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Exercise as Medicine for the Treatment of Brain Dysfunction: Evidence for Cortical Stroke, Cerebellar Ataxia, and Parkinson's Disease

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This review addresses the role of exercise as an intervention for treating neurological disease. It focuses on three major neurological diseases that either present in acute or neurodegenerative forms—Parkinson's disease, cerebellar ataxia, and cortical stroke. Each of the diseases affects primarily different brain structures, namely the basal ganglia, the cerebellum, and the cerebrum. These structures are all known to be involved in motor control, and the dysfunction of each structure leads to distinct movement deficits. The review summarizes current knowledge on how exercise can aid rehabilitation or therapeutic efforts. In addition, it addresses the role of robotic devices in enhancing available therapies by reviewing how robot-aided therapies may promote the recovery for stroke survivors. It highlights recent scientific evidence in support of exercise as a treatment for brain dysfunction, but also outlines the still open challenges for unequivocally demonstrating the benefits of exercise.

Keywords: ataxia, basal ganglia, cerebellum, cortex, human, movement

Exercise as an intervention for treating neurological disease has received widespread attention in the last two decades. There is a growing body of scientific studies that outlines the potential benefits of exercise for treating various forms of brain or central nervous system dysfunction. When considering exercise prescriptions as a treatment for neurological disease, one first needs to question what purpose shall be achieved with exercise. Is the main emphasis of exercise to avoid the comorbidities of brain dysfunction? Or, shall exercise serve as a therapeutic intervention to actually treat neurological disease? And, if so, is the goal of exercise to restore lost function, or to maintain existing function? An answer to these questions is important when evaluating scientific evidence on exercise and brain dysfunction, because it drives the decision of what type of exercise is most beneficial for treating a particular neurological condition. For example, if the goal of exercise is to counter the comorbidities that can be associated with neurological disease such as muscle atrophy, or decreased cardiac function due to increasing immobility, then the aim of exercise might be to gain muscular strength and to improve cardiopulmonary or cardiovascular function. If the emphasis is to improve balance function and to reduce a patient's risk of falling, one may opt to employ a training program that focuses on improving neuromuscular function and sensorimotor control by exposing the patient to guided and safe movement scenarios that challenges neurophysiological mechanisms of postural control. Finally, the goal of exercise might be to directly intervene in the neurological disease process. In this case, can exercise aid neuroprotection or regeneration? That is, does it promote neural processes that release neuroprotective agents or enhance the regeneration of neural tissue? Finally, exercise needs to conform to the type of neurological condition. In other words, one needs to consider if the disease is caused by an acute event, such as stroke or traumatic brain injury, or if it is a neurodegenerative disease. In the former case, the reasoning behind prescribing exercise will be to restore lost function, while the latter will be to maintain function. This review will focus on three major neurological diseases that either present in acute or neurodegenerative forms—Parkinson's disease, cerebellar ataxia, and cortical stroke. Each of the diseases primarily affects different brain structures, namely the basal ganglia, the cerebellum, and the cerebrum. These structures are all known to be involved in motor control, and the dysfunction of each structure leads to distinct movement deficits. It is the aim of this review to summarize the current knowledge on how exercise can aid the rehabilitation or therapeutic effort, and to highlight distinct scientific evidence in support of exercise as a treatment for brain dysfunction, while also outlining the still open challenges for establishing and unequivocally demonstrating the benefits of exercise.

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Exercise and Parkinson's Disease

Parkinson's disease (PD) is a chronic neurodegenerative disease affecting the basal ganglia, a set of five subcortical nuclei. The disease leads to a loss of dopaminergic neurons in one of the nuclei, the *substantia nigra* (Bradshaw & Mattingley, 2013; Lima, Scianni, & Rodrigues-de-Paula, 2013), that ultimately causes dopamine deficiency in the striatum (Dauer & Przedborski, 2003), the input nuclei of the basal ganglia (see Figure 1). The onset of the disease is typically late middle adulthood. It is estimated that over 7 million people worldwide are suffering from PD (Uhrbrand, Stenager, Pedersen, & Dalgas, 2015), with its incidence rate expected to rise as human life expectancy increases. PD affects both motor and nonmotor function. The cardinal motor symptoms include a tremor at rest, rigidity (upregulated muscle tone), and slowness of movement (*bradykinesia*). PD is known to be associated with a deterioration of muscle strength, cardiorespiratory fitness, balance, and postural instability, as well as a slowed gait with freezing episodes (Bradshaw & Mattingley, 2013; Dauer & Przedborski, 2003; Lima et al., 2013; Uhrbrand et al., 2015). Nonmotor symptoms include increased fatigue, sleep disturbances, depression, an altered sense of smell, and decreased proprioceptive function (Conte, Khan, Defazio, Rothwell, & Berardelli, 2013; Konczak et al., 2009; Patel, Jankovic, & Hallett, 2014; Uhrbrand et al., 2015).

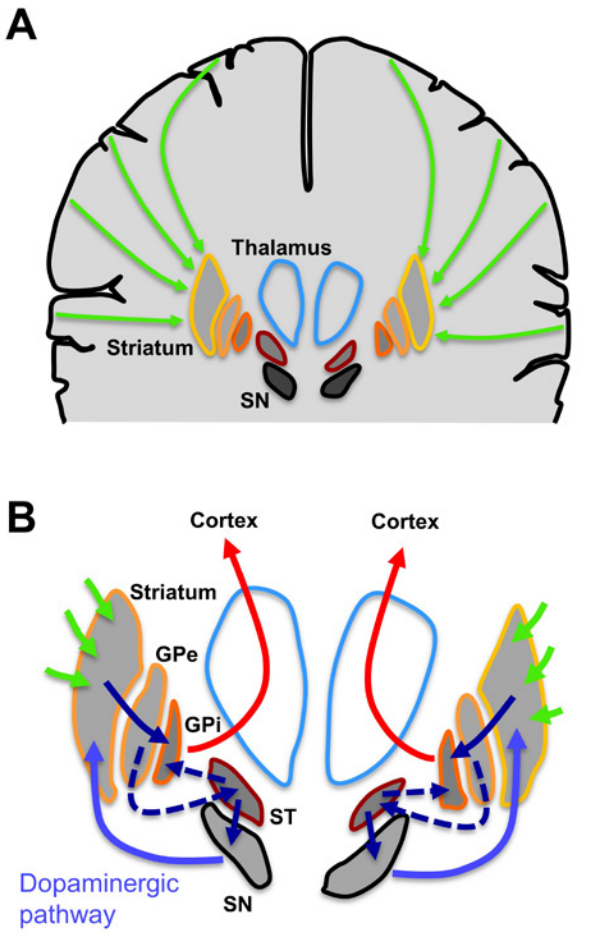

Figure 1 — Overview of the neuroanatomy of the basal ganglia. (A) The basal ganglia are comprised of five different nuclei: striatum, globus pallidus externus (GPe), globus pallidus internus (GPi), subthalamic nucleus (ST), and the substantia nigra (SN). The striatum is the input structure of the basal ganglia and receives input from nearly all areas of the cortex. (B) Processing diagram of signals within the basal ganglia. One distinguishes a *direct pathway* (striatum → GPe → GPi) and the other an *indirect pathway* (striatum → GPe → ST → GPi). The dopaminergic pathway from SN to striatum is altered in Parkinson's disease.

From a movement perspective, the dopamine deficiency in the striatum ultimately affects motor unit recruitment leading to reduced muscle strength (Allen, Canning, Sherrington, & Fung, 2009; Cano-de-la-Cuerda, Pérez-de-Heredia, Miangolarra-Page, Munoz-Hellín, & Fernández-de-las-Penas, 2010; Lima et al., 2013), which then triggers a cascade of other health problems, such as reduced levels of physical activity and problems in balance control. While dopamine replacement therapy and deep brain stimulation of targets in the basal ganglia are firmly established therapies that help to ameliorate motor symptoms such as bradykinesia and tremor, they are often less effective in improving balance and gait function especially at advanced stages of the disease. In this context, exercise as an adjuvant form of therapy has been advocated with the aim to counter the many comorbidities associated with physical inactivity (Lima et al., 2013; Uhrbrand et al., 2015). In addition, another important focus of exercise as an intervention for PD is to understand to what extent physical activity can slow down or even stop neural decline by directly intervening in the neural pathomechanism of PD. Resistance training, endurance training, or others forms of intensive training, such as yoga, dancing, and boxing, have been studied as potential exercise therapies for PD (Brienesse & Emerson, 2013; Uhrbrand et al., 2015). Because PD has a major influence on postural stability and balance, the majority of exercise studies focused on the lower limb or whole body training.

Resistance or Endurance Training?

Resistance exercises to gain strength and to train neuromuscular mechanisms involved in balance control are an obvious candidate to be applied to PD populations. Indeed, numerous studies investigated how people with PD respond to resistance training. For example, a recent report showed that a 12-week intervention program (45 min; twice a week) led to improvements in leg and hip muscle power (Paul, Canning, Song, Fung, & Sherrington, 2014). In another exercise study, Shulman et al. (2013) recruited 67 PD patients to perform three types of interventions (high- and low-intensity treadmill, stretching, and resistance exercise) for three times a week for 3 months. High-intensity and low-intensity treadmill

endurance training mildly increased cardiovascular fitness (7–8% increase), although this difference was statistically not significant. However, resistance training and stretching significantly improved muscle strength by 16% in this group of PD patients. The authors suggest that a training consisting of a combination of treadmill and resistance exercise would be most beneficial for PD patients (Shulman et al., 2013). Both of the above studies indicate that people with PD may show cardiovascular or skeletal muscular adaptations to training that are similar to older adults without PD. While these physiological responses to exercise are welcome, one needs to ask if such physiological adaptations also lead to meaningful changes in motor function.

There is indeed emerging evidence indicating that resistance training improves the performance of various motor systems. For example, Hass, Buckley, Pitsikoulis, and Barthelemy (2012) showed that a 10-week progressive resistance training program may improve gait kinematics such as stride length and gait velocity in PD. Solid support for the usefulness of resistance training comes from a phase II clinical trial that followed two groups of PD patients for 24 months (Corcos et al., 2013). One group received so-called *progressive resistance exercise* (PRE) that included stretching, balance, and a weight-lifting component, while another group received a *modified fitness counts* program (mFc) that also included stretching, balance, and strengthening exercises. The mFc is an exercise program recommended by the National Parkinson Foundation. However, the strengthening exercises of this program are not progressive and do not involve regular weight-lifting with loads comparable to those experienced by the PRE group. Patients exercised twice a week with 51 participants completing the 24-month intervention. Both the mFc and PRE group showed significant improvements in section 3 of the Unified Parkinson's Disease Rating Scale (UPDRS-III). This section is part of a larger clinical rating scale with UPDRS-III focusing on the motor signs of PD. In addition, biomechanical variables of muscle strength (elbow flexor torque) and movement velocity (elbow joint angular velocity) also improved (see Figure 2). While both groups made rapid gains within the first 6 months, these gains were not sustained in the mFc group, but were maintained in the PRE group.

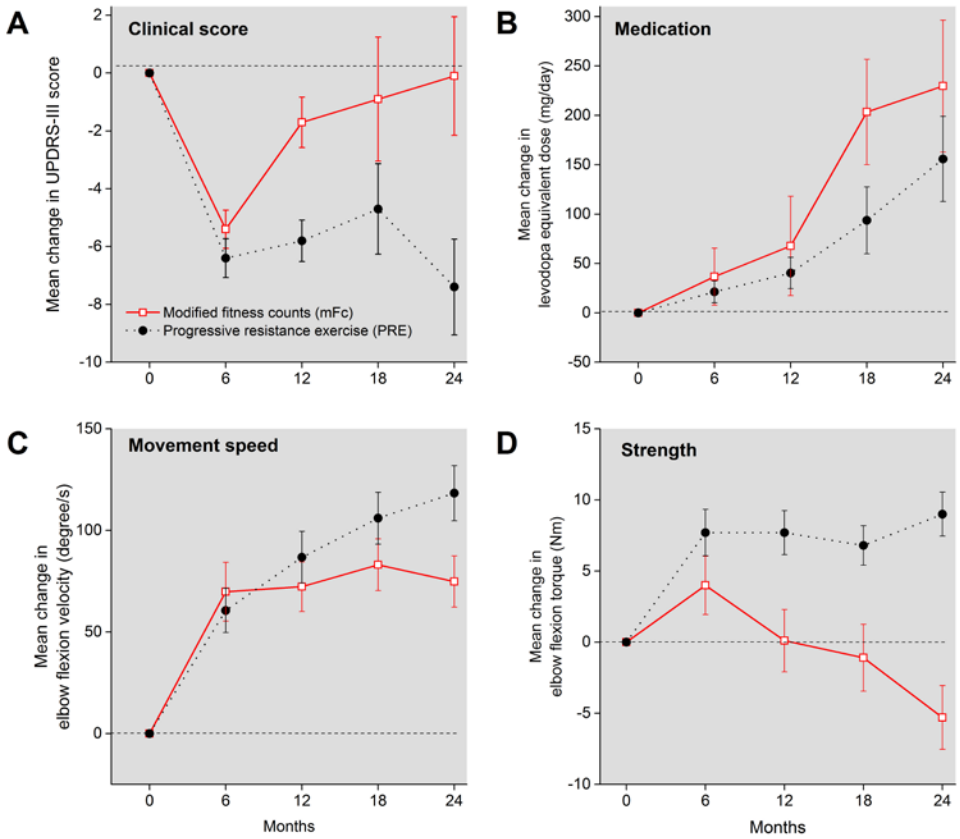

Figure 2 — Effects of exercise on motor symptoms and medication in Parkinson's disease. PRE = progressive resistance exercise; mFc = modified fitness counts program. Shown are the mean changes in four outcome variables measured at 0, 6, 12, 18, and 24 months. (A) Unified Parkinson's Disease Rating Scale motor subsection score (UPDRS-III). The subsection assesses 14 aspects of motor function (low score = less severe; maximum score = 56). (B) Levodopa equivalent dosage. (C) Elbow joint angular velocity during flexion. (D) Elbow flexor torque. Data derived from Corcos et al. (2015).

In summary, there is strong evidence that resistance training can improve muscle strength in PD. There is moderate evidence that it improves cardiorespiratory fitness in PD populations. Finally, there is mild to inconsistent evidence that intensive exercise therapy (endurance or resistance) has beneficial effects on balance and walking performance. (For further reviews, see Brienesse & Emerson, 2013; Uhrbrand et al., 2015.)

Exercise as a Neuroprotective Therapy for PD

While there is growing evidence that exercise may positively influence cardiovascular or skeletal muscle function in PD that leads to meaningful changes in the quality of life, another important question about the value of regular exercise in PD is to ask whether it directly influences neural function. Specifically, does exercise have a neuroprotective effect that may slow down the known processes of neurodegeneration in PD? Currently, no drug treatment is available that unequivocally has proven neuroprotective properties.

At present, we lack firm evidence from human trials that exercise acts like a neuroprotective agent in PD. However, studies on Parkinsonian animal models reveal that vigorous exercise may provide protection from dopaminergic neurotoxins such as 1-methyl,4-phenyl,1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OH-DA) that are known to induce Parkinsonism. In these rodent studies, exercise was controlled using running wheels or treadmills. By its nature, these running exercises focused more on endurance than on the resistance aspect of training. The available related literature may be summarized as follows:

1. Parkinsonian signs can be markedly attenuated by endurance-related exercises (O'Dell et al., 2007; Tajiri et al., 2010; Tillerson, Caudle, Reveron, & Miller, 2003) in 6-OH-DA models of hemiParkinsonism.
2. Markers indicating the integrity of the dopaminergic terminals (Tajiri et al., 2010; Tillerson et al., 2003; Tillerson et al., 2002; Tillerson et al., 2001) or neurons (Tajiri et al., 2010) suggest a neuroprotective effect from exercise. However, this was not confirmed in one study (O'Dell et al., 2007).
3. Midbrain dopaminergic neuronal counts corroborated a neuroprotective effect from exercise in some (Ahmad, Park, Stenho-Bittel, & Lau, 2009; Gerecke, Jiao, Pani, Pagala, & Smeyne, 2010), but not in all, studies that used MPTP rodent models.
4. Effect is likely mediated by neuroplasticity and the expression of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) (Ahlskog, 2011).

Based on the available animal literature, it can be concluded that exercise potentially has neuroprotective effects for slowing down the neurodegenerative processes associated with PD. However, results of Parkinsonian animal models may not directly transfer to the human form of PD, because of differences in neuroanatomy and because the animal disease models do not exactly mimic the neurodegenerative process of human PD. Thus, while the current results of exercise as a neuroprotective therapy for PD are promising, we will need more solid evidence from carefully conducted human studies in the future.

Exercise and Cerebellar Ataxia

Ataxia refers to the observable dyscoordination of movement in the absence of muscular weakness. It is typically caused by damage to the cerebellum or by lesions that interrupt its afferent sensory input or the cerebellar efferent projections (see Figure 3A). The primary symptoms of cerebellar ataxia are signs of dyscoordination that can affect nearly every motor system. For example, it can lead to an unsteady and insecure gait, an overshooting of movement targets (*dysmetria)* that cause difficulties in executing fine motor skills (e.g., writing, eating or reaching, grasping), speech dysarthria, or problems in the control of eye movements (Bastian, 2011).

Cerebellar ataxia can either have a hereditary (chronic) cause or an acute onset. For acute onset cerebellar ataxia, the causes are primarily cerebrovascular accidents, hemorrhagic stroke, tumor, and trauma affecting the cerebellum. Hereditary or spinocerebellar ataxias are classified by chromosomal location and pattern of inheritance, including: *autosomal dominant*, in which the affected person inherits a normal gene from one parent and a faulty gene from the other parent; and *autosomal recessive*, in which both parents pass on a copy of the faulty gene. Over 30 genetic subtypes of spinocerebellar ataxia (SCA) have been identified. Hereditary ataxias are relatively rare, with estimated prevalence ranging between 0.1–11.2/10,000 people (Ruano, Melo, Silva, & Coutinho, 2014). Among the more common inherited ataxias are *Friedreich's ataxia* and *Machado-Joseph disease*—also called spinocerebellar ataxia Type 3 (SCA3).

To understand the mechanisms of recovery of motor function after cerebellar injury or the continued decline of motor function in hereditary ataxia, it is meaningful to briefly review the input and output projections of the cerebellum as well as its functional compartmentalization. Although the Latin meaning of cerebellum is "little brain," the cerebellum is estimated to contain substantially more neurons (101 billion) than the cerebrum (21–26 billion neurons) (Andersen, Korbo, & Pakkenberg, 1992; Pelvig, Pakkenberg, Stark, & Pakkenberg, 2008). It receives massive afferent projections via the spinocerebellar tract that carries signals from proprioceptive and tactile receptors to the cerebellum, in essence, providing it with information about the position and orientation of the body and its limbs, whether it is in contact with surfaces and objects in the environment. At the same time the cerebellum receives efferent signals from motor cortical areas, a so-called efference copy of

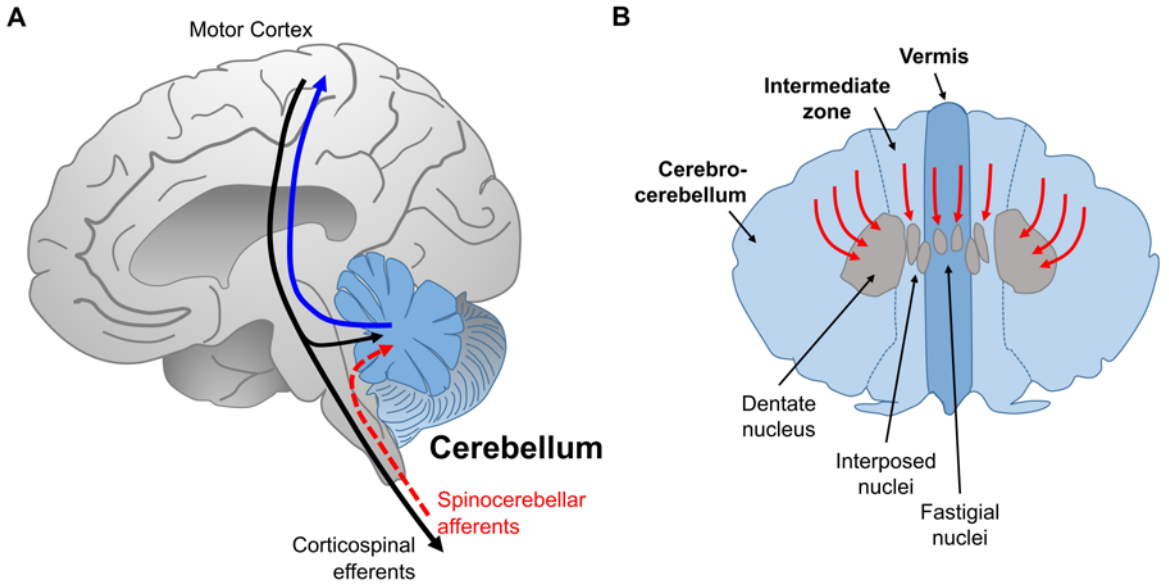

Figure 3 — Overview of the neuroanatomy of the cerebellum. (A) The cerebellum receives sensory afferent information via spinocerebellar projection and a copy of the efferent signals that motor cortical areas send to the spinal and brain stem motor neurons. (B) A two-dimensional representation of the cerebellum illustrating the three cerebellar zones (cerebrocerebellum = lateral zone; intermediate or paravermal zone; vermis = vermal zone). All neural inputs to the cerebellum are processed in the cerebellar cortex and with the Purkinje cells in the cerebellar cortex of each zone projecting to respective deep cerebellar nuclei (dentate nucleus, interposed nuclei, fastigial nucleus).

motor commands sent to the spinal and brain stem motor neurons (Tseng, Diedrichsen, Krakauer, Shadmehr, & Bastian, 2007; von Holst, 1973) (see Figure 3A for an overview of cerebellar connectivity).

Recovery After Acute Cerebellar Lesions

The effects of rehabilitation training in patients with acute cerebellar ataxia is an understudied area. There are two reasons that might explain why the role of exercise in the recovery from acute cerebellar ataxia has received little attention. First, the incidence rate of cerebellar infarction is relatively small—approximately 1.5 cases per 1,000 persons (Macdonell, Kalnins, & Donnan, 1987). That is, it is logistically difficult to obtain a large sample of acute cerebellar stroke cases in a single clinical site. Second, recovery from acute cerebellar injury is relatively fast when compared with cortical stroke with lesion location due to tumor resection or due to high variability of cerebellar stroke between patients, and thus the degree and course of recovery are variable. In general, motor recovery is fast, with the majority of gains in upper limb function occurring in the first 2 weeks after the acute phase (Konczak et al., 2010). However, recent research has demonstrated that the key determinants of the level of motor recovery in acute cerebellar ataxia are the lesion locations instead of lesion volume of the cerebellum (Konczak et al., 2010; Konczak, Schoch, Dimitrova, Gizewski, & Timmann, 2005). Specifically, if the cerebellar lesion involved the deep cerebellar nuclei, then motor recovery will be limited and ataxic signs will persist (see Figure 3B).

Exercise to Maintain Motor Function in Hereditary Ataxia

The prognosis for patients with hereditary ataxia is not positive. There is no cure for the disease and treatment options are limited. Behavioral or physical therapy interventions were thought to be ineffective, because of the progressive nature of the disease and because motor learning is known to be compromised and may even be abolished at the later stages of the disease (Maschke, Gomez, Ebner, & Konczak, 2004; Morton & Bastian, 2006; Thach & Bastian, 2004). However, recent studies have demonstrated that movement therapy can be beneficial to maintain and possibly slow down the decline in motor function.

At present we lack solid evidence from randomized controlled clinical trials. Available rehabilitation studies had limited samples and focused primarily on balance and coordination training. For example, Keller and Bastian (2014) recruited 14 middle-aged adult patients with degenerative cerebellar ataxia for a 6-week individualized home-based balance exercise training (20 min a day, 4–6 days a week). Because of the varying degree of ataxia among the patient group, exercise was tailored to the balance ability of each participant and based on their pretraining performance. Each balance program was developed by a physical therapist and included static

and dynamic exercise in sitting and standing positions. Retention of training effects was assessed at 2-week and 7-week follow ups. The results indicated that after 6 weeks of training, walking speed and kinematic gait measures such as stride length and double-limb support time improved significantly by 8–16% when compared with pretraining. The effects on gait were sustained at a 1-month follow up.

In another study that investigated the efficacy of exercise in spinocerebellar ataxia, 16 patients trained for 3 hr a week for 4 weeks, where the intensive coordination training was guided by a physical therapist. This in-clinic training was followed by 1-hr-a-day, self-monitored exercise for 8 weeks (Ilg et al., 2009). Training consisted of static and dynamic balance exercises, whole body movements, fall prevention strategies, and exercise to prevent contracture (i.e., the permanent shortening of muscle or joint tissues). Four assessments were performed: 8 weeks before, immediately before, directly after, and 8 weeks after training. Significant improvements in motor performance and reduction of ataxia symptoms were observed in clinical scores after training and were sustained at follow-up assessment. Patients with predominant cerebellar ataxia revealed more distinct improvement than patients in which the spinocerebellar afferent projections were involved (so-called afferent ataxia), indicating that the lack of proprioceptive information will negatively impact on motor learning and therapeutic success (see Figure 4).

To evaluate the long-term benefits and the translation of training to daily life, the motor performance and achievements in the activities of daily living were assessed in the same patient group 1 year after the initial 4-week training (Ilg et al., 2010). Despite a gradual decline of motor performance and the gradual increase of ataxic symptoms due to disease progression, the gains in motor performance and the achievements in activities of daily living largely persisted.

These initial results were later corroborated by a larger sample exercise study that monitored the short- and long-term effects of exercise in 43 patients with hereditary cerebellar ataxia (Miyai et al., 2012). The participants received balance, gait, muscle strength, and occupational training for activities of daily living every day for 4 weeks. At the end of training, clinical measures (Scale for the Assessment and Rating of Ataxia [SARA] and Functional Independence Measure [FIM]) had improved significantly between 10–20%. Patients also showed a reduced number of falls, and increased gait speed (16% improvement). After 2 months of detraining, the gains in SARA and FIM scores as well as in gait speed were still maintained. After 5 months the training-induced improvements in gait speed were still measurable, but the less sensitive clinical measures no longer indicated a training effect. When considering each patient's disease severity at the beginning of training, it became clear that those who were less affected at the beginning of training (lower SARA score) also showed more sustained training gains.

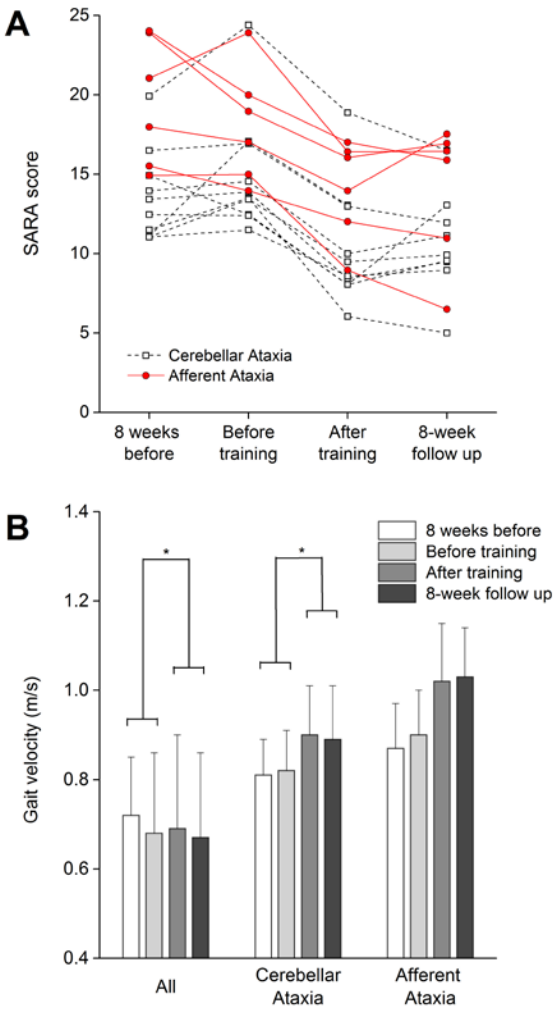

Figure 4 — Effects of exercise on clinical exam scores and gait speed in patients with degenerative cerebellar ataxia. Outcome measures were assessed 8 weeks before training, immediately before training, immediately after 4 weeks of training, and after 8 weeks self-monitored training. (A) Changes in clinical score (Scale for the Assessment and Rating of Ataxia [SARA]) at the four assessment times for each patient. Ten patients presented with primary hereditary cerebellar ataxia and six patients with afferent ataxia indicating spinocerebellar afferents involvement. (B) Mean and standard error of gait speed. Each bar indicates a different assessment time: white = 8 weeks before training, light gray = immediately before training, dark gray = immediately after 4 weeks of training, and black = after 8 weeks self-monitored training. Data derived from Ilg et al. (2009).

In summary, there is converging evidence that exercise induces improvements in coordination and gait function in patients with spinocerebellar ataxia. Knowing that the cerebellum plays a crucial role in motor learning, this is good news for patients with hereditary cerebellar ataxia, given the earlier skepticism of whether patients can even learn or relearn motor sequences required for activities of daily living. The empirical findings show that

functionally-relevant improvements can be seen after 4–8 weeks of training. However, considering the progressive nature of the disease, training gains may vanish quickly, indicating the need for continued, regular exercise. In addition, gains are better maintained in patients who are less affected, which also argues for initiating exercise regimens as early as possible after disease onset.

Based on the available knowledge, future therapies for treating hereditary ataxias should include exercises that aim to improve balance and to stabilize posture, which is imperative for maintaining an independent and functional gait. Moreover, exercise programs for patients with cerebellar ataxia need to consider (a) the different disease types (e.g., acute type or chronic type), (b) the disease stage (e.g., acute or chronic, or early, mild, or severe stage of neurodegeneration), (c) the frequency and accessibility of a training program, and (4) its safety (Synofzik & Ilg, 2014).

Exercise and Cortical Stroke

Cortical stroke is an acute vascular injury such as a cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage (Sacco et al., 2013). Stroke is the fifth leading cause of death in the United States, affecting an estimated 6.4 million Americans with nearly 800,000 new cases of stroke every year (Mozaffarian et al., 2016). The clinical characteristics of stroke are diverse, but a common impairment caused by stroke affecting the medial cerebral artery is motor impairment (Rathore, Hinn, Cooper, Tyroler, & Rosamond, 2002). The cardinal motor signs of stroke include: paralysis or plegia, flaccidity (downregulated tone) in the acute stage, spasticity (upregulated tone), and slowness (bradykinesia). Conventional physical or occupational therapy interventions for stroke rehabilitation may include strength, balance, coordination, stretching, weight-bearing, and manual dexterity exercises (e.g., grasping) as well as practicing functional tasks (Wang, Zhao, Zhu, Li, & Meng, 2011). There is a substantial body of research on the efficacy of stroke therapy and what type of exercise and training regimen are most effective in promoting recovery. It is beyond the scope of this article to comprehensively review this literature (for recent detailed reviews see Hatem et al., 2016; Hornby, Moore, Lovell, & Roth, 2016). Instead, we will focus on the use of robotic devices for treating upper extremity function after stroke.

Robotic Rehabilitation in Stroke

Rising health care costs are a main driver for the introduction of robotic devices to aid the motor recovery after stroke. Conventional, therapist-guided treatment is expensive and thus is often limited in intensity and duration. Robotic rehabilitation therapy may present a cost-effective alternative or augment conventional therapies (Lum, Reinkensmeyer, Mahoney, Rymer, & Burgar, 2002) by providing high-intensity training opportunities for patients without the constant supervision of a therapist (Chang & Kim, 2013). In addition, rehabilitation robots often have a series of in-built sensors that allow therapists to objectively monitor therapeutic success by assessing changes in movement amplitude, speed, direction, or joint coordination patterns, and they allow for the introduction of tightly controlled perturbations into therapy (Hidler & Sainburg, 2011). In general, rehabilitation robots can be divided into assistive and therapeutic categories. The purpose of utilizing *assistive robots* is compensation of the lost function, whereas *therapeutic robots* are mostly used for task-specific training (Lum, Godfrey, Brokaw, Holley, & Nichols, 2012). With respect to motor training, two main classes of robotic devices are available. End-effector devices that apply mechanical forces to distal limb segments and exoskeleton-type devices that are "worn" by the patient and where the robot joint axes are aligned with the joint anatomical axes of the wearer (e.g., see Figure 5). End-effector type robots have the advantage of easy set-up but provide limited control of the proximal limb joints, which can result in abnormal movement patterns. In contrast, exoskeletons provide direct control of individual joints and can guide limb movement and thus minimize the appearance of abnormal posture or movement patterns. Their construction, however, is more complex and they are generally more expensive than that of the end-effector robots.

Several forms of robotic neurorehabilitation can be distinguished (Orihuela-Espina et al., 2016). Passive training occurs when the robot passively moves a patient's limb because the patient is unable to move the limb, while in active-assisted training the robot assists the patient in the voluntary contraction of muscles. Finally, in active-resistive training, the robot provides forces that resist the desired movement and the patient generates muscle forces that overcome the resistance.

Robot-assisted therapy has been used for the functional recovery of both the upper and lower limbs during the acute and chronic stages of recovery from stroke. Currently, several robotic devices are commercially available for training of the paretic hand and gait in stroke patients. The scientific evidence of the efficacy of robotic rehabilitation is still mixed. Studies on the clinical efficacy of rehabilitation exoskeletons are rare, especially for lower limb robotic devices. The extent of the associated neuroplastic changes are largely unmapped. Although over 30 upper limb exoskeletons are reported in the literature, only 11 of these devices have been tested in any patient population (Jarrasse et al., 2014).

In 2010 the American Heart Association (AHA) issued new guidelines for stroke care that state that robot-assisted therapy can provide the amount of motor practice needed to relearn motor skills with less therapist assistance (Miller et al., 2010). Based on data derived from multiple randomized controlled trials, AHA suggested that robot-assisted therapy for the upper extremity can deliver class I benefits for stroke care in outpatient and chronic care settings (meaning that the benefit is much larger than the risk and that the procedure/treatment should be performed/administered).

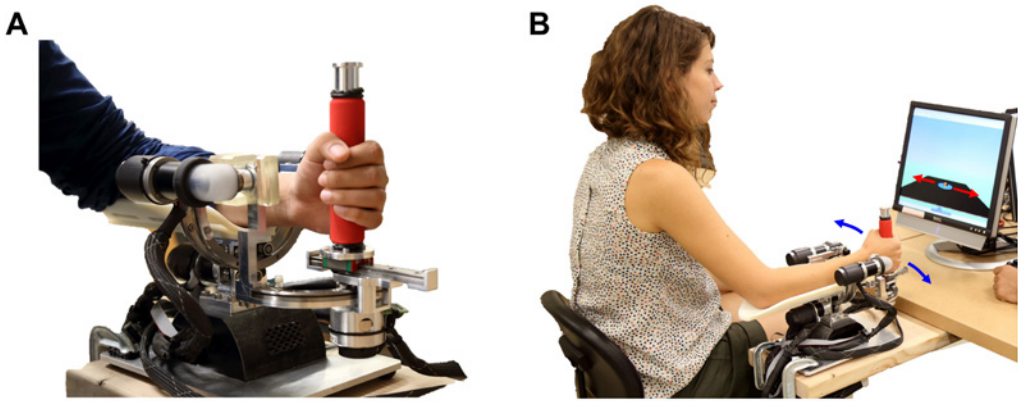

Figure 5 — A robotic exoskeleton for the wrist. This prototype was developed at the Italian Institute of Technology (Masia, Casadio, Giannoni, Sandini, & Morasso, 2009). (A) The robot allows for controlled wrist motion in the 3 degrees-of-freedom of the wrist/hand complex (wrist flexion/extension, wrist abduction/adduction, and forearm supination/pronation). The robot is powered by four brushless DC motors that allow for gravity compensation and can provide assistive or resistive forces. (B) The robot is coupled with a visual virtual environment. Here a user needs to balance a virtual ball on the screen by making controlled wrist flexion/extension movements. Images courtesy of the Human Sensorimotor Control Laboratory, School of Kinesiology, University of Minnesota.

In addition, it can provide class IIa benefits for stroke care in inpatient settings (meaning the benefit is larger than the risk, so it is reasonable to perform procedure/administer treatment).

Currently, one can find sufficient evidence that upper extremity robot therapy improves motor function in subacute and chronic stroke. One of the most comprehensive studies available is the VA-ROBOTICS randomized clinical trial, which included 127 chronic stroke patients who were at least 6 months poststroke (Fugl-Meyer assessment: 7–38 of 66 points for the upper extremity; low score indicating impairment; 66 points indicating normal function). Treatment duration was 3 sessions per week for 12 weeks. Three groups were tested: usual care: ≈ 45 guided arm movements per session; robot therapy: = 1,024 arm movements per session; intensive care therapy: ≈ 1,000 arm movements per session. The intensive care therapy was administered by therapists and mimicked the same intensity as the robotic therapy. Results showed that all therapies led to improvements in motor function, but based on the Fugl-Meyer score, the extent of motor improvement due to robotic therapy was not superior to standard care (Lo et al., 2010; Volpe et al., 2009) (see Figure 6). A more recent clinical trial (Orihuela-Espina et al., 2016) compared robot active-assisted therapy with conventional occupational therapy in a much smaller sample (N = 17). Both groups received 40 sessions ensuring at least 300 repetitions per session. Results showed that robot-aided hand training was superior to conventional occupational therapy based on the Fugl-Meyer scores, but failed to reach significance when using the Motricity index, another clinical scale to evaluate motor symptoms in stroke (Demeurisse, Demol, & Robaye, 1980). A summary of available additional studies on the efficacy of upper-extremity robot therapy is provided in Table 1,

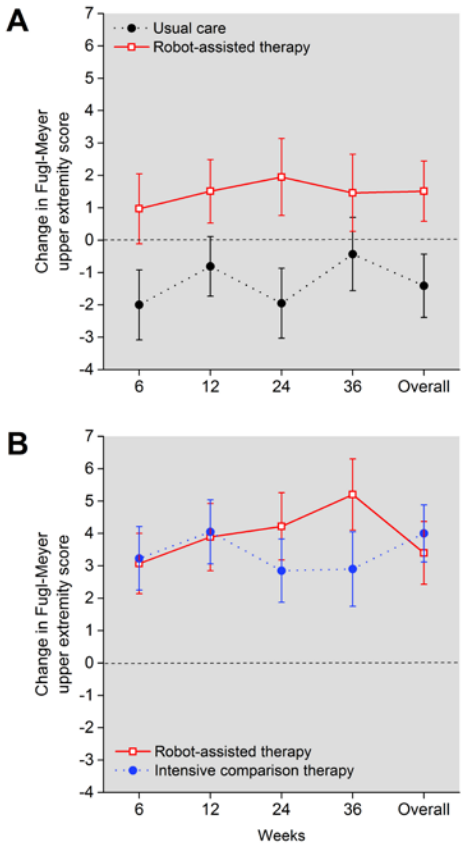

Figure 6 — Effects of exercise on clinical exam scores (Fugl-Meyer) in cortical stroke patients. Shown are the training-induced mean changes in Fugl-Meyer upper extremity scores during 36 weeks of intervention period as compared with baseline. (A) Usual care versus robot-assisted therapy. (B) Robot-assisted therapy versus intensive comparison therapy. Cohorts in A were different from B. Data derived from Lo et al. (2010).

Table 1 The Effect of Robotic Rehabilitation Exercise Training on Treating Stroke in Comparison with Conventional Therapy

Authors	Device Type	Stroke Level	N	Training Intensity	Effect Compared with Conventional Therapies
Susanto et al., 2015	Exoskeleton	Primary and moderate stroke	19	20 one-hour sessions, 3–5 times a week	More effective
McCabe et al., 2015	End effector	Chronic	39	60 sessions, 5 days a week, 5 hr a day	No significant difference
Brokaw et al., 2013	Exoskeleton	Chronic	12	12 hr of therapy in 1 month	More effective
Hesse et al., 2014	End effector	First-time supratentorial stroke	50	4 weeks, 1 hr per workday	Combination of robot and individual therapy was equally effective as double session of individual therapy
Timmermans et al., 2014	End effector	Chronic	22	8 weeks, 4 times a week, two 30-min sessions a day	No significant difference
Klamroth-Marganska et al., 2014	Exoskeleton	Chronic	77	8 weeks, 3 times a week, 1 session per day	More effective
Masiero et al., 2014	End effector	Hemiparetic	34	5 weeks, 5 days per week, 120 min per day	No significant difference
Wu et al., 2012	End effector	Chronic	42	4 weeks, 5 days per week, 90–105 min	No significant difference
Hsieh et al., 2011	End effector	Chronic	54	High-intensity: 20 sessions, 4 weeks, 5 days per week, 90–105 min	High: More effective
				Low-intensity: same amount, but only half of the number of repetitions	Low: No difference
Conroy et al., 2011	End effector	Chronic	57	6 weeks of three 1-hr sessions per week	No significant difference
Burgar et al., 2011	End effector	Chronic	54	3 weeks of five 1-hr sessions per week	No significant difference
Lo et al., 2010	End effector	Chronic	127	A maximum of 36 sessions over 12 weeks	No significant difference
Hesse et al., 2005	End effector	Subacute	44	6 weeks of five 30-min sessions per week	More effective
Fasoli et al., 2004	End effector	Subacute	56	5 weeks of five 1-hr sessions per week	More effective

corroborating the assessment that robotic rehabilitation can be effective, but is not necessarily superior to conventional therapy.

In summary, both end-effector-based and exoskeleton-based rehabilitation therapy can lead to improvements of upper extremity function after stroke. A combination of robot-assisted therapy and conventional physiotherapy seems to result in the higher improvements of limb function when compared with conventional physical therapy. The increased exercise intensity is likely the most important benefit of robot-assisted therapy for upper limb motor recovery in patients with chronic stroke (Chang & Kim, 2013).

Concluding Remarks

Research on the efficacy of exercise for treating neurological disease has documented a series of potential benefits. There is substantial evidence that exercise as a neurorehabilitation treatment can attenuate signs of Parkinsonism in animal models of PD as well as in humans with PD. Patients with PD respond well to resistance training and show the expected muscular and cardiopulmonary and cardiovascular adaptations to exercise. Exercise likely has a neuroprotective effect in patients with PD, but the exact neural mechanism of its effectiveness is not yet firmly established. For people with hereditary cerebellar

ataxia, exercise can be effective in improving balance function and activities of daily living, especially if such exercise starts early in the disease process. Its effects on spontaneous recovery from acute cerebellar ataxia are less clear, because spontaneous recovery is relatively fast. However, lesion symptom studies have established that lesions of the deep cerebellar output nuclei are associated with permanent damage, and the usefulness of exercise for this patient group is questionable. Finally, exercise mediated by robotic devices has the potential to markedly change cortical stroke rehabilitation, but evidence on its effectiveness is still only moderate or inconsistent. For all three presented disease entities, future studies will have to delineate optimal exercise dosage and exercise intensity and map how disease severity and disease states influence the potential benefits of exercise in ameliorating symptoms.

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