (Cruickshank et al., 2015; Manca et al., 2019). Meta-analysis revealed increases in MVC force with small-to-moderate effect sizes, which was interpreted as diminished responsiveness of PwMS to RT (Jorgensen et al., 2017). Whether the increases in MVC force also translate into improved gross-motor function is unclear. While there is a relationship between walking speed and leg MVC force in PwMS (Thoumie et al., 2005), RT improved walking speed only with low effect sizes (0.35) (Manca et al., 2019). Sporadic data suggest that RT can also improve chair rise, stair ascent, and 10-m walking speed, and distance walked in 6 minutes (Dalgas et al., 2009). The evidence is weaker for RT to improve upper extremity function in PwMS (Lamers et al., 2016).

In the MS literature minimal attention has been devoted so far to whether or not RT-induced neuroplasticity could underlie the increases in MVC force. There were parallel increases in sEMG activity of the knee extensors and flexors and MVC force of these muscles (Dalgas et al., 2013; Kjohlhede et al., 2015a). Likewise, sEMG activity and superimposed V-wave amplitudes in ankle plantarflexors increased after 3 weeks of maximal intensity RT in PwMS (Fimland et al.,

2010). Control of submaximal leg muscle isometric force correlated with walking speed in PwMS suggesting that moderate declines in the walking performance were more strongly associated with impairments in force control rather than decreases in MVC force (Davis et al., 2020). In sum, the limited evidence seems to suggest that RT is an effective method to increase efferent motor output of spinal motor neurons in PwMS. However, correlations between changes in sEMG-based outcomes and increases in MVC force were not reported. Likewise, there is a lack of data on the relationship between changes in markers of neuroplasticity and changes in gross motor function.

3.4 RT-induced neuroplasticity and motor function in PwS. Muscle weakness limits motor activity in PwS (Ada et al., 2006; Canning et al., 2004). MVC force in the affected limb can be as low as one half of healthy age- and sex-matched controls (Neckel et al., 2006). Meta-analytical evidence suggests that RT can increase MVC force in the lower extremities of chronic PwS (Dorsch et al., 2018; Wist et al., 2016). The efficacy of RT to increase MVC force in the upper extremity in PwS (Harris and Eng, 2010) and in the acute state (i.e., up to three months after a stroke) is uncertain (Salter et al., 2016).

It is also unclear if RT-induced increases in MVC force are related to improvements in motor function. While RT improved MVC force in lower extremity muscles substantially (effect size = 1.1), no improvements occurred in motor function assessed by the timed-up-and-go test (effect size = 0.4) (Dorsch et al., 2018). The RT effects were also minimal on upper limb functions (effect size = 0.2). Reviews conclude that RT-induced gains in MVC force, in general, do not transfer to functional improvements in PwS (Tiozzo et al., 2015). One exception is gait speed (Wonsetler and Bowden, 2017), which improved (effect size: 0.4-0.7) above the minimally important difference for habitual (+0.11 m/s) and fast walking speed (+0.18 m/s) after RT (Clark and Patten, 2013). High-intensity RT of upper extremity muscles combined with functional task practice also improved MVC force and a number of functional outcomes in parallel (Patten et al., 2013), alluding to the possibility that a combination of functional tasks with RT would increase the task-specificity of RT to daily tasks. However, the role of RT-induced neuroplasticity remains unclear in improvements in MVC force and gross motor performance in PwS.

4 RT-induced neuroplasticity for increasing athletic performance

Athletes use RT to improve MVC force with an expectation based on the assumption and research evidence that contractile force and speed are associated with athletic performance. However, based on the principle of Specific Adaptation to Imposed Demands (Fox and Mathews, 1988) and the concept of training specificity (Sale and MacDougall, 1981), RT normally does not explicitly train athletic skills (Sale, 1988). We examine this assumption with respect to sprint and distance running performance, in highly resistance-trained athletes in whom the Sale model (Sale and MacDougall, 1981) predicts little or no RT-induced neuroplasticity and in prepubertal children who could improve athletic performance after RT almost exclusively due to neuroplastic changes. (See for this section Recommendation 5.5.)

4.1 Sprint running performance. Sprinters use RT to increase running speed (Haugen et al., 2019). During sprinting, athletes accelerate body mass by rapidly applying high forces to the ground. Sprinters use high-speed RT to increase leg muscle power by improving contractile force and velocity while minimizing muscle mass gains (Behm et al., 2017; Delecluse, 1997). The

evolving neural adaptations reduce torque generation time through heightened motor unit recruitment and discharge rates in the agonist muscles (Del Vecchio et al., 2019a; Del Vecchio et al., 2019b) and an earlier recruitment of high threshold motor units (Del Vecchio et al., 2019b). An increase in motor neuron excitability after RT would also increase MVC force in response to input from supraspinal drive and spinal Ia afferents, and would increase the stiffness of the muscle-tendon unit, aiding force production and reducing ground contact times (Aagaard et al., 2002; Ross et al., 2001).

Currently, there are no studies showing a relation between RT-induced increases in MVC force, markers of neuroplasticity, and sprint times. RT is expected to increase H-reflex amplitude, i.e., motor neuron excitability, and decrease presynaptic inhibition (Aagaard et al., 2002) but sprinters compared with distance runners had a *lower* H-reflex amplitude (Casabona et al., 1990; Maffiuletti et al., 2001). Because H-reflex arises from the activation of low threshold motor neurons, the lower H-reflex amplitude may result from the lower proportion of low- vs. high-threshold motor units, resulting in the activation of fewer motor neurons contributing to the H-reflex during stimulation intensities at which the H-reflex is not cancelled by the antidromic propagation of the action potential (Casabona et al., 1990). Longitudinal studies are needed to answer this question.

While RT improves sprinters' MVC force and produces neuroplastic changes, these changes weakly correlate with improved sprint times (Harris et al., 2000; Lyttle et al., 1996; McBride et al., 2002; Moir et al., 2007; Wilson et al., 1993). Differences in the pattern of muscle activation during RT and sprinting and being a novice vs. elite sprinter might explain the poor relationship (Barr et al., 2014; Styles et al., 2016). In contrast, resisted sprint training over short distances compared with RT improved sprint times more effectively, suggesting that the spatiotemporal structure of training stimulus is an important factor to improve sprint times (Bachero-Mena and Gonzalez-Badillo, 2014; Behm and Sale, 1993; Bolger et al., 2015; Petrakos et al., 2016; Rumpf et al., 2016). The extent of specificity is not entirely clear because isometric training conducted on a cycle ergometer also improved world class cyclists' peak leg power output (Kordi et al., 2020). Together, the data suggest that similarity in muscle activation during the training (resisted sprinting) and the target tasks (unresisted, 'real life' sprinting) affords the greatest specificity hence effectiveness of training but it is unclear if RT-induced neuroplasticity acts as the enabling mechanism to improve sprint times.

4.2 Distance running performance. Distance runners also use RT to improve distance-running times (Trowell et al., 2019). The assumption is that RT improves trained muscle groups' MVC force and athletes' ability to activate these muscles. Improved activation would increase angular acceleration of the leg during swing, increasing running speed. However, there is no correlation between training-induced increases in MVC extensor torques and running economy following RT, implying that improvements in hip and knee joint torques might contribute to increase maximal but not submaximal running speed used during distance races (Alcaraz-Ibanez and Rodriguez-Perez, 2018; Macadam et al., 2019; Trowell et al., 2019; Young, 2006).

RT-induced neuroplasticity could enable faster running by modifying inter-muscular coordination within a muscle group and inter-joint coordination in movements that are specific for, and similar to, the training exercises (Enoka, 1988; Folland and Williams, 2007). The

modifications include increases in selective and synergistic muscle activation and decreases in antagonist muscle activation. Such changes could reduce the neural drive needed for submaximal contractions. Increases in motor neuron excitability after RT could also reduce motor unit discharge rate compensated by motor unit recruitment during prolonged submaximal exercise (Vila-Cha et al., 2012). RT would thus reduce the metabolic cost of each step. However, muscle activation during running has never been measured after RT in competitive runners. It is therefore unknown if RT could improve ground force application through altered coordination or would modify motor unit recruitment, leading to improved metabolic cost and running economy, fatigue resistance, and ultimately running speed.

Indeed, the evidence seems to favor a mechanical rather than a neural mechanism of RT improving distance-running times. Seemingly against the principle of training specificity, *isometric* RT improved distance-running performance (Lum and Barbosa, 2019). This is possible because as the Achilles tendon becomes stretched in the stance phase and muscle fibers of the knee and ankle extensors are in an isometric state (Bohm et al., 2018; Roberts et al., 1997), thereby increasing push-off force. Lower extremity RT also improves running economy by 4% due to increased tendon stiffness that results in increase in elastic energy and a redistribution of muscular output while running (Albracht and Arampatzis, 2013). A combination of heavy and explosive RT training can improve neural control, muscle force, and elasticity, which in turn could shorten ground contact times and improve running economy (Balsalobre-Fernandez et al., 2016; Blagrove et al., 2018; Johnston et al., 1997; Paavolainen et al., 1999), although the relationship between these changes is inconsistent (Blagrove et al., 2018; Jung, 2003). Distance runners certainly experience improvements from RT, even though neuroplastic adaptations cannot be ruled out, the evidence for performance improvements through mechanical changes is more likely.

4.3 RT-induced neuroplasticity in trained athletes. Sale suggested that neural adaptations to RT plateau after the initial weeks of RT when hypertrophy becomes the predominant determinant of strength gains (Sale, 1988). Cross-sectional studies do not address this issue, but provide clues that neuroplastic changes continue past the arbitrary initial period. For example, reductions in the force evoked by TMS during muscle contraction suggested that RT-induced neuroplasticity was evident in RT-trained healthy adults who continued RT (del Olmo et al., 2006). Chronically RT-trained healthy adults displayed abolished TMS-evoked cortical inhibition during voluntary forces of $\geq 40\%$ MVC (Lahouti et al., 2019). In RT-trained individuals who continued RT, motor neuron adaptations continued (Pearcey et al., 2014) and antagonist muscle activation was reduced after 4 years of RT, suggesting that inter-muscular coordination is a longer-term neural adaptation (Balshaw et al., 2019). In contrast to these data in support of neuroplastic changes extending over years after the start of RT, agonist muscle activation measured by sEMG did not differ after 12 weeks or 4 years of RT, however changes in co-activation were not examined. A case series of two power lifters and one weight lifter with many years of RT showed improvements of up to 10% in maximal back squat strength without muscle hypertrophy (Zourdos et al., 2016). RT-induced changes in markers of neuroplasticity were shown to continue in elite junior skiers (<15 years) who improved vertical jump performance alongside (but not correlated with) increase in spinal excitability, suggesting increases in motor neuronal output with long-lasting RT (Taube et al., 2007). The evidence shown here makes the plateau proposed by Sale seem unlikely.

4.4 RT-induced neuroplasticity in prepubertal athletes. Due to a lack of circulating androgens in prepubertal children, RT-induced gains in MVC force are primarily caused by neural rather than muscular factors (Behringer et al., 2011; Granacher et al., 2011). For example, RT for 20 weeks increased VA of the elbow flexors and knee extensors measured by twitch interpolation in 9-11-year-old prepubertal boys (Ramsay et al., 1990). However, no study has reported correlated neuroplastic changes and concomitant increases in MVC force and/or motor skills. Nonetheless, given their hormonal profile, it is likely that RT-induced neuroplastic changes underlie the increases in athletic performance after RT in these children. Future studies could determine the relationship between RT-induced neuroplasticity and functional performance in these children in paradigms that combine RT with event-specific practice known to induce neuroplasticity (Behm et al., 2008).

5 Recommendations

Historical studies introduced the idea that neuroplasticity underlies the rapid initial increases in MVC force and gross motor performance after RT. In an effort to provide an update of this idea, we reviewed and extracted experimental evidence from previous reviews concerning the functional relevance of RT-induced neuroplasticity in increasing motor performance. If RT-induced neuroplastic changes did occur, the majority of studies reported a ‘parallel’ increase in changes in markers of neuroplasticity, MVC force, or gross motor performance. However, we found little evidence that individual variations in RT-induced performance gains were associated with individual variations in markers of neuroplasticity. We therefore make the following recommendations to improve the efficacy of exercise training athletes perform and rehabilitation patients receive. We make these recommendations with the understanding that correlation is not causation yet it serves as an important starting point for (causal) mediation analyses. Such models could serve as basis for an update of the descriptive Sale model the field has been relying on for some 40 years.

5.1 We recommend the use of advanced methods for the identification of neuroplasticity and its functional relevance. These could include the quantification of synergist and antagonist muscle activation sEMG-to-sEMG coherence, sEMG-EEG cortico-muscular coherence, sEMG-based synergy and wavelet analyses instead of the use of single-muscle detection sEMG approaches, to determine RT-induced neuroplasticity. These methods might provide new insights into RT-induced neuroplasticity in the form of intra- and inter muscle-group coordination, corticomuscular coupling, and in the organization of synaptic input to motor neurons (Aagaard et al., 2020). We recommend the use of multi-array sEMG-derived motor unit recordings to longitudinally track changes in single motor unit activation across multiple sessions (Casolo et al., 2020; Del Vecchio et al., 2019a; Del Vecchio et al., 2019b);(Vila-Cha et al., 2012; Vila-Cha et al., 2010). We recommend the determination of TMS and peripheral nerve stimulation outcomes especially during muscle contraction instead of rest (Taube et al., 2020), the combination of stimulation-based measurements with EEG and MRI, providing a new methodological-analytical framework (Raffin et al., 2020), and the exploration of alternative paths for RT-produced neuroplasticity such as the lateral reticulospinal tract (Baker and Perez, 2017; Choudhury et al., 2019; Fernandez-Del-Olmo et al., 2014; Glover and Baker, 2020).

5.2 We recommend to place the data derived by these methods into mediation analyses to determine the causative links between RT-induced neuroplasticity and improvements in MVC force or gross motor performance in health and disease (Nuzzo et al., 2019a; Steele et al., 2020; Textor et al., 2016; Tollár et al., 2019a) (Fig. 2A); such analyses should be performed before, during (i.e., longitudinal measurements), and after RT (Hortobágyi et al., 2011). We recommend to estimate the relative contribution of these outcomes to motor performance before, during, and after RT through hypotheses testing using (causal) mediation analyses (Fig. 2B).

5.3 Brain network analyses would be highly informative after RT even in healthy young adults as controls to contrast with the functional role played by network adaptations in the recovery of motor function in PwPD, PwMS, and PwS (August et al., 2006; Bajaj et al., 2015; James et al., 2009). Network changes following RT could additionally be informative about the localization and extent of neuroplasticity in these patients and this could be assessed through (causal) mediation analyses (Bologna et al., 2020; Hallett et al., 2020) (Fig. 2C). This recommendation is supported by data suggesting that RT-induced neuroplasticity could reduce structural and functional disconnections caused by lesions in PwS and that RT-improved connectivity predicts motor and behavioral changes (Salvalaggio et al., 2020).

5.4 We recommend to examine retention and transfer of the skill developed by RT. Notwithstanding animal data (Remple et al., 2001) and the invariance in the spatial and temporal structure of single and multi-joint exercises, RT often involves skill learning (Lundbye-Jensen et al., 2005). Retention and transfer are hallmarks of motor learning (Dayan and Cohen, 2011; Krakauer et al., 2019; Tablerion et al., 2020; Wanner et al., 2020). Such studies are needed because there is very little data on the relationship between neuroplastic detraining, mal-adaptation, and strength loss following a retention period. To increase the specificity of these measurements, the inclusion of an active control group could confirm that the RT stimulus and not just non-specific contractile activity giving rise to neuroplasticity. This recommendation is supported by a demonstrated need to examine ‘... specific neural changes that might result from exercise prescriptions that are specifically designed to induce certain functional changes’ in health and disease (Sandroff et al., 2020).

5.5 We recommend to determine the effects of RT on gross motor performance. Some studies suggest that training the target movement itself with loads or against resistance may be beneficial for example, to increase motor performance in older adults with (Messa et al., 2019) and without PD (Brach et al., 2017; Brach and Vanswearingen, 2013; Brach et al., 2020), improve athletic performance in judoka (Blais and Trilles, 2006; Helm et al., 2018a; Helm et al., 2018b), rugby (Harrison and Bourke, 2009), kayaking (Logan et al., 1997), and sprint cycling (Kordi et al., 2020). Therefore, to improve gross motor performance by RT, we recommend to train target movements with loads or against resistance. Such a RT modality ensures that the ensuing neuroplasticity is functionally relevant because the underlying neural adaptations become the enabling mechanisms for the incorporation of newly acquired muscle strength in the target movement. This is possible due to the similarities between 1) the spatial and temporal structure of the training and the target movements, and 2) between brain and muscle activation patterns during movement preparation and execution in the training and target movements such as walking, jumping, throwing, and reaching.

6 Conclusions

Sale's model of RT-induced neuroplasticity has served outstandingly for many decades. We recommend updating the model with (causal) mediation analytical, hypothesis-driven models. There is a need for studies that examine the association between changes in muscle function, markers of neuroplasticity, and indices of muscle and tendon architecture in response to RT through causal mediation analysis (Nuzzo et al., 2019a; Steele et al., 2020; Tollár et al., 2019a). Akin to aerobic training (Voss et al., 2020), there is a need to determine the relationship between changes in performance outcomes and changes in functional and effective (structural) connectivity measures within the nervous system. This could be explored using electrophysiological methods and brain imaging before and after RT, and after a period of detraining using an active control group. In addition, the relationship between changes in indices of neural adaptations to RT and the increases in muscular performance could be complicated by early changes in skeletal muscle structure that amount to ~10% (DeFreitas et al., 2011; Folland and Williams, 2007; Seynnes et al., 2007; Stock et al., 2016); therefore, inclusion of muscle-tendon architecture is warranted in future studies and mediation models. As the time-course of neural, tendon and muscle adaptations to RT differ (Csapo et al., 2011; Kubo et al., 2010) only studies incorporating a combination of such measures will be successful in determining the holistic picture of how RT improves gross motor function across the lifespan in performance, health and disease.

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Table 1. *Definition of key terms and markers of plasticity*

Key term (abbreviation)	Definition
Corticospinal excitability, CSE	Likelihood and magnitude of responses to transcranial magnetic stimulation of excitable structures of the corticospinal tract, from the primary motor cortex to muscle.
Gross motor performance	Multi-joint functional activities such as walking, jumping, throwing.
Hoffman reflex, H-reflex	Response to weak peripheral electrical nerve stimulation, an estimate of the excitability of spinal motoneurons and Ia-afferent presynaptic inhibition.
Maximal compound muscle action potential, Mmax	Response to maximal intensity peripheral electrical nerve stimulation, representing the sum of dispersed action potentials of the motor units under the territory of a recording electrode on the skin surface.
Maximal voluntary contraction force, MVC force	Force generated during a maximal effort muscle contraction at a single joint against a resistance with or without continuous feedback.
Motor unit discharge rate	Frequency at which motor units discharge action potentials during a muscle contraction.
Motor unit recruitment	Number of active motor units during a muscle contraction.
Movement related cortical potentials, MRCP	Negative surface potentials detected at the scalp during voluntary movements that reflect cortical activity.
Neuroplasticity / Neural adaptations	Structural and functional modifications in specific brain and spinal circuits.
Resting-state connectivity	Associations between the fluctuations in the hemodynamic signal of brain regions.
Short-interval intracortical inhibition	Response to paired pulse transcranial magnetic stimulation, reflecting the efficacy of intracortical inhibition mediated by low-threshold inhibitory GABA-a intracortical neurons.
Silent Period	Response to single pulse transcranial magnetic stimulation, reflecting the efficacy of inhibition mediated by GABA-b intracortical neurons.
Surface electromyographic activity, sEMG	Sum of action potentials discharged by recruited motor units under the territory of EMG electrodes during a muscle contraction.
Volitional wave, V-wave	Response to supramaximal intensity peripheral nerve during a maximal voluntary contraction, reflecting the efferent spinal motoneuron output to muscle.
Voluntary activation, VA	Computed response to maximal intensity, millisecond-duration peripheral nerve stimulation at rest and during maximal voluntary muscle contraction, reflecting the ability of skeletal muscle to become activated by voluntary command.

Figure 1. Potential sites of and methods to assess neuroplasticity induced by resistance training. We address resistance training induced neuroplasticity and its functional relevance at: Site A in sections 2.2, 2.3, 2.4 and 2.5; Site B in sections 2.2, 2.3, and 2.4, and at Site C in sections 2.1 and 2.3. Dashed lines symbolize connectivity between frontal (cognitive), motor, and temporal (memory) areas known to become modified by resistance training. The vertical arrows in the text denote the direction of changes (increase, decrease, no change). This simplified model does not show several additional potential sites where adaptations to resistance training could occur such as corticoreticular connections, reciprocal reticular connections, reticulospinal projections to interneurons, corticospinal projections to interneurons, and corticomotoneuronal synapses (see Glover and Baker 2020). fMRI, functional resonance imaging; EEG MRCP, electroencephalographic movement related cortical potentials; TMS, transcranial magnetic stimulation; VA, voluntary activation; V-wave, voluntary wave evoked by peripheral nerve stimulation; H-reflex, Hoffman-reflex; sEMG, surface electromyography; HDsEMG, high-density sEMG.

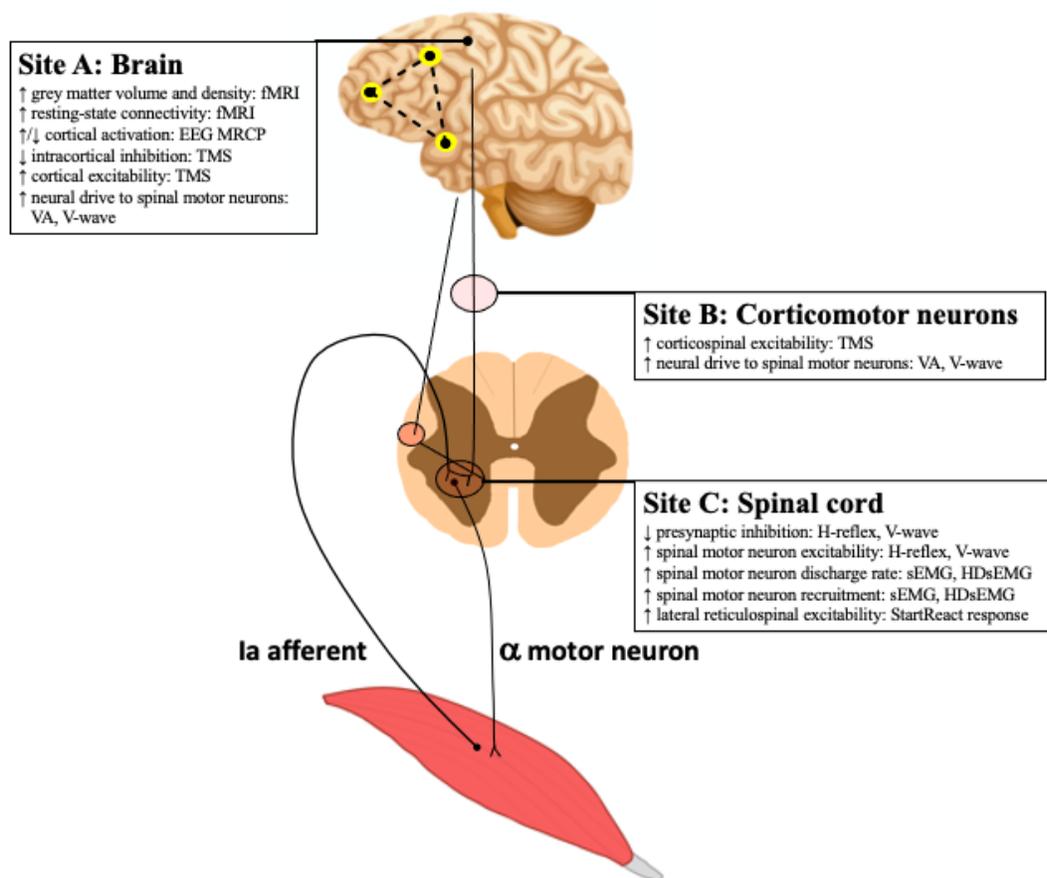


Figure 2. Directed acyclic graphs (DAG) illustrating the update and extension of the Sale model. 2A. A DAG, illustrating causal paths between increases in maximal voluntary isometric (MVC) force after resistance training. Experimental data modify the descriptive Sale model, assigning putative roles to neural and musculotendinous factors in the increases in MVC force during the initial phases of resistance training. Theory-based mediators include motor unit discharge rate, motor unit number, hypertrophy markers, and tendon stiffness. Potential confounders are not shown but might include age, baseline MVC force, baseline muscle size, and gender.

Fig. 2A.

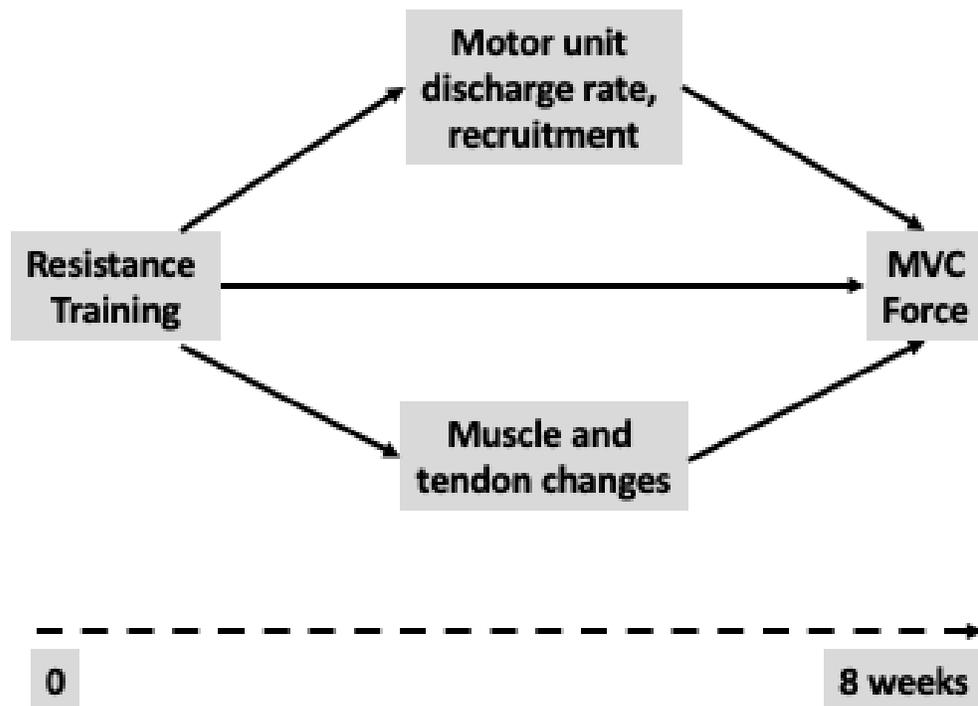


Fig. 2B. DAG further specifying mechanistic paths illustrated in Fig. 2A, between resistance training and increases in MVC force. Adaptations in central drive are assessed by determining the relationship among magnetic brain stimulation outcomes at baseline (0), during (4), and after (8 weeks of) resistance training as mediators increases in MVC force. Repeated measurements would help to determine the relative contribution of those different outcomes to motor performance at different stages of training by using mediation analysis and if any causative adaptation to RT changes with time. Magnetic brain stimulation outcomes: Motor threshold (MT); motor evoked potential (MEP) size, intracortical inhibition (IHI), silent period (SP). Structural equation modeling identifies the relationship between individual brain stimulation outcomes underlying the time course and relative role of these outcomes in increases in MVC force.

Fig. 2B.

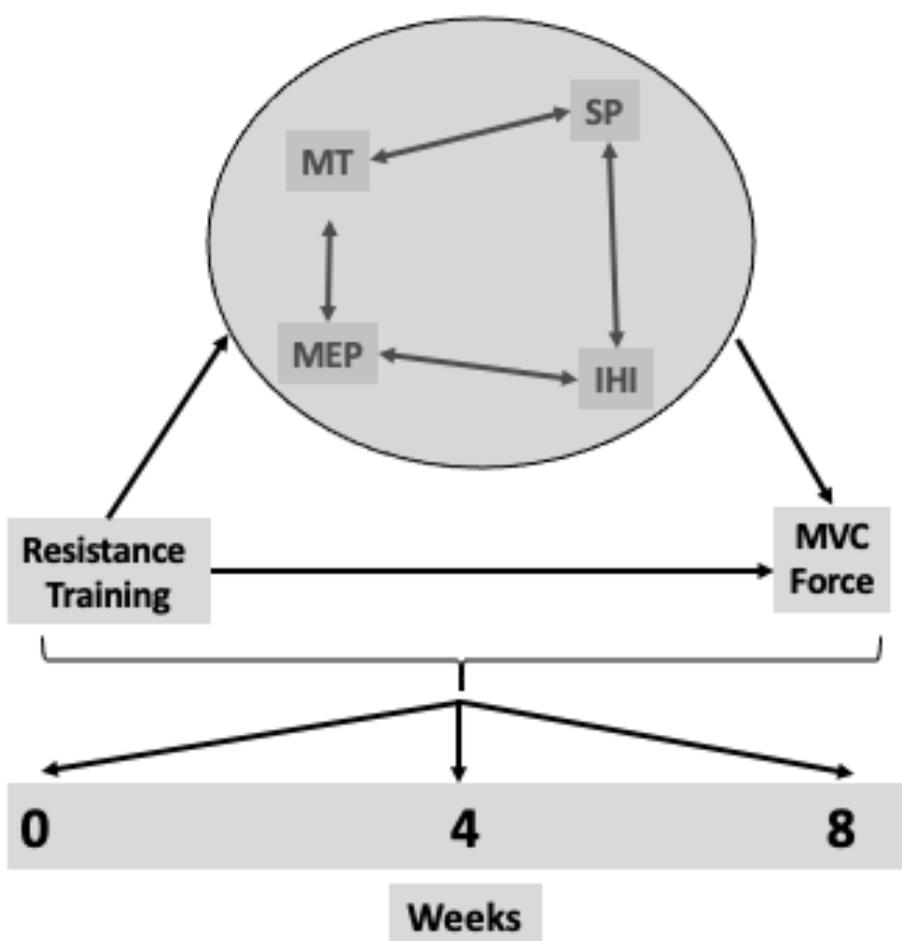


Fig. 2C. DAG illustrating mechanistic paths through which resistance training can improve MVC force and clinical symptoms through functional and structural network alterations in Parkinson's disease based on (Bologna et al., 2020). Resistance training activates the primary motor and sensorimotor cortices, basal ganglia, and cerebellum involved in generating and controlling the slowed, weak, narrow amplitude, and error-prone sequences in voluntary movements. Resistance training variables (contraction intensity, duration, frequency, repetition of individual movements, variation in force induced by perturbations, moving weighted sensory implements) (Tollár et al., 2019a; Tollár et al., 2019b) affect brain and muscle activation duration, variables that can in turn be tuned to reduce individual clinical dysfunctions. The DAG illustrates compensatory paths through which resistance training could act while ON-dopamine. The oval shape identifies the putative network examined for activation and connectivity by brain imaging and its confounder-adjusted relationship with increases in MVC force. The upper DAG highlights the motor loop and lower DAG depicts cerebello-thalamo-cortical network involved in movement feedback loop. Confounders are differences in baseline clinical and motor symptoms, drugs, comorbidities, age, and gender. The DAGs extend the Sale model to clinical conditions using a mechanistic instead of a descriptive approach. M1, primary motor cortex; S1, sensorimotor cortex; BG, basal ganglia; CL, cerebellum; MVC, maximal voluntary contraction.

Fig. 2C.

