HHS Public Access

Author manuscript

Ageing Res Rev. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

Ageing Res Rev. 2022 February ; 74: 101543. doi:10.1016/j.arr.2021.101543.

The Protective Role of Exercise Against Age-Related Neurodegeneration

Alyson L. Sujkowski[1,2], **Luke Hong**[2,3], **R. J. Wessells**[1], **Sokol V. Todi**[2,3,*]

[1]Department of Physiology, Wayne State University School of Medicine

[2]Department of Pharmacology, Wayne State University School of Medicine

[3-]Department of Neurology, Wayne State University School of Medicine

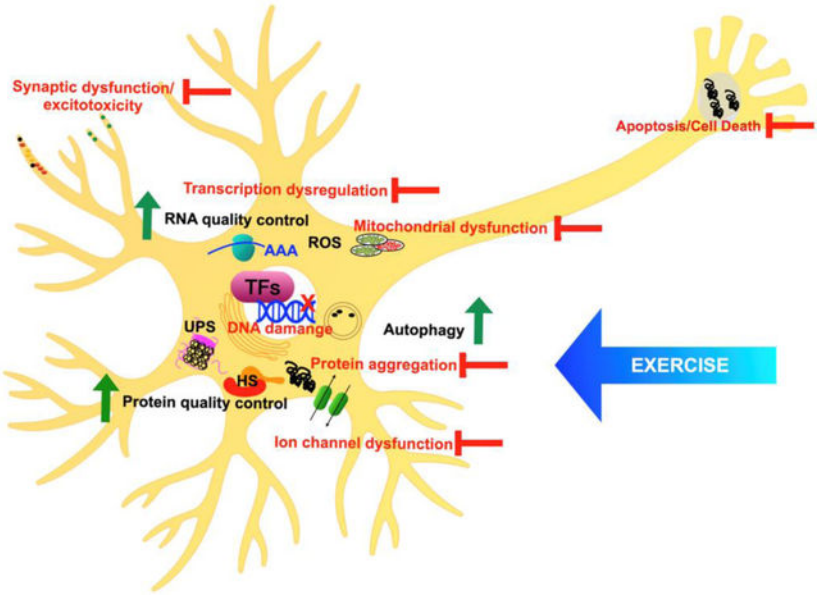
Abstract

Endurance exercise is a widely accessible, low-cost intervention with a variety of benefits to multiple organ systems. Exercise improves multiple indices of physical performance and stimulates pronounced health benefits reducing a range of pathologies including metabolic, cardiovascular, and neurodegenerative disorders. Endurance exercise delays brain aging, preserves memory and cognition, and improves symptoms of neurodegenerative pathologies like Amyotrophic Lateral Sclerosis, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, and various ataxias. Potential mechanisms underlying the beneficial effects of exercise include neuronal survival and plasticity, neurogenesis, epigenetic modifications, angiogenesis, autophagy, and the synthesis and release of neurotrophins and cytokines. In this review, we discuss shared benefits and molecular pathways driving the protective effects of endurance exercise on various neurodegenerative diseases in animal models and in humans.

Graphical Abstract:

[*]**Correspondence:to** 540 E Canfield, Scott Hall Rm 3108, Detroit, MI 48201, USA. stodi@wayne.edu.

Conflicts of Interest: The authors declare that they do not have any conflicts of interest to disclose.



Summary of Exercise benefits in Age-Related Neurodegeneration. Some of the shared pathogenic mechanisms of neurodegenerative diseases discussed in this review are highlighted in red text. Common targets that exercise may upregulate are indicated by green arrows. Common disease pathways that exercise may inhibit are indicated by red lines. For detailed descriptions and citations please see Tables 1 and 2.

Keywords

Exercise; Mitochondria; Muscle; Neurodegeneration; Proteinopathy

Introduction

Endurance exercise has well-established, powerful benefits with impact on multiple tissues and organ systems across various species (Laranjeiro et al., 2019; Marosi et al., 2012; Piazza et al., 2009). Endurance exercise, often referred to as aerobic exercise, is one of four types of exercise that additionally includes strength, flexibility, and balance. Endurance activities are characterized by periods of increased heart rate and respiration and are typically performed at sub-maximal intensity. Among the different types of exercise, endurance training is particularly well-suited to improve global metabolism and healthspan (Morici et al., 2016). Regular exercise improves physical performance and brings about striking health benefits that combat a remarkable range of pathological conditions including various types of cancer as well as cardiovascular, metabolic, and neurodegenerative diseases (Buchman et al., 2012; Colditz et al., 1997; Hu et al., 2001; Manson et al., 1999). In fact, physical fitness is a predictor of all-cause mortality and a measure of quality of life (Kodama et al., 2009). Despite experimental evidence supporting the broadly acting, diverse benefits of endurance exercise, overnutrition and sedentary lifestyle continue to pose a major health problem (Ang and Gomez-Pinilla, 2007). One organ system significantly impacted by physical activity and exercise is the brain. Recently, major progress has been made towards understanding

the relationship between regular exercise and neurological health. Studies in animal models and humans demonstrate that regular exercise improves memory, cognition, and mood, and prevents several neurodegenerative diseases (Di Liegro et al., 2019). Still, much remains to be discovered about the benefits of endurance exercise and the underlying mechanisms driving its neuroprotective effects.

Aging is the main risk factor for neurodegeneration and prevalence increases further with age (Hirth, 2010; Hou et al., 2019). (Broadly speaking, by aging here we refer to the cellular and organismal changes that occur during the course of an organism's lifespan; in our use of the word, aging is also characterized by senescence, or the progressive deterioration of physiological and anatomical processes the lead to decline in function over time (da Costa et al., 2016).) Most neurodegenerative diseases are associated with misfolded proteins and pathogenic oligomers that form toxic aggregates and coincide with progressive neuronal cell loss, collectively referred to as proteinopathies (Hirth, 2010). These progressive disorders may be idiopathic or hereditary diseases associated with genetic mutations. Heritable disorders often exhibit genetic anticipation, characterized by the lengthening of abnormal nucleotide repeat expansions in subsequent generations. Genetic anticipation leads to more severe protein misfolding and neuronal loss, resulting in earlier disease onset and increased disease severity (Cooper-Knock et al., 2014). There is no cure for the majority of age-related neurodegenerative disorders and diseases tend to progress irreversibly (Hou et al., 2019).

Epidemiological studies have shown that endurance exercise not only improves overall brain health, but also acts as a potent anti-aging therapeutic with minimal negative effects (Frederiksen et al., 2018). Endurance exercise enhances neuronal survival, promotes synaptic plasticity, and slows disease progression in multiple models of neurodegeneration (Dauwan et al., 2021). The neuroprotective effects of endurance exercise include reduced insulin resistance, reduced neuroinflammation and decreased stress and anxiety, and benefits like increased sleep, increased growth factor release, neurogenesis, and angiogenesis (Mahalakshmi et al., 2020). These changes result in enhanced overall psychological and neuropsychological health (Mahalakshmi et al., 2020). Moreover, endurance exercise protects against ischemic insult and increases skeletal muscle mitochondrial content, both important factors in neurodegenerative diseases (Azizbeigi et al., 2014; Wright et al., 2007).

Dissecting the mechanisms driving these protective effects is critical to our understanding of not only the benefits of endurance exercise, but also its role in decelerating neurodegenerative disease progression. Robust evidence from animal models has provided insight into the neuroprotective molecular pathways activated by exercise. Here, we discuss the effects of endurance exercise on several neurodegenerative disorders, focusing on common pathogenic mechanisms that may be alleviated by the broadly acting pro-healthspan effects activated by endurance training. The molecular mechanisms underlying the neurological benefits of endurance exercise are of significant research interest, and understanding these neuroprotective pathways may open the door to identifying targeted therapeutics that can be deployed for the population at large and especially for patients who are unable to reap the benefits of exercise.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis is a neuromuscular disorder characterized by progressive motor neuron degeneration of the upper and lower neurons at the spinal or bulbar level, leading to paralysis and death within 2–4 years of disease onset (Chio et al., 2009). Considered a multisystemic disease, various cell types contribute to the complexity of ALS pathogenesis and there is currently no cure (Cozzolino et al., 2008; Tsitkanou et al., 2019). Mechanisms implicated in motor neuron cell death during ALS progression include axonal transport defects, neurofilament aggregation, and excitotoxicity (Cooper-Knock et al., 2014; Morfini et al., 2009; Spreux-Varoquaux et al., 2002; Williamson et al., 1998). Other factors contributing to ALS pathogenesis include protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, inflammation, and microRNA expression (Blokhuis et al., 2013; Faes and Callewaert, 2011; Halter et al., 2010; Henkel et al., 2004; Russell et al., 2013).

The multisystemic nature of ALS makes pharmacotherapy difficult; endurance exercise counteracts many of the pathogenic mechanisms contributing to ALS progression or, alternatively, activates beneficial pathways in parallel, making it an attractive therapeutic option (Figure 1). Nonetheless, endurance exercise implementation in ALS patients is complex because of the rapid nature of disease progression. As a result, studies in both animal models and humans have garnered mixed results (Tsitkanou et al., 2019) (Tables 1, 2).

Idiopathic and familial ALS are clinically indistinguishable, but about 20% of familial ALS patients harbor a point mutation in the superoxide dismutase 1 gene (SOD1) and SOD1 may also contribute to disease progression in sporadic ALS (Abati et al., 2020). While the mechanisms of SOD1 dysfunction and ALS progression are not completely understood, toxic gain-of-function yielding protein misfolding and aggregation of mutant SOD1 may contribute to motor neuron toxicity (Abati et al., 2020; Carreras et al., 2010). Studies in a transgenic mouse model of ALS ($SOD1^{G93A}$) compared the effects of sex, exercise duration, intensity, mode, and SOD1 transgene expression level (Tsitkanou et al., 2019); (a summary of selected findings in animal models is in Table 1). Disease onset and survival in $SOD1^{G93A}$ ALS mice varies depending on transgene copy number, exercise intensity, metabolic parameters, and sex. (Carreras et al., 2010; Desseille et al., 2017; Kaspar et al., 2005; Veldink et al., 2003). Moderate intensity exercise had significant benefit to $SOD1^{G93A}$ ALS mice, whereas high-intensity exercise reduced survival and motor performance (Carreras et al., 2010). Swimming exercise delayed disease onset and improved motor performance, while $SOD1^{G93A}$ mice that completed a comparable treadmill running program did not improve either parameter (Desseille et al., 2017). Furthermore, swim-trained $SOD1^{G93A}$ ALS mice expressed favorable changes to GLUT4 expression and lipid synthesis, while treadmill-trained $SOD1^{G93A}$ ALS mice did not, indicating differential responses to specific types of exercise in this murine ALS model (Desseille et al., 2017). Sex-specific effects were also observed in $SOD1^{G93A}$ ALS mice, which may explain the male-specific disease prevalence in this model. Treadmill-trained female $SOD1^{G93A}$ ALS mice improved survival while males did not, suggesting that estrogen may play a neuroprotective role (Veldink et al., 2003).

A second study in SOD1^{G93A} mice also found that exercise intensity is important to the prevention of ALS phenotypes (Carreras et al., 2010). SOD1^{G93A} ALS mice were divided into sedentary, moderate-intensity exercise, and high-intensity exercise groups and were examined for changes in body weight, motor function, and motor neuron counts, previously shown to be markedly decreased in this model (Liebetanz et al., 2004). SOD1^{G93A} mice in the moderate-intensity cohort performed treadmill exercise for 30 minutes per day, 3 days per week for 45 days at a speed of 10 meters/minute, while those in the high-intensity cohort performed treadmill exercise of 50 minutes per day, 5 days per week at 20 meters/minute (Carreras et al., 2010). Moderate-intensity exercising of SOD1^{G93A} mice resulted in lower body weight and delayed characteristic declines in performance on the rotarod by more than 10 days compared to sedentary controls. The moderate-intensity group also had higher motor neuron cell count in the ventral horn of the lumbar spinal cord. Although high-intensity exercise also reduced body weight and increased motor neuron density at day 120 in SOD1^{G93A} mice, motor performance was not improved at any age (Carreras et al., 2010), indicating that exercise intensity differentially affects motor performance and motor neuron preservation in this model.

It bears mentioning that the aforementioned studies utilized animal models of forced exercise. In the case of forced treadmill training, experimental parameters such as speed, intensity, and duration can be precisely controlled, and swim exercise recruits whole body systems to induce effective aerobic exercise (Guo et al., 2020). Voluntary wheel running, which tends to be less stressful, is also frequently used in murine models but results in greater individual variation among subjects (Guo et al., 2020). Forced exercise tends to better activate neurogenesis pathways and neuroprotective mechanisms (Hitoshi et al., 2007; Leasure and Jones, 2008), while voluntary running is associated with transcriptional and global metabolic changes (Do et al., 2018). Mechanisms of neuroprotection between forced and voluntary exercise overlap and both can benefit neurodegenerative disease like ALS. Since exercise intensity can be critical to experimental outcomes, it is important to carefully consider the advantages and disadvantages in each system.

In general, cardiovascular exercise is recommended to improve both functional independence and psychological parameters in people (Merico et al., 2018). A 2020 meta-analysis of 94 ALS patients with a wide range of disease severity (1.64 to 20.05 months) who performed variable types of exercise achieved moderate benefits to respiratory and limb function after therapeutic aerobic exercise, but only if treatment was initiated early in disease progression (Park et al., 2020). (A summary of selected findings from human studies is in Table 2). In a second study, ALS patients with mild to moderate disabilities who performed moderate treadmill exercise plus programmed isometric contractions responded with improved muscle power, oxygen consumption, and endurance compared to control patients assigned to standard rehabilitation (Merico et al., 2018). In a third study, sixteen patients diagnosed with ALS, determined by the revised El Escorial criteria (Brooks et al., 2000) (it was not specified whether the ALS participants were sporadic or familial) were selected and randomly assigned to either a trained group or untrained control (Ferri et al., 2019). Patients were characterized by mean disease duration of 20.5 +/− 20.3 months and trained group participants were assigned combined endurance cycling and strength training programs tailored to their exercise capacity and disease stage (Ferri et al., 2019). Patients

in the combined endurance and strength exercise group showed significantly improved "Timed Up and Go Time" (TUGT) scores, ALS Functional Rating Scale-revisited scores, ALS-Severity Scale, and quality of life scores compared to the untrained control patients (Ferri et al., 2019).

Historically, exercise treatment for ALS has been controversial for two primary reasons: 1) Athletics and exercise have been associated with increased incidence of ALS; 2) There are concerns that exercise-induced muscle damage may exacerbate progressive functional declines (Lisle and Tennison, 2015). While exercise reduces oxidative stress, decreases inflammation, and protects against cell senescence, strenuous exercise generates high ROS levels that may accelerate disease pathology (Kuraszkiewicz et al., 2020). Furthermore, certain types of long-term physical activity were reported to correlate with a higher incidence of ALS, although recent studies suggest a causal relationship only in genetically at-risk individuals (Julian et al., 2021). Recently, evidence from both humans and animal models has suggested that exercise may in fact improve function and slow disease progression (Lisle and Tennison, 2015). Unfortunately, small sample sizes, variations in protocols and genetic background, lack of subjects, and high cost result in a lack of coordinated data from which to draw conclusions about the effects of exercise on ALS onset and progression. The aforementioned investigations and others suggest that mild-to-moderate exercise may benefit ALS patients, particularly if initiated early in disease progression. Evidence suggests that moderate exercise programs precisely tailored to individuals are particularly useful to improve functional outcomes and protect against neurodegenerative phenotypes in ALS patients. These positive effects, and the lack of negative effects, support the use of exercise as a beneficial therapeutic option for those suffering from ALS.

Alzheimer's Disease (AD)

Alzheimer's Disease, the most common type of dementia, is a neurodegenerative disorder characterized by neuronal loss and cognitive decline. Proposed mechanisms of AD onset and progression include abnormal protein accumulation, altered inflammatory response, cholinergic and free radical damage, and genetic contribution (Breijyeh and Karaman, 2020). Beta-amyloid (Aβ) plaques and hyperphosphorylated tau that contribute to neurofibrillary tangles are two major histopathological features of AD (Brown et al., 2019).

Aβ peptides are proteolytic fragments of amyloid precursor protein, and tau is a microtubule associated protein enriched in axons and expressed exclusively in the brain (Bloom, 2014). Studies in animal models of AD describe exercise-induced reductions in both Aβ and tau aggregates coincident with improved disease phenotypes (Brown et al., 2019) (Figure 2). In contrast to animal models, human studies have provided inconsistent evidence on the effects of physical exercise on biomarkers like Aβ and tau and on AD symptoms (Brown et al., 2019). One possible reason for these differences is that while animal models of exercise can be carefully controlled, human studies tend to have greater heterogeneity between patient cohorts, exercise modalities and intensities. Similar to ALS, changes in physiology and relevant biomarkers may critically rely on exercise timing, frequency, and intensity. Still,

endurance exercise and physical activity are generally recommended to prevent and treat AD (Cass, 2017; Meng et al., 2020; Valenzuela et al., 2020) (Figure 2).

Oxidative stress and neuroinflammation, for example, are two additional pathogenic factors implicated in AD etiology (Yin et al., 2016). Regular exercise supports angiogenesis, neurotrophin synthesis and metabolism, and increases the capacity of neurons and supportive tissues to withstand oxidative stress, all important in neurogenesis, memory, and neuroplasticity (Radak et al., 2010). Studies in humans and animal models suggest that exercise has protective effects against AD and other neurodegenerative disorders, but the underlying mechanisms at play require further investigation (Cass, 2017; Meng et al., 2020; Valenzuela et al., 2020).

Observations from animal models of AD indicate that exercise improves learning and memory concurrent with reductions in Aβ peptide and hyperphosphorylated tau (Laranjeiro et al., 2019; Liu et al., 2011; Wu et al., 2018; Zhang et al., 2019). Treadmill running in APP/PS1 (amyloid precursor protein/human presenilin 1) double transgenic mice, a commonly used rodent model for AD, improved learning and memory in the Morris water maze task and was associated with enhanced long-term potentiation (Liu et al., 2011). Furthermore, five months of treadmill-training in APP/PS1 mice reduced both hippocampal Aβ deposition and tau phosphorylation in comparison to untrained transgenic control mice, concurrent with reductions in APP phosphorylation and PS1 expression, both associated with non-amyloidogenic processing in the hippocampus (Liu et al., 2013b). Exercise inhibited tau phosphorylation via GSK3α/β but not CDK5, providing a potential mechanism by which exercise prevents AD pathology (Liu et al., 2013b).

In a separate study, treadmill running in APP/PS1 mice inhibited Aβ accumulation by decreasing cholesterol dysregulation and formation of lipid rafts, prominent features of the amyloidogenic pathway and subsequent AD progression (Zhang et al., 2019). Twelve weeks of treadmill exercise reduced Aβ generation by downregulating ADAM10 (a disintegrin and metalloproteinase domain-containing protein 10) and BACE1 (β-site amyloid precursor protein cleaving enzyme 1) levels, both required for APP processing and Aβ generation. AD therapies are being targeted to these APP processing and amyloidogenic pathways and reducing lipid rafts (Zhang et al., 2019).

The majority of AD is sporadic, characterized by late onset at 80–90 years of age (Masters et al., 2015). One animal model of sporadic AD relies on intracerebroventricular injection of streptozotocin (STZ), a diabetogenic compound that decreases brain glucose metabolism, depleting energy reserves and mimicking dementia symptoms reminiscent of AD (Chen et al., 2013). In a rat model of STZ-induced sporadic AD, swim exercise pretreatment before symptom onset inhibited cognitive dysfunction and induced expression of nuclear factor erythroid 2-related factor (Nrf2) and downstream antioxidant gene expression. Pre-treated, exercised STZ rats also showed reductions in both endogenous Aβ peptide and hyperphosphorylated tau, accompanied by decreased hippocampal neuronal cell loss compared to unexercised STZ control rats (Wu et al., 2018). This study examined the effects of 3 weeks of endurance exercise pre-treatment on young adult rats in which STZ-

induced AD was not induced until swim exercise was complete (Wu et al., 2018). It will be interesting to test the effects of swimming exercise in later stages of this AD model.

Invertebrates have also provided important information about the effects of exercise on neurodegeneration. Simple animal models such as *C. elegans* and *Drosophila melanogaster* have highly conserved, well characterized genetics and comparatively simple nervous systems, allowing for molecular dissection of the pathways underlying both neurodegenerative disease and endurance exercise (Laranjeiro et al., 2019; McGurk et al., 2015; Sujkowski and Wessells, 2018). Long-term swim exercise, in which in *C. elegans* perform multiple daily swim sessions of 90 minutes, induces several healthspan-extending parameters that are similar to the effects of mammalian endurance exercise (Laranjeiro et al., 2017; Laranjeiro et al., 2019). In wild-type *C. elegans,* swim exercise increases muscle gene expression, locomotory performance, mitochondrial respiration and midlife survival (Laranjeiro et al., 2017; Laranjeiro et al., 2019). In a *C. elegans* model of AD that expresses human Aβ peptide pan-neuronally, swim exercise rescued premature decline in chemotaxis, a phenotypic hallmark of this AD disease model (Laranjeiro et al., 2019; Wu et al., 2006). Swim exercise in *C. elegans* also reduced gaps in GABAergic motor neurons in an aggregating tau background, improving defects in nerve cord morphology related to declining mobility (Fatouros et al., 2012; Laranjeiro et al., 2019) (Figure 2). These studies highlight the utility of animal models for the molecular dissection of pathways crucial for the potential benefits of endurance exercise in AD. Animal models have been consistently instrumental to elucidate neuroprotective molecular pathways activated by exercise by pinpointing neurogenesis, protection against inflammation and protein aggregation, and synaptic maintenance as critical exercise-induced pathways capable of alleviating neurodegenerative phenotypes.

Importantly, human studies have shown mechanistic (e.g. reduced neuroinflammation) and functional (e.g. preserved cognition) improvements in AD patients who exercise. During 52 weeks of exercise, pre-clinical AD patients adapted to training with increased cardiorespiratory performance, albeit without significant changes to amyloid levels, hippocampal volume, or cognition compared to sedentary control patients. (Vidoni et al., 2021). In a second study, participants with early-stage AD were divided into 2 groups: 1) stretching and toning, performing a series of non-aerobic exercises, or 2) aerobic exercise, performing 60 minutes of exercise at 40–55% maximum heart rate (HR) per week, gradually increasing to 150 minutes per week at 60–75% HR. After 26 weeks, aerobic exercise participants increased functional independence and decreased disability scores in comparison to stretching and toning participants (Vidoni et al., 2019).

In a different study, cognition and quality of life were assessed separately. Mini Mental State Examination (MMSE) scores were used to measure cognitive function, whereas ability to perform activities of daily living (ADL) values were used as a measurement of general quality of life. Later-stage AD patients with a mean age of 84 years assigned to either 30 minutes of walking per day or to a sedentary control group were observed after 24 weeks of moderate walking exercise (Venturelli et al., 2011). MMSE scores remained stable and ability to perform ADLs increased in walking group patients, while both parameters declined in the control group participants. These findings indicate that moderate walking

exercise prevents AD-related negative changes in both cognitive and functional performance, even in the presence of advanced AD progression (Venturelli et al., 2011).

A 4-month study of AD patients with mild dementia, which prescribed 30 minutes of treadmill walking at 60% HR twice per week, described similar benefits. After the training period, exercise group and controls were cognitively assessed using the Cambridge Cognitive Examination in combination with tests for verbal fluency, memory, executive function, and attention. Functional capacity was measured using TUGT (timed up and go time), Sit-to-Stand test, tests for balance and reach, and standard exercise physiology assessments like EKG and VO_{2max}. After 16 weeks, participants in the exercised group showed improved scores in the Cambridge Cognitive Examination evaluation while control group participant scores declined. Exercise group participants also maintained verbal fluency and executive function scores while control participant scores also declined in these measures. In functional assessments, exercise group participants significantly outperformed controls in all parameters, except Sit-to-Stand, in which there was no significant difference whether exercised or not (Arcoverde et al., 2014). Taken together, these studies strongly indicate that walking exercise is a promising intervention to alleviate both cognitive and functional deterioration in AD patients.

Although general physical activity is recommended, it is unclear whether endurance exercise is an effective therapeutic intervention for AD patients. Two separate studies examined executive function, verbal fluency, cognition, and neuropsychological function in patients with mild-to-severe dementia by looking at MMSE scores, ADLs, and the AD Assessment Scale–Cognitive subscale both before and after moderate and high-intensity exercise: all assessments remained unchanged whether AD participants were exercised or not (Lamb et al., 2018; Toots et al., 2017).

One possible explanation for differences observed in human findings may be a variation in genetics. In the case of AD, various environmental, clinical, and genetic risk factors for developing the disease have been identified. While physical inactivity is a major environmental risk factor, a primary genetic risk factor for developing AD is the apolipoprotein-E (APOE) ε4 allele (Jensen et al., 2019; Strittmatter and Roses, 1996). Hypotheses about the APOE genotype and its influence on AD pathophysiology involve pathways related to inflammation, vascular dysfunction, cholesterol dysregulation and Aβ deposition (Liu et al., 2013a). In the brain, endurance exercise can inhibit Aβ deposition, reduce abnormal cholesterol accumulation, and decrease neuroinflammation in both normal subjects and in the presence of neurodegeneration (Johnson and Stolzing, 2019; Zhang et al., 2019). Cerebral blood flow is also altered by endurance exercise, improving cognition during both normal aging and disease (De la Rosa et al., 2020). Long-term studies examining the interaction between endurance exercise and APOE carriership may elucidate the mechanisms by which APOE contributes to AD disease progression.

A study of 91 patients with mild-to-moderate dementia assigned to either exercised or control groups performed 12 weeks of low-intensity exercise followed by 12 weeks of high-intensity exercise, or attention-matched flexibility and recreational activities. At the end of the exercise-training period, MMSE scores trended toward increased values

without reaching significance for exercised non-APOE ε4 carriers, while the same scores decreased for all other groups (Sanders et al., 2020). All other tested cognitive measures and all functional measures — endurance, mobility, balance, and leg strength — were not statistically different between exercised and control cohorts. However, exercised patients retained significantly faster gait speed, an important clinical measure associated with quality of life and cognition (Dumurgier et al., 2017; Sanders et al., 2020). These results were inherently limited by the cognitive deficits of the research subjects; one would also expect physiological adaptations from the exercised group independent of AD pathophysiology. It is possible that exercised subjects did not fully grasp the instructions of the research assistants (Sanders et al., 2020), potentially blunting a response to exercise.

In contrast, a separate post-hoc analysis of 200 early-stage AD patients examined cognitive function through the Neuropsychiatric Inventory and assessed mobility using TUGT: exercised APOE ε4 carriers had significant improvements in all outputs reported, while exercised non-carriers did not improve (Jensen et al., 2019). One key difference in this study was in the exercise modality. Study participants chose either treadmill or cycling exercises, with most selecting cycling as their preferred mode of intervention. Participants reported feeling “unsafe” on the treadmill, which require better trunk strength, coordination, and balance (Jensen et al., 2019). While both studies implicated APOE in AD pathology, neither provided a mechanism by which genotype and exercise modify disease progression. It is possible that exercise modifies the effects of APOE4 ε4 on synaptic function, protein aggregation, vascular function, lipid metabolism, or inflammation, although the relative importance of these factors on AD progression is unclear (Safieh et al., 2019).

A number of lifestyle factors influences the risk for AD; low level of physical activity is one factor that increases the risk of developing AD (De la Rosa et al., 2020). While pharmacological interventions exist for AD, there is currently no cure. Evidence suggests that physical exercise can slow the progression of cognitive declines associated with AD, particularly when intervention occurs early in disease (Cui et al., 2018). Human studies further underscore that exercise improves cognition and function in AD patients, but often fail to reach significance in biomarkers related to disease progression (Dumurgier et al., 2017; Sanders et al., 2020; Venturelli et al., 2011).

Observations in humans associate higher levels of physical activity with reduced cognitive decline and higher overall cognition; nonetheless, study outcomes related to the protective and therapeutic effects of exercise on Alzheimer’s dementia are varied (Jensen et al., 2019). Exercise is one potential therapeutic strategy that may delay brain aging and cognitive decline, perhaps through maintenance of hippocampal volume, perfusion, and neurogenesis (Barnes, 2015). Evidence from human and animal models also suggests that exercise promotes favorable changes in the microbiome, particularly those that increase antioxidant and anti-inflammatory pathways (Gubert et al., 2020). While pharmacotherapy is aimed at treating advanced stages of AD and dementia, exercise in preclinical patients may be able to reduce the likelihood of AD onset and progression (Meng et al., 2020). Exercise protects both muscle and neural functions (Rafalski and Brunet, 2011), including cognitive processes (Erickson and Kramer, 2009), by mechanisms like increased mitochondrial biogenesis/efficiency (Ascensao et al., 2011), decreased triglyceride storage (Kennedy et al., 2004),

improved insulin sensitivity (Corcoran et al., 2007; Mittendorfer et al., 2001), and reduced neural inflammation, pathways known to be dysregulated in AD (Valenzuela et al., 2020). In addition, these remodeling events lead to increased physiological capacity in both cardiac and skeletal muscle that may improve quality of life in AD patients in a way that may be additive to other treatments. While these results are encouraging, it is clear that further investigation is needed to reach evidence-based conclusions about the mechanistic effects of exercise on AD. Ultimately, the identification of converging protective pathways triggered by exercise regimens may lead to the generation of therapeutics that can be deployed widely among AD patients, regardless of the precise precipitant(s) of the disease in a specific patient population.

Parkinson's Disease (PD)

Parkinson's Disease, the most common progressive neurodegenerative movement disorder, is clinically identified by motor symptoms like resting tremor, rigidity, bradykinesia or akinesia, and postural instability (Balestrino and Schapira, 2020). While age is the most important risk factor for developing PD, environmental factors like pesticide exposure, β-adrenergic antagonist use, and male gender also increase PD risk (Gillies et al., 2014; Lee and Gilbert, 2016; Mittal et al., 2017). Familial forms of PD account for only 5–15% of cases, but studies in these families have provided invaluable insight on the pathogenesis of the disease (Balestrino and Schapira, 2020). For example, mutations in parkin, an E3 ubiquitin ligase, and PINK1, a kinase, cause early-onset PD. These genes act in the same pathway to remove damaged mitochondria from cells, mitigating oxidative damage and inflammation (Sliter et al., 2018). Similarly, mutations in the oxidative stress sensor DJ-1 are causative in some forms of familial PD, providing further support that oxidative damage may contribute to PD pathogenesis (Hijioka et al., 2017). Missense or triplication mutations in *SNCA*, the gene that encodes α-synuclein, cause rare, highly penetrant autosomal dominant PD (Kim and Alcalay, 2017). α-synuclein is a major component of Lewy bodies, fibrillar aggregates that are a major pathological hallmark of PD (Wakabayashi et al., 2013).

Like previously discussed neurodegenerative disorders, studies in animal models and humans suggest that the effects of exercise on PD are broadly acting: modifying synaptogenesis and activity, increasing neurotrophic factors and angiogenesis, and reducing inflammatory pathways (Ahlskog, 2018) (Fig. 3). PD is characterized by loss of dopaminergic neurons in the substantia nigra pars compacta (Petzinger et al., 2013). Loss of dopamine (DA) causes motor and cognitive dysfunction as well as mood disorders (Petzinger et al., 2013). While DA-replacement therapy effectively alleviates some motor symptoms, less benefit to cognitive function is observed (Schapira et al., 2009). Endurance exercise enhances mobility and cognition in healthy endurance athletes, partly by modifying both dopaminergic signaling and sensitivity, making exercise an attractive therapeutic target for PD (van Breda et al., 2015).

Rodent models of PD have revealed targeted, activity-dependent effects of exercise including increased endogenous BDNF signaling, enhanced DA release, reductions in DA transporter expression and nigrostriatal DA-ergic cell loss, as well as preservation and restoration of DA-ergic neurons in the midbrain (Ellis and Rochester, 2018). In a

chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD (MPD), in which MPTP causes acute potentiation and long-term depletion of striatal DA (Lau et al., 1990), MPD mice subjected to 18 weeks of treadmill exercise preserved both number and morphology of DA-ergic neurons in the substantia nigra pars compacta compared to sedentary MPD control mice (Lau et al., 2011). Exercise-trained MPD mice also performed better than unexercised controls in both foot slip and latency to fall from a balance beam (Lau et al., 2011). Exercised MPD mice had region-specific increases in the neurotrophic factors BDNF and GDNF in comparison to both unexercised MPD and C57BL/6 genetic background control cohorts, with higher BDNF in the substantia nigra and increased GDNF concentrations in the striatum. Increased neurotrophic factors were associated with exercise-induced recovery in DAergic neural cells and behavior (Lau et al., 2011). Furthermore, exercised MPD mice sustained less striatal oxidative damage and mitochondrial dysfunction than unexercised MPD mice, with respiratory control ratios and expression of striatal antioxidant enzymes MnSOD and Cu-Zn SOD closer to normal C57BL/6 mice than unexercised MPD siblings (Lau et al., 2011). Proper regulation of these antioxidant enzymes is crucial for preventing reactive oxygen species-induced neural injury in the substantia nigra pars compacta, where DAergic neurons are highly sensitive to damage induced dysfunction and death (Callio et al., 2005).

Perhaps surprisingly, two separate, additional studies observed that exercise suppressed defects in gait, spontaneous activity, balance, and cardiorespiratory adaptations without restoring learning or DA-ergic defects in the nigrostriatal pathway of MPD mice (Al-Jarrah et al., 2007; Pothakos et al., 2009). Furthermore, amphetamine-induced locomotion, a stereotypic behavior that depends on DA receptors, was not rescued by endurance exercise (Al-Jarrah et al., 2007; Conti et al., 1997; Pothakos et al., 2009). Exercised PD mice had a slight but not statistically significant increase in Tyrosine Hydroxylase, the rate limiting enzyme in DA synthesis (Al-Jarrah et al., 2007; Nagatsu, 1995). While differences in genetic background, MPD administration and sample size likely contribute to variability in results, it is striking that endurance exercise might restore function even in the absence of significant nigrostriatal restoration.

Gene mutations leading to loss of neuroprotection or toxic gain-of-function are additional contributing factors to PD onset and progression (Zhou et al., 2017). As mentioned above, mutations implicated in Parkinson's pathogenesis include α-synuclein, Parkin, DJ-1 and PINK1, as well as LRRK2 and VSP35 (Bonifati, 2014). Toxic gain-of-function of α-synuclein, a result of either a single amino acid mutation or triplication of the gene, causes some forms of dominantly inherited PD (Polymeropoulos et al., 1997; Singleton et al., 2003). A mouse model of PD ectopically expressing human mutant α-synuclein (Y39C) pan-neuronally and provided with free access to a running wheel maintained endurance capacity compared to unexercised controls. These exercised mice also maintained exercise capacity and protection from Parkinsonian-like declines in cognitive and motor function, performing better than controls on both rotarod and Morris Water maze (Zhou et al., 2017). Exercised Y39C mice also showed increased protein levels of BDNF, the molecular chaperone HSP70, and DJ-1 (Clements et al., 2006; Kim et al., 2020a; Zhou et al., 2017). DJ-1 is a neuroprotective, PD-associated gene that stabilizes the cytoprotective transcription factor Nrf2 and upregulates antioxidant response (Clements et al., 2006; Tonelli et al., 2018;

Zhou et al., 2017). Brain α-synuclein was reduced in exercised Y39C mice while plasma α-synuclein levels increased, indicating that exercise may modify brain α-synuclein levels, improving disease phenotypes (Zhou et al., 2017).

While a comprehensive understanding of the mechanisms underlying the benefits of endurance exercise in PD progression is incomplete, it is well established that PD patients who exercise improve physiologic, functional, clinical, and molecular outcomes compared to inactive patients (Ellis and Rochester, 2018). Similar to previously discussed neurodegenerative disorders, variability in intervention, disease penetrance, environment and study conditions contribute to mixed results in PD. Diverse meta-analyses of treadmill exercise in PD patients with mild-to-moderate disability generally describe maintenance or improvement in United Parkinson's Disease Rating Scale using mobility outcomes like walking speed, stride, and step length (Flach et al., 2017; Robinson et al., 2019).

Researchers often adjust exercise protocols according to participant disease stage in order to increase patient compliance and the probability of successful outcomes. Varying exercise modality according to specific tasks (i.e. obstacle avoidance or backwards walking) may also provide information about whether exercise adaptations are organ-specific or systemic (de Oliveira et al., 2018; Rawson et al., 2019). Furthermore, progressive disability often limits patient capacity to complete an exercise program, so a "one-size-fits-all" approach is not always appropriate. In a study of 96 patients diagnosed with idiopathic, mild-to-moderate PD, participants were assigned to either 12 weeks of treadmill exercise, or comparable times and intensities of tango dancing or stretching. Only patients assigned to treadmill exercise improved both forward and backward walking. In this case, the diffuse effects of endurance exercise, as opposed to training targeted to specific deficits (e.g., only tango includes backward motion), provided maximum benefit to PD patients (Rawson et al., 2019).

Exercise intensity is another parameter frequently modified to alter therapeutic outcomes in PD. In an 8-week study of 30 early-stage PD patients, participants were randomly assigned to body weight supported, high-intensity treadmill training, low-intensity exercise, or a zero-intensity control group. Exercised groups or zero-intensity controls were assessed using United Parkinson's Disease Rating Scale, biomechanical analysis, walking, Sit-to-Stand and transcranial magnetic stimulation, a non-invasive tool to assess the excitability of the corticospinal motor system (Fisher et al., 2008). The high-intensity group improved in all motor performance parameters including gait speed, stride and step length, joint excursion, gait velocity, range of motion, and Sit-to-Stand. The high-intensity group was the only group to show reduced corticomotor excitability. Corticomotor excitability is generally higher in patients with PD and corticomotor inhibition is associated with improved movement (Fisher et al., 2008; Mak, 2013). Modest mobility improvements in the low-intensity exercise cohort suggested some benefit from increased activity. These findings pointed to dose-dependent improvements in mobility accompanied by normalization of corticomotor excitability in PD patients who completed 12 weeks of high-intensity exercise (Fisher et al., 2008).

As with other neurodegenerative diseases, there is currently no cure for PD. Pharmacotherapy is the primary treatment option for patients (Mak and Wong-Yu, 2019).

Diminishing effects of long-term DAergic treatments and persistent motor impairments in PD limit the therapeutic potential of pharmaceutical interventions (Feng et al., 2020; Mak and Wong-Yu, 2019). Physical activity and exercise are promising, complementary interventions with short- and long-term benefits to PD patients, and animal models have provided clues about the mechanisms underlying functional and molecular improvements (Feng et al., 2020; Mak and Wong-Yu, 2019). Physical exercise may alleviate motor and non-motor phenotypes in PD patients by improving corticomotor plasticity and restoring DAergic activity, but further studies are nonetheless needed to clarify the cellular pathways by which exercise modifies PD (Feng et al., 2020). Most likely different, and perhaps overlapping, mechanisms of protection will be activated by exercise depending on the cause of PD in a specific patient population, the stage of disease, and type of regimen. These mechanisms may well include changes in neuroprotective factors, such as BDNF, engagement of anti-oxidative stress factors, and increases in molecular chaperones that can help maintain protein folding during stress.

Huntington's Disease (HD)

Huntington's Disease, the most common inherited neurodegenerative disorder, belongs to the large family of proteinopathies (Finkbeiner, 2011) that also includes ALS, AD, PD and the polyglutamine (polyQ) diseases. Proteinopathies present in mid-adulthood despite expression of disease genes during development (Barnat et al., 2020). HD is caused by a highly penetrant tandem repeat expansion of the triplet nucleotide CAG(A) that encodes glutamine (Q), resulting in extended polyQ tracts in the huntingtin (HTT) protein (Huntington, 2003; Macdonald et al., 1993; Mo et al., 2015). The *HTT* gene normally harbors between 6 to 35 CAG repeats; alleles with 36–39 repeats yield an increased risk of developing HD. *HTT* alleles with 40 or more repeats confer fully penetrant HD (Bates, 2005). While disease progression is driven by genetics, recent work has also established that environmental factors, like activity level and exercise, have pronounced disease-modifying effects (Mo et al., 2015). Like AD, substantial evidence exists that exercise protects against HD neurodegeneration in preclinical patients, perhaps by enhancing neuroplasticity, antioxidant resistance, anti-inflammatory pathways and epigenetic regulation. Exercise-induced alterations in microbiome composition that reduce apoptosis and inflammation may also play a protective role in genetically at-risk patients, even before the onset of symptoms (Gubert et al., 2020). Clinical presentation of HD includes motor, cognitive, psychological, and behavioral decline with advanced disease progression resulting in complete lack of independence and early mortality (Mueller et al., 2019b). Studies in animal models and humans provide evidence that endurance exercise may alleviate HD symptoms, but, like other neurodegenerative disorders, the mechanisms are not well understood, and the results have been mixed (Fig 4.).

Whether or not exercise can delay HD onset is a common research question given that expression of its disease gene precedes symptom presentation by decades. R6/1 HD model mice, which express the isolated, human exon 1 of *HTT* with a pathogenic CAG expansion, were given access to a running wheel; they showed delayed onset of motor deficits as measured on the static horizontal rod and in abnormal rear paw clasping when compared to R6/1 mice without wheel access. Interestingly, delayed phenotypes occurred despite

exercised R6/1 HD mice having no significant change in protein aggregates or shrinkage in the striatum or anterior cingulate cortex, pathological hallmarks of HD (van Dellen et al., 2008). Also unclear from this study was whether exercise was solely responsible for the observed benefits, or whether environmental enrichment by the presence of the running wheel was a contributing factor.

Similar to other proteinopathies, mitochondrial dysfunction is one pathogenic mechanism that may contribute to HD. In mouse models, mutant HTT (mHTT) directly interacts with mitochondria, modifying bioenergetics (Yu et al., 2003). Endurance exercise has well established effects on mitochondrial dynamics in multiple tissues, improving mitochondrial respiration, biogenesis, fission-fusion, and mitophagy (Laker et al., 2014; Moore et al., 2019; Safdar et al., 2011). R6/1 mice develop symptoms similar to juvenile-onset HD, and several studies observed the reduction of phenotypes without preventing mHTT aggregation (Mangiarini et al., 1996; van Dellen et al., 2008), similar to the study mentioned above. Treadmill running in R6/1 mice for 10 or 20 weeks starting at 7 weeks of age prevented abnormal hindlimb clasping and partially rescued defects in mitochondrial content and function at 17 weeks that persisted until week 27. Exercised R6/1 mice maintained higher mtDNA in the cortex and striatum, regions particularly susceptible to apoptotic cell death in HD. Exercise also prevented the loss of muscle mitochondrial number and function by 17 weeks, and maintained striatal mitochondrial complexes I and III, preserving complex I respiration at 27 weeks (Herbst and Holloway, 2015). These results suggest that endurance exercise normalizes both mitochondrial content and function in R6/1 HD model mice in various tissues (Herbst and Holloway, 2015).

Another molecule that may contribute to HD pathology by altering mitochondrial enzymatic activity is nitric oxide (NO) (Caldwell et al., 2020). Precise regulation of NO both as a retrograde neurotransmitter and as a post-translational modifier in the CNS is essential for healthy brain function, its supply with blood, and the immune response, playing a role in both neuron survival and premature cell death (Dzoljic et al., 2015). Neuronal NO production is downregulated in HD and may exacerbate negative phenotypes and cell loss through excitotoxicity, reactive oxygen species (ROS) generation, and activation of cell death pathways (Deckel, 2001; Padovan-Neto et al., 2019). Studies in humans and animal models showed that endurance exercise elevates NO in muscle and CNS in normal subjects and in the presence of neurodegeneration in HD (Caldwell et al., 2020; Qi et al., 2020; Virarkar et al., 2013); consequently, increasing NO may restore deficits in neuronal mitochondrial complex activity by reversing aberrant elevation of mitochondrial bioenergetics during HD progression (Bernassola et al., 1999; Chen et al., 2006; Kingwell, 2000). In a CAG^{140} knock-in (KI) mouse model of HD, 12 weeks of treadmill exercise increased NO and normalized levels of transglutaminase, a multi-functional enzyme that can cross-link mitochondrial proteins and is elevated during neurodegenerative disease (Kumar et al., 2012). Abnormally high transglutaminase activity may contribute to inappropriate protein aggregation, sensitivity to reactive oxygen species, and cell death (Kumar et al., 2012). Endurance exercise also increased aconitase activity in CAG^{140} HD mice, critical for tricarboxylic acid cycle-mediated cellular metabolism and reduced in the caudate and putamen in HD (Caldwell et al., 2020; Kim et al., 2005; Martinez-Reyes and Chandel, 2020). Restoration of NO levels and mitochondrial complex activity was accompanied by

improved rotarod performance (Caldwell et al., 2020). Altogether, these studies strongly indicate that exercise can improve HD phenotypes, at least in part by restoring mitochondrial content and oxidative phosphorylation complex activity.

It is also possible that endurance exercise improves HD phenotypes in mice in a non-mutually exclusive manner by directly reducing hyperactive cell death. Inappropriate activation of apoptosis may contribute to HD progression, and *in vitro* studies linked apoptosis and mHTT protein (Hickey and Chesselet, 2003; Petersen et al., 1999). In an HD mouse model in which the NMDA receptor agonist, quinolinic acid is injected intrastriatally to induce excitotoxicity (Bruyn and Stoof, 1990), 14 days of treadmill exercise increased anti-apoptotic BCL2 protein expression in hippocampus and decreased expression of the apoptotic indicators caspase-3 and BAX relative to unexercised HD controls. Molecular changes were accompanied by improved spatial learning on the radial 8-arm maze and improved rotarod performance (Ji et al., 2015). This study suggests that exercise reduces HD-related deficits triggered by hippocampal apoptosis, where dysfunction contributes to learning and memory impairments (Vidal-Sancho et al., 2020), even after a relatively brief period of endurance training.

Exercise effects have also been tested in a *C. elegans* HD model in which touch neurons are specifically affected by polyQ expansion (Parker et al., 2001; Vayndorf et al., 2016). Long-term exercise in *C. elegans* increases organismal healthspan, improving mitochondrial respiration, survival, and function in multiple organ systems including muscle, gut, and nervous system (Laranjeiro et al., 2019). Premature deficits in touch sensitivity were alleviated by swim exercise across ages relative to sedentary HD worm controls, suggesting that long-term exercise improves neuronal healthspan (Laranjeiro et al., 2019).

C. elegans models take advantage of short lifespan, easily manipulated genetics, and a fully mapped nervous system composed of 302 neurons, making them a powerful organism to study the molecular and genetic underpinnings of both exercise and neurodegenerative disease (Liang et al., 2020). Interestingly, swim exercise in *C. elegans* provides the greatest long-lasting benefit when initiated early, and overtraining yields maladaptive effects, highlighting the importance of exercise timing and intensity to protect against neurodegenerative phenotypes, as observed in patients with ALS, AD and PD.

While multiple studies in animal models indicate health benefits from exercise in HD and propose several potential mechanisms of neuroprotection, less work has been reported in humans. Similar to previously discussed neurodegenerative diseases, exercise is generally recommended in HD, but benefits tend to be related to cardiovascular, metabolic, and psychological health (Mueller et al., 2019b). Effects of exercise on HD progression, if present, tend to be neutral or modest (Mueller et al., 2019b). For example, muscle biopsies from 13 HD patients with low-disease severity and 11 healthy controls completing a 26 week program of 30–50 minutes of 65% max HR cycling demonstrated restoration of mitochondrial bioenergetics by increasing citrate synthase activity, which is known to increase during normal exercise and used as a biomarker of aerobic capacity and mitochondrial density (Leek et al., 2001), complex III and V activity, and Succinate Cytochrome c Reductase activity. These muscle-specific changes were accompanied by

decreased complex I and II activities. Respiratory capacity of complexes I and IV, fatty acid oxidative capacity, and oxidative phosphorylation capacity also increased (Mueller et al., 2017). A follow-up study by the same group compared muscle biopsies in 10 early- and intermediate-stage HD patients and 9 healthy controls. Here, no post-exercise changes were observed in myosin heavy chain cross sectional area, myonuclear cell count, or satellite cell count in the samples from HD patients. In contrast, exercised healthy patients showed increases in all histological parameters. Exercised HD patients failed to induce satellite cell activation and proliferation after exercise, suggesting that impaired tissue remodeling and myofiber turnover may contribute to muscle wasting phenotypes sometimes seen in HD patients (Mueller et al., 2019a).

Progression of motor function in HD can be quantified using the Unified Huntington's Disease Rating Scale motor section, and neuropsychological function can be quantified using tests like the Mattis dementia rating scale, Hopkins verbal learning tests, and the Stroop tests (Hungtington Study Group, 1996; Hodges et al., 1990; Lemiere et al., 2004; Salmon et al., 1989). In a study of 12 male HD patients and 12 healthy age- and sex-matched controls completing 6 months of cycling exercise at 65% VO_{2peak}, exercised HD patients were adapted to endurance exercise with increased VO_{2peak} and improved body composition; also, the Unified Huntington's Disease Rating Scale and neuropsychological parameters did not decline, suggesting generalized stabilization of disease progression (Frese et al., 2017). Importantly, there were no negative outcomes from this type of training, although HD patients performed worse than healthy controls in all motor and neuropsychological outcomes. This study highlighted that exercise can improve quality of life in HD patients without negatively impacting disease phenotypes.

Accumulating evidence suggests that exercise training in HD patients is a safe option without negative effects on disease progression (Mueller et al., 2019b). Studies in animal models and humans show benefits to cardiovascular, cellular, and mitochondrial function (Caldwell et al., 2020; Frese et al., 2017; Mueller et al., 2019a; Mueller et al., 2019b), while effects on motor function and cognition are less clear (Frese et al., 2017). Although these studies provide support for the use of exercise as complementary intervention to maintain quality of life in HD patients, additional genetically controlled animal investigations and long-term patient studies are needed to strengthen evidence-based conclusions about the potential benefits of exercise and to uncover specific molecular steps that underscore any potential benefits, which may enable clinical intervention for those unable to conduct exercise regimens.

Spinocerebellar Ataxias (SCAs)

Spinocerebellar Ataxias, characterized by progressive loss of balance and coordination as well as speech disruption, include inherited and sporadic diseases (Klockgether et al., 2019). Familial forms of SCAs comprise a form of dominantly inherited ataxias, of which there are over 40 genetically distinct subtypes (Klockgether et al., 2019). SCAs are further subdivided into those caused by dynamic repeat expansions, which we will discuss here, and those caused by non-repeat mutations. The five SCAs on which we will focus are caused by

expanded CAG(A) repeats, similar to HD, encoding abnormally long polyQ regions in their disease proteins (Figure 5), thus referred to as polyQ SCAs (Klockgether et al., 2019).

PolyQ disorders share common pathogenic mechanisms, involving primarily a toxic gain-of-function acquired by the disease protein. PolyQ disorders are progressive, show aggregation of the toxic protein, and usually manifest in adults (Buijsen et al., 2019; La Spada and Taylor, 2003; Lieberman et al., 2018; Paulson et al., 2017; Todi et al., 2007; Zoghbi and Orr, 2000). The potential impact of exercise has been examined to a limited extent in patients with advanced polyQ SCAs: some types of exercise might help in certain cases but not others (Chang et al., 2015; D'Abreu et al., 2010; de Oliveira et al., 2018; Wang et al., 2018). Here, we review recent work in animal models and in patients that highlights the effects of endurance exercise on most polyQ SCAs, focusing on underlying mechanisms and changes in disease phenotypes (Fig. 6).

SCA1

Spinocerebellar Ataxia Type 1 (SCA1) is a rare autosomal dominant disorder characterized by dysarthria, hypermetric saccades, impaired gait and balance, progressive loss of motor skills, and other neurological symptoms (Perez Ortiz and Orr, 2018). Like other SCAs, the disease protein, ATXN1 is broadly expressed, but in SCA1, cerebellar Purkinje cells and deep cerebellar and brainstem nuclei are particularly prone to dysfunction and premature cell death (Zoghbi and Orr, 2009). Normal alleles of *ATXN1* have CAG repeats from 6–35, intermediate alleles have 36–38 repeats, and fully penetrant pathogenic alleles have repeats of 39 or greater (Nethisinghe et al., 2018).

To test the neuroprotective potential of mild exercise in a rodent model of SCA1, a 4-week long, fixed-speed rotarod program was tested in $Atxn1^{154Q}$ KI mice. Although no significant improvement in motor performance was described, exercise significantly extended lifespan in $Atxn1^{154Q}$ mice compared to unexercised $Atxn1^{154Q}$ siblings (Fryer et al., 2011). Lifespan extension was accompanied by increased brainstem expression of EGF and reduction of the transcriptional repressor Capicua (Cic) (Fryer et al., 2011). Furthermore, a 50% reduction of Cic in $Atxn1^{154Q}$ mice ($Atxn1^{154Q}$;Cic-$L^{+/-}$) rescued motor performance in the open-field assay, dowel test (in which investigators score the number of times a mouse reaches the enclosed end of a suspended 0.9 cm dowel), rotarod, and a conditioned fear assay of learning and memory. $Atxn1^{154Q}$;Cic-$L^{+/-}$ mice also retained Purkinje cell number and integrity, were able to increase body weight, and showed extended survival (Fryer et al., 2011). These results suggested that exercise improves longevity of $Atxn1^{154Q}$ KI mice by reducing brainstem Cic levels, and that constitutive Cic reduction may rescue SCA1 motor phenotypes by increasing cerebellar neuron activity and metabolism by ameliorating transcriptional hyper-repression (Fryer et al., 2011). Here, exercise alleviated premature mortality and revealed transcriptional mechanisms important to SCA1 disease progression.

Pathogenesis of SCA1, as with the other polyQ SCAs, is associated with the accumulation of protein aggregates in neurons. The mechanistic target of rapamycin (mTOR) pathway regulates cell growth, survival, and proliferation, and has multiple roles in the CNS, including regulation of autophagy (Perluigi et al., 2015). In the broader context of polyQ proteinopathies, both mTOR activation and inhibition have alleviated bioenergetic and

neurodegenerative dysfunction (Sanchez et al., 2016; Sarkar, 2013), and endurance exercise is known to modulate mTOR activity (Lloyd et al., 2017; Watson and Baar, 2014). One mechanism by which mTOR activity may alter neurodegeneration is by modifying autophagy, a cellular pathway that degrades several aggregation-prone proteins (Sarkar, 2013).

A study using SCA1^{82Q} transgenic mice described the effect of early exercise intervention on the deterioration of cerebellar neurons, mobility, neuron survival and activity, and the expression of mTOR and autophagy related proteins (Chuang et al., 2019). After 4 weeks of daily treadmill exercise, SCA1^{82Q} transgenic mice improved motor performance on the rotarod compared to untrained SCA1^{82Q} controls (Chuang et al., 2019). Exercised SCA1^{82Q} mice also showed reduced cerebellar Purkinje cell loss compared to the untrained group and had increased phosphorylated ribosomal protein S6 (rpS6) in the cerebellum, a marker of mTOR activity. Autophagic markers P62 and microtubule-associated protein light chain 3 (LC3) did not increase in exercised SCA1 mice, although both increased in exercised wild type control mice (Chuang et al., 2019). This research presented the capacity of endurance exercise to improve mobility and Purkinje cell stability via an autophagy-independent mechanism, at least in part by increasing rpS6. While rpS6 phosphorylation modulates cell size, neuron activity, glucose metabolism and cell proliferation, this study shows that endurance exercise increased mTOR overexpression in both cortical neurons and other cell types, suggesting mTOR-mediated cell proliferation may drive enhanced neuron survival in this context (Chuang et al., 2019). Based on these studies, endurance exercise restores metabolic dysfunction in neurons by regulating both transcription and post-translational modifications, increasing neuron survival in SCA1.

SCA2

Spinocerebellar ataxia type 2 (SCA2), caused by CAG repeat expansion in *ATXN2*, is a hereditary polyQ disorder characterized by progressive ataxia and slow saccades (Scoles and Pulst, 2018). Toxic gain-of-function from expanded polyQ in the ATXN2 protein results in slow Purkinje cell firing and eventual neuron loss (Scoles and Pulst, 2018). SCA2 patients experience similar symptoms to other SCA patients and clinically distinct signs like muscle cramping, slow or absent saccades, neuropathy, muscle spasticity, and frontal-executive dysfunction (Ashizawa et al., 2013). SCA2 phenotypes arise almost exclusively from the cerebellum, with the exception of distinct features that originate from the oculomotor brainstem (Gwinn-Hardy et al., 2000). CAG repeats ≥33Q cause SCA2, but intermediate repeats between 27 and 33Q are associated with an increased risk for ALS (Elden et al., 2010). As with other SCAs, there is no cure for SCA2 and therapies are designed to control symptoms. Prevention of toxic aggregate accumulation and examination of endogenous gene function, namely RNA quality control, Ca^{2+} homeostasis, and ATXN2 expression, are routes considered for therapeutic intervention (Liu et al., 2009; Ragothaman and Muthane, 2008; Ralser et al., 2005).

Like in SCA1, mTOR signaling has been implicated in ATXN2 regulation. Poly(A)-binding protein interacts with the polyA end of mRNA during the initiation of protein translation, and Poly(A)-binding protein and ATXN2 physically interact (Ralser et al., 2005). Cultured

mouse embryonic fibroblasts null for *Atxn2* show increased levels of phospho-S6K and 4EBP1, which are downstream targets of mTOR signaling. Additionally, *ATXN2* mRNA levels are higher in cultured SH-SY5Y cells treated with rapamycin, a specific inhibitor or mTOR, suggesting *ATXN2* activation under the translational regulation of Poly(A)-binding protein when mTOR is inhibited (Lastres-Becker et al., 2016). Despite the diverse effects of endurance exercise on the genetic programs related to improved healthspan, little work has been done directly linking exercise to SCA2. Limited investigations in small patient cohorts suggest that exercise may be beneficial.

One study included a controlled trial of prodromal SCA2 patients undergoing 12 weeks of neurorehabilitation. Study participants were prescribed a 12-week walking exercise, balance and coordination regimen for four hours per day, five days per week (Velazquez-Perez et al., 2019). Participants were assessed before and after exercise for five-meter (5-m) tandem gait on the floor, 5-m tandem gait on a mattress, and time upholding tandem position with eyes closed on the floor, on a mattress, and on a seesaw. Secondary outcomes were finger-nose test and heel-shin test, along with time to complete the 9-hole peg board, a test of manual dexterity (Velazquez-Perez et al., 2019). The scores of both the Scale for the Assessment and Rating of Ataxia (SARA) and the Inventory of Non-Ataxia Symptoms were obtained at the end of rehabilitation (Schmitz-Hubsch et al., 2008; Schmitz-Hubsch et al., 2006). Exercised subjects showed significantly reduced times in the 5-m tandem gait over the floor and mattress, and significantly increased time upholding stance over both the mattress and seesaw. Finger-nose and heel-shin tests also improved in the rehabilitated group (Velazquez-Perez et al., 2019). Although molecular mechanisms were not investigated in this study, improvements in gait, posture, and coordination provide an important link between physical exercise and preservation of motor function in SCA2.

A pilot study of early-stage SCA2 patients and other participants with diverse ataxias (SCA1: 1 participant, SCA3: 2 participants, Friedreich's Ataxia: 5 participants) used a proprioceptive stabilizer during physical rehabilitative training that uses vibratory energy to lengthen muscles and modulate spinal reflex excitability (Leonardi et al., 2017). After three weeks of 40-minute physiotherapy sessions wearing the device, participants improved their SARA scores, PATA dysarthria scores (patients repeat the syllables "PA-TA" as quickly as possible), six-minute walking time, and space-time gait parameters like cadence, length of gait cycle, and gait/cycle ratio. Interestingly, positive effects were lasting: patients maintained performance in most outputs after three weeks of continued physiotherapy, even after they stopped wearing the proprioceptive stabilizer (Leonardi et al., 2017).

SCA3

Spinocerebellar Ataxia Type 3 (SCA3), also known as Machado-Joseph disease, is the most common dominantly inherited ataxia worldwide (Carr et al., 2019). SCA3 results from abnormal CAG expansion greater than 54 repeats in its disease gene, *ATXN3,* which encodes a deubiquitinase. The accumulated disease protein is most often seen as ubiquitin-positive intranuclear inclusions in pontine neurons (Matos et al., 2019; Paulson, 2012; Paulson et al., 1997; Perez et al., 1998; Uchihara et al., 2001; Yamada et al., 2001). Much like the aforementioned SCAs, SCA3 is progressive and results in cell loss in the brain

stem, cerebellum, pontine, and other select areas. Progressive neuromotor dysfunction in the brainstem, oculomotor system, pyramidal and extrapyramidal pathways, lower motor neurons, and peripheral nerves leads to gradual weakening of muscles and neurogenic atrophy (Cancel et al., 1995; Dürr et al., 1996; Friedman, 2002; Friedman et al., 2003; Lin and Soong, 2002; Matos et al., 2019; Matsumura et al., 1996; Paulson, 2012; Rub et al., 2004; Rüb et al., 2003; Rüb et al., 2004; Rüb et al., 2002a; Rüb et al., 2002b; Sasaki et al., 1995; Schöls et al., 1996; Sequeiros and Coutinho, 1993; Soong et al., 1997; Takiyama et al., 1994; Watanabe et al., 1998; Zhou et al., 1997). Onset of symptoms begins with gait imbalance, vestibular dysregulation, and speech problems, progressing to advanced pathology including dysphagia and complete loss of mobility. There is no cure for SCA3 and death usually results from asphyxia within 20–25 years of symptom onset (Klockgether et al., 2019; Paulson, 2012).

Extending the period of healthy mobility is of high importance to individuals suffering from ataxia. In fact, among Aboriginal families in communities across Australia's top end, where SCA3 is more prevalent than in any other global region, patients describe "staying strong on the inside and outside" and "exercising your body" as major factors allowing them to do "what mattered most to them in life" (Carr et al., 2019). Although few investigations directly examined the effect of endurance exercise on SCA3 progression, some work was done that supports the benefits of physical activity on SCA phenotypes.

A study of early-stage SCA patients, including six individuals with SCA3 (and one participant each with SCAs 2 and 7) observed the effects of partial body weight support treadmill training on function and quality of life (de Oliveira et al., 2018). The first stage of the study examined gait performance, treadmill inclination, exercise duration, and cardiorespiratory capacity via cardiopulmonary exercise testing with ventilatory expired gas analysis and respiratory oxygen uptake during exercise (VE_{peak}/ VO_{2max}). Participants significantly improved gait balance during partial body weight supported treadmill walking, cardiorespiratory capacity, and treadmill inclination (de Oliveira et al., 2018). Five participants moved onto stage two, in which partial body weight supported treadmill walking was combined with catching a ball, testing balance and coordination. Although SARA scores, ADLs and VE_{peak}/ VO_{2max} did not significantly change, the score in the Berg balance scale, a measure of postural control, increased significantly (de Oliveira et al., 2018; Miyamoto et al., 2004).

A second study by the same investigators examined the impact of static and dynamic balance exercises on Berg balance scale scores before and after intervention in a similar patient cohort (SCA3: 8 participants, SCA2: 2 participants, SCA7: 1 participant) (Santos de Oliveira et al., 2015). In contrast to endurance exercise, which centers around cardiorespiratory performance, balance exercises are geared toward increasing balance and reducing fall rates, particularly important in preventing comorbidities and improving independence in patients with neuromotor defects (Halabchi et al., 2017). Berg balance scale scores significantly increased after balance training for all study participants, even after modifications in the protocol that tailored frequency and intensity downward to account for participant ability, to increase participation and feasibility (Santos de Oliveira et al., 2015).

Conventional balance training has also been directly compared to core stability training in early to moderate stage SCA3 patients able to walk a minimum distance of 10 meters to see if balance and fear from falls was differentially affected depending on training subtype (Tabbassum et al., 2013). After 4 weeks of hourly sessions performed three times per week, participants in the core stability training group significantly increased Balance Evaluation Systems Test Efficacy Scale scores compared to the conventional training group, but neither group improved Modified Falls Efficacy Scale scores, suggesting that more targeted, core-specific training may enhance physiotherapy by improving dynamic balance in SCA patients (Tabbassum et al., 2013).

Exergaming has also been studied to assess whether or not the use of interactive video games during exercise training improves therapeutic outcomes in early stage SCA3 patients (Wang et al., 2018). Patients were assigned to either traditional balance and coordination training or a comparable program paired with an exergaming program and with a Microsoft Xbox Kinect Sensor (Wang et al., 2018). Here, both groups improved SARA scores at the end of the conditioning period. Interestingly, after four weeks of intervention, only the exergaming participants improved gait-posture SARA scores, suggesting that the Kinect Sensor may provide real-time motor-specific feedback to the cerebellum of SCA patients that helps guide performance, often a challenge during normal balance and coordination training (Shih et al., 2016; Wang et al., 2018).

SCA6

Spinocerebellar Ataxia Type 6 (SCA6) is a late-onset, slowly progressing ataxia mainly characterized by cerebellar signs and eye movement problems (Globas et al., 2008; Maruyama et al., 2002; Stevanin et al., 1997). SCA6 results from CAG repeat expansions from 20 to 33 in the *CACNA1A* gene that encodes the α1A subunit of a P/Q type voltage gated Ca^{2+} channel and the transcription factor α1ACT (Du et al., 2013; Fujioka et al., 2013; Tsou et al., 2016). Disease can last over 25 years with some individuals maintaining unassisted mobility more than 20 years after onset (Gomez et al., 1997). Penetrance is nearly 100% in SCA6 patients, but unlike other SCAs, anticipation is not observed (Ishikawa et al., 1997; Yabe et al., 1998). Atrophy is observed in the cerebellum, pons, brainstem, and basal ganglia (Eichler et al., 2011; Murata et al., 1998; Nagai et al., 1998; Soong et al., 2001).

Characterizations of cerebellar ataxic gait include increased step width, variable foot placement, and trajectory, all resulting in a stumbling walking path and increased fall risk (de Warrenburg et al., 2005; Morton and Bastian, 2004). Thus, fall prevention by coordinative training is a primary therapeutic measure. A study of 16 degenerative cerebellar mild to moderate-severity ataxia patients – including SCA6 patients and patients with degeneration in afferent pathways – examined the motor performance effects of intensive coordinative training using pre-training assessments as an intra-patient control (Ilg et al., 2009). Physiotherapy methods included static and dynamic balance training (including sidesteps and stair climbs), whole-body movement, trunk-limb coordination, and fall-prevention strategies. Primary outcomes included SARA scores for gait and posture, speech, and limb-kinetic function as well as ataxia assessment by the international cooperative ataxia rating scale (Ilg et al., 2010; Schmitz-Hubsch et al., 2006). Balance was tested using Berg

balance scale and individual goals were selected using a goal attainment score (Miyamoto et al., 2004). Motor performance was also measured using motion capture to assess velocity, step length and width, and lateral body sway. After weeks of intense coordinative training, both SCA6 patients and those with afferent cerebellar degeneration improved their SARA, International Cooperative Ataxia Rating Scale, and Berg balance scale scores. Interestingly, after an additional four weeks of home-based self-training, only the SCA6 patients retained a long-lasting benefit (Ilg et al., 2009). Gait analysis revealed similar improvements for SCA6 patients, while the afferent group did not improve motor performance (Ilg et al., 2009). SCA6 participants also achieved better results in their individual goal attainment performance than ‘afferent’ participants (Ilg et al., 2009).

The same patients were reexamined one year later in an effort to study the long-term effects of an intensive coordinative training protocol on motor performance and goal attainment (Ilg et al., 2010). Participants were asked to continue an at-home program in which they performed individualized exercises for an hour daily. After one year, disease progression caused an increase in SARA scores, but they did not reach baseline levels (i.e., before coordinative training intervention) (Ilg et al., 2010). While both Berg balance scale and Goal attainment scores were stable or even improved after one year, quantitative movement analysis revealed that improvements in gait and joint coordination in SCA6 patients did not persist long-term (Ilg et al., 2010). These studies showed specific, long-lasting effects of physical activity on SCA6, namely retention of balance and goal attainment, and highlighted the importance of continued intensive physiotherapy to retain motor function.

Obstacle avoidance during ambulation provides an additional challenge for ataxia patients, contributing to a higher risk of comorbidities from falls (Bakker et al., 2006; Fonteyn et al., 2014). A study of 10 early-stage ataxia patients, including patients with SCA6, compared pre- and post-training obstacle avoidance on a treadmill, as well as measures of dynamic stability and performance on an overground obstacle course upon completion of the program (Fonteyn et al., 2014). The treadmill projected visual obstacles and stepping targets onto the belt and provided real-time feedback of gait parameters that could adjust the timing and visual cues according to participant performance (Fonteyn et al., 2014; Roerdink et al., 2008). Success rates on the obstacle avoidance task on the treadmill increased from 78.5% pre-training to 94.8% post-training, with patients typically increasing dynamic stability by shortening steps to avoid obstacles (Fonteyn et al., 2014). SARA scores and the obstacle subtask of functional ambulation also improved (Baer and Wolf, 2001; Fonteyn et al., 2014). These promising trials demonstrated the adaptive potential of SCA6 patients and others to physiotherapy and underscore the importance of exercise as a therapeutic intervention.

SCA7

Spinocerebellar Ataxia Type 7 (SCA7) results from abnormal CAG expansion in the *ATXN7* gene, which is part of Spt-Ada-Gcn5 acetyltransferase (SAGA), a conserved transcriptional coactivation complex (Garden and La Spada, 2008; Helmlinger et al., 2004). SAGA has chromatin remodeling activities essential for RNA polymerase II transcription and modifies autophagy, mitochondrial homeostasis, cell-cell interactions, and neuronal differentiation (Bonnet et al., 2014; Niewiadomska-Cimicka and Trottier, 2019). Like previously discussed

SCAs, progressive neuronal loss in the cerebellum and brainstem lead to ataxia, while blindness from retinal cell loss is an exclusive feature of SCA7 (Niewiadomska-Cimicka and Trottier, 2019). Studies in cell culture and animal models showed that gene expression and transcriptional regulation contribute to SCA7 pathogenesis, and epigenetic factors like acetylation and microRNAs also play an important role (Abou-Sleymane et al., 2006; Kizilyaprak et al., 2011; Tan et al., 2014; Yoo et al., 2003).

Although there is no cure for SCA7, exercise is known to modify autophagy, mitochondrial health, gene expression, and epigenetics, all important in disease progression (Fernandes et al., 2017; Kim et al., 2020b; Laker et al., 2014). Furthermore, physical training significantly improved outcomes and biomarkers in SCA7, suggesting exercise may provide a non-pharmacological treatment option for patients (Niewiadomska-Cimicka and Trottier, 2019; Tercero-Perez et al., 2019). In a six-month long study of SCA7 patients with moderate disease severity, subjects randomly assigned to an intensive training group or moderate training group performed two-hour sessions of neurorehabilitation exercises five or three days per week, respectively. Neuro-rehabilitative techniques that were utilized included: balance training; relaxation and breathing exercises; stretching, which is particularly helpful in the prevention of muscle spasticity and contracture; and resistance exercise, which can improve fatigue and ambulation (Halabchi et al., 2017; Tercero-Perez et al., 2019). Outcomes from exercised groups were compared to an untrained control group (Tercero-Perez et al., 2019). Physical activities were adjusted according to the visual acuity of the patients and focused on motor control, gait adjustment, coordination, static and dynamic balance, physical conditioning, and muscular strengthening (Tercero-Perez et al., 2019). Participants were assessed pre-training, after 12 weeks, and post-training. SARA scores improved at 12 weeks and post-training in both the moderate and intensive training groups for gait, posture, dysarthria, dysmetria, tremor, and stance, while no significant effect was observed in the control group. Extracerebellar scores and Inventory of Non-Ataxia Signs were unaffected by training (Tercero-Perez et al., 2019). Finally, trained participants had decreased levels of dityrosine, malondialdehyde, and lipid hydroperoxides, markers of protein and lipid damage, which suggested that neurorehabilitation prevents protein damage and enhances antioxidant activity in SCA7 patients (Tercero-Perez et al., 2019).

Large, well-controlled investigations of the motor features and functional declines in SCA patients are partially limited by variability in exercise compliance and participant composition, often comprising patients from multiple SCA classifications (Fonteyn et al., 2014; Leonardi et al., 2017; Miyai et al., 2012; Tabbassum et al., 2013). Tercero-Perez et al., summarized above, report specific, therapeutic effects of exercise in SCA7 patients, namely improved cerebellar symptoms and increased circulating antioxidant defense markers (2019). Future studies may identify clinical and molecular features of distinct ataxias by applying uniform exercise protocols to each ataxia individually.

Few studies have explored the effect of endurance exercise on polyQ SCA phenotypes, but positive associations exist between increased activity and enhanced quality of life (Fujioka et al., 2013). While investigations using animal models of exercise and ataxia are limited, there is consistent clinical evidence that exercise and physical rehabilitation improve function, quality of life, mobility, and balance (Milne et al., 2017). There is a clear

need for additional, well-controlled animal studies and longitudinal clinical investigations to clarify both the effects of exercise on specific polyQ SCAs and the mechanisms behind these effects. These studies will allow us to distinguish whether increased physical exercise directly alleviates polyQ SCA phenotypes or complements care.

Spinobulbar Muscular Atrophy (SBMA)

Spinobulbar Muscular Atrophy, also known as Kennedy's Disease, is another polyQ disorder. Unlike the previously discussed HD and SCAs, the SBMA-causing mutation is not autosomal but occurs in the androgen receptor (AR) gene on the X chromosome (Brooks and Fischbeck, 1995; Dahlqvist and Vissing, 2016; La Spada et al., 1991). Normal polyQ AR length ranges from 9–36Q, while expansions from 38–62Q residues are pathogenic (Parodi and Pennuto, 2011). SBMA is a slowly progressing disease characterized by lower motor neuron dysfunction yielding weakness and atrophy of bulbar and extremity muscles (Dahlqvist and Vissing, 2016). Disease progression may be a result of motor neuron loss and muscle denervation; direct skeletal muscle involvement is likely another significant contributing factor (Cortes et al., 2014; Giorgetti et al., 2016; Soraru et al., 2008). In other words, motor dysfunction may be a result of toxic gain-of-function in both neurons and muscle. Fortunately, exercise has powerful effects in multiple tissues (Leal et al., 2018; Sujkowski et al., 2015; Sujkowski et al., 2020; Sujkowski et al., 2017; Sujkowski et al., 2019) and may benefit patients with SBMA. Observations in humans and animal models suggest that exercise may improve SBMA phenotypes through enhanced mitochondrial equilibrium, activation of dysfunctional AR by testosterone, and increased levels of insulin-like growth factor-1 (IGF-1) that are normally low in SBMA (Palazzolo et al., 2009; Petzinger et al., 2013; Ranganathan et al., 2009).

Like previously discussed progressive neurodegenerative disorders, evidence from animal models suggests that exercise may act through conserved pathways to improve SBMA phenotypes, but excessive modulation of these same pathways may also contribute to dysfunction. Several murine studies show that SBMA progression is characterized by metabolic dysfunction, mitochondrial dysregulation, and defects in autophagy, pathways that are modified by endurance exercise (Chua et al., 2014; He et al., 2012; Kim et al., 2020b; Laker et al., 2014; Rocchi et al., 2016; Sujkowski et al., 2012). In a transgenic mouse model of SBMA (ARQ113), RNAseq showed reduction in carbohydrate metabolism genes and upregulation of lipid mobilizing genes, indicating a shift from glycolytic to oxidative metabolism. SBMA mice had altered mitochondrial number and morphology as well as dysfunctional metabolic and physiological responses to exercise (Giorgetti et al., 2016). SBMA mice fatigued faster than exercised background genetic controls, relying on mobilization of lipid stores to cope with exercise-induced increases in energy requirements and failing to display muscle adaptations characteristic of exercise (Giorgetti et al., 2016). SBMA mice also failed to improve grip strength or endurance, and both Type I and Type II muscle fibers were reduced after exercise, suggesting that endurance exercise may not be well tolerated (Giorgetti et al., 2016).

A second study in ARQ113 mice implicates increased muscle-specific expression of Transcription Factor EB, critical for lysosomal biogenesis, and increased autophagy as

important factors contributing to SBMA disease progression (Chua et al., 2014). Here, observations in cultured cells revealed reduced mTOR-signaling, providing a potential mechanism for upregulation of autophagy in ARQ113 cells. Muscle histology from ARQ113 mice identified mTOR-dependent upregulation of Transcription Factor EB and subsequent increases in both baseline and exercise-induced autophagy in muscles (Chua et al., 2014). Although these studies do not suggest exercise-induced improvements in SBMA phenotypes, they provide important clues about the mechanisms of disease progression. Taking these investigations into account, clinical studies may be able to modify protocols to maximize desirable cellular adaptations without inducing maladaptive effects, as indicated by human studies, discussed next.

Studies in SBMA patients have suggested that varying exercise intensity may be one way to improve disease phenotypes without exacerbating degeneration. For example, 50 moderate-severity SBMA patients were recruited to a home-based functional exercise program and assigned to either low-intensity exercise or stretching program control groups; both groups tolerated exercise well but did not achieve significantly different outcomes in the Adult Myopathic Assessment Tool or secondary outcomes like activity level, muscle strength, and balance regardless of training assignment (Harris-Love et al., 2014; Shrader et al., 2015). However, post-hoc analysis that divided participants into low- and high-functioning subgroups noted significant improvement in Adult Myopathic Assessment Tool scores for the exercised, low-functioning subgroup (Shrader et al., 2015). This study suggested dose-dependent benefits of exercise in SBMA patients, and that exercise intensity should be prescribed according to function.

In a second study, eight SBMA patients, pre-screened for baseline ability to complete 20 minutes of uninterrupted cycling, performed 30 minutes of cycling at 65–70% VO_{2max}, gradually increasing session frequency until the end of the 12-week training (Preisler et al., 2009). Primary outputs included VO_{2max}, performed workload, and self-reported ADLs; secondary outputs were muscle morphology, citrate synthase activity, body composition, EMG, static strength, and lung function (Preisler et al., 2009). Moderate-intensity exercise was not well tolerated, and frequency was decreased prior to the end of the training program. At the end of the 12-week cycling program, moderate exercise led to increases in performed workload and citrate synthase activity, but no other output was significantly affected (Preisler et al., 2009). The authors also examined the plasma levels of creatine kinase (CK), a biomarker of muscle degeneration. They found increased levels of CK during intense exercise, indicating primary myopathy. Primary myopathy, in combination with motor neuron dysfunction, likely mitigated any therapeutic potential of moderate-intensity exercise in this disease (Preisler et al., 2009).

A third investigation studied the effects of high-intensity interval training (HIIT) in pre-screened SBMA patients who exercised less than one hour per week. Investigators hypothesized that HIIT would be better tolerated by patients since it requires less time than low- and moderate-intensity training and therefore motor neurons would be active for less time (Heje et al., 2019). Participants were randomized to either a training or a control group and assessed before, during, and after training. The intervention lasted 16 weeks: 8 weeks supervised and 8 weeks unsupervised. HIIT was based on the 30-20-10 s concept in

which an eight-minute warm up was followed by five-minute high-intensity blocks where patients trained 30 s in low, 20 s in moderate intensity and 10 s all out five times repeatedly, separated by three minute breaks (Gunnarsson and Bangsbo, 2012). Primary outcomes were VO_{2max} and performed workload, and secondary outcomes were the six-minute walk test, pedometer-recorded changes in activity levels, self-reported levels of activity, fatigue, and pain. Serum CK was measured as a marker of muscle damage (Heje et al., 2019). After eight weeks of HIIT, both VO_{2max} and performed workload significantly increased compared to the non-trained groups. Improvements in VO_{2max} and performed workload persisted after an additional eight weeks of at-home HIIT, indicating that supervised training was not necessary for benefits (Heje et al., 2019). CK levels did not rise, and self-rated fatigue, pain, and activity remained stable throughout the 16 weeks of intervention, suggesting that HIIT is well tolerated in SBMA patients (Heje et al., 2019). Participants also described a preference for HIIT over low- and moderate-intensity exercise (Heje et al., 2019).

Taken together, these studies describe maximum benefit to SBMA patients when exercise programs are prescribed based on both intensity and participant disease stage, with maximum benefit and compliance from short duration, high-intensity programs. Evidence suggests that individually tailored interventions – centered around both disease stage and exercise intensity – are essential for SBMA patients to receive maximum benefit. Also, patients must be carefully monitored for maladaptive biomakers in order to prevent muscle damage and worsening of disease phenotypes.

Conclusions

As the population ages, concerns about increased health care responsibilities, including the impact of progressive degenerative diseases, have been amplified (Houde and Melillo, 2009; Yazdanyar and Newman, 2009). Interventions that can preserve body function across ages and diseases are thus of substantial importance. As highlighted by studies with various degenerative disease models and in patients, one promising therapeutic intervention to impede progressive functional decline is endurance exercise. Endurance training induces remodeling in muscle tissue that alters the metabolic health of the entire organism (Bo et al., 2010; Gibala, 2009; Ventura-Clapier et al., 2007). Evidence from humans and model organisms strongly suggests that endurance exercise has substantially protective effects on various indices of healthspan (Cutler and Mattson, 2006).

The potential impact of endurance exercise and physical activity on progressive neurodegenerative disease has been examined in *C. elegans,* rodent models, and in humans. New tools and model systems provide significant information about the molecular mechanisms driving the beneficial effects of endurance exercise in neurodegenerative disease. However, substantial obstacles exist against widespread application of endurance exercise therapy in human neurodegeneration patients. Activation of beneficial pathways is inherently dependent on exercise capacity, and progressive neurodegeneration often limits patient capability and compliance to a training program. Generally, higher activity levels correlate with delayed disease onset. Despite this relationship, researchers have yet to differentiate whether exercise mechanisms are disease-modifying or neuroprotective.

Rodent models have been invaluable to the identification of conserved mechanisms underlying the benefits of endurance exercise on neurodegenerative disease (Dar et al., 2020). Recently, invertebrate model systems have emerged as another valuable tool for the study of exercise in the context of neurodegeneration. Model organisms like *Drosophila* and *C. elegans* have been used to study neurodegeneration for some time, leveraging their easily-manipulated genetics and relatively simple nervous systems (McGurk et al., 2015). Now, endurance exercise paradigms have been established for both *Drosophila* and *C. elegans,* opening the door for complex molecular dissection of neuroprotective pathways (Laranjeiro et al., 2019; Sujkowski and Wessells, 2018). Studies in *C. elegans* have examined exercise effects on both AD and HD phenotypes, highlighting the utility of isogenous, genetically controlled invertebrate models with which to further our understanding of exercise benefits during neurodegeneration. Rapid generation time and short lifespans allow for large-scale, complex longitudinal analysis of genetically identical populations, reducing background effects and allowing for precise physiological and cellular assessments *in vivo*. Many genetic invertebrate models already exist, providing the necessary tools for investigations that build a strong foundation for translational research (McGurk et al., 2015).

It is precisely because of these model organisms and their genetic flexibilities that we have begun to uncover some mechanisms of neuroprotection from exercise. Accumulating DNA damage, caused by exogenous (environmental, physical, biochemical) and endogenous (defective DNA repair, reactive oxygen species) factors, plays a major role in both aging and neurodegeneration, while exercise helps maintain genomic stability during normal aging and neurodegeneration (Madabhushi et al., 2014; Rebelo-Marques et al., 2018). The oxidation-sensitive chaperone DJ-1 has been linked to ALS, PD, HD, and ataxias, and can act as a transcriptional co-activator with Nrf2 and nuclear factor kappa B, improving DNA repair (Islam, 2017; Madabhushi et al., 2014; Rebelo-Marques et al., 2018). Similarly, the exercise-induced transcriptional cofactor peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) augments DNA repair mechanisms both during normal aging and in the presence of neurodegenerative diseases like ALS, PD, and HD (Radak et al., 2002; Wrann et al., 2013). In addition, both DJ-1 and PGC1-α are important for oxidative stress response and mitochondrial homeostasis, critical factors in neurological health and preservation (Onyango et al., 2017).

Oxidative stress is strongly linked to the etiology of chronic neurodegenerative diseases (Akbar and Ashizawa, 2015; D'Amico et al., 2013; Streck et al., 2013; Yan et al., 2013). Neurons are particularly susceptible to oxidative damage-induced dysfunction and cell death due to high energy demands and low antioxidant defense mechanisms (Streck et al., 2013). Evidence from rodent models suggests that exercise increases not only DJ-1 and PGC1-α activity, but also SOD1 and the mitochondrial antioxidant enzymes MnSOD/Cu-ZnSOD, required in neurons for defense against reactive oxygen species generated in the presence of neurodegeneration (Carreras et al., 2010; Lau et al., 2011).

Based on these and other studies, PGC1-α has emerged as a major exercise-induced factor that exerts neuroprotection by modulating several intersecting pathways. Not only does PGC1-α coordinate mitochondrial biogenesis and function; its activity is also required to improve cognitive deficits. In mice, PGC1-α acts via FNDC5, a muscle protein induced by

exercise and cleaved and secreted as irisin, to increase hippocampal expression of BDNF (Wrann et al., 2013). Furthermore, PGC1-α is essential for regulating neural responses to environmental, metabolic, and genotoxic stress, and plays a role in the prevention of inappropriate protein aggregation and premature cell death (Jones et al., 2012).

Preventing the abnormal accumulation of protein aggregates is another shared pathway by which exercise may alleviate neurodegenerative phenotypes. Autophagy is upregulated by exercise and can degrade cargo material such as aggregation-prone proteins and damaged mitochondria (mitophagy), contributing to intraneural homeostasis (He et al., 2012; Laker et al., 2014; Menzies et al., 2017). Evidence from animal models suggests that increased autophagy is linked to reductions in Aβ and tau oligomers as well as removal of damaged mitochondria, reducing neuroinflammation and abnormal protein aggregation in diseases like AD, PD and several polyQ diseases (Newman and Shadel, 2018; Ohia-Nwoko et al., 2014).

An additional, recently identified molecular target that is required for exercise adaptations and healthy aging is the stress-inducible, exercise-mimicking protein, Sestrin (Kim et al., 2020b). Sestrins are induced by oxidative and genotoxic stress in flies and mammals and promote autophagy (Budanov and Karin, 2008; Lee et al., 2010); they protect against oxidative stress-induced fly neuronal death (Singh and Chowdhuri, 2018); and they reduce accumulation of abnormal protein aggregates in mammalian cells (Reddy et al., 2016). As already mentioned, increased oxidative stress plays a harmful role in diseases like AD, PD and polyQ disorders, contributing to neurodegeneration via mitochondrial dysfunction, excitotoxicity, and apoptotic processes (Chen et al., 2019). Autophagy dysregulation is also implicated in neurodegenerative diseases. Proteins such as Sestrin – that can counteract detrimental effects and regulate neuroprotective pathways – may be critical to identifying effective treatments for neurodegenerative disease (Chen et al., 2019).

In wild-type *Drosophila*, expression of fly *Sestrin* is sufficient to extend speed and endurance, and has no additive effect with exercise, consistent with a role as a key effector of exercise (Kim et al., 2020b). In addition, *Sestrin* mutations nullify gains from exercise in both flies and mice, highlighting this gene as a primary player in exercise-dependent benefits (Kim et al., 2020b). Previous work in flies and mice suggests that Sestrins potentiate TORC2 activity and slightly inhibit TORC1, mimicking exercise by enhancing metabolic health without the unwanted negative effects of chronic mTOR activation (Kim et al., 2020b). These findings suggest that activating Sestrin in neurodegenerative disease patients may enable the development of innovative therapeutics that preserve mobility and quality of life, even in patients no longer able to complete an exercise program. To date, it is not clear how Sestrin is involved in exercise-based benefits in neurodegenerative diseases. Still, the data on this intriguing gene collectively suggest it as a target ready for investigation.

Evidence is clear that various types of exercise positively impact age-related problems, including neurodegenerative diseases. Endurance exercise appears to be nearly universally beneficial in animal models and in patients suffering from various diseases of the nervous system — whether motor-related, cognitive-related, or both. Still, additional long-term studies in humans and better-standardized protocols are needed to clarify the mechanisms

that drive the benefits of exercise in neurodegenerative disease. Current limitations include differences in protocols and study design. While studies in animal models allow for tightly controlled experimental conditions, studies in human patients comprise variable exercise modalities, intensities, and patient makeup, making it difficult to form concrete conclusions that are relevant across diseases, biomarkers, and treatments. Genetics, age, and disease stage are also difficult factors to control in human trials. Future efforts to systematically examine which neurodegenerative diseases are responsive to exercise, and what the key mechanisms of exercise effects are, may depend on large, long-term human studies in combination with highly controlled exercise regimens in model organisms. In this way, it may be possible to identify exercise-based molecular mechanisms that can be targeted in the clinic in the future, in lieu of exercise, especially for individuals suffering from severe neurodegeneration who are unable to undergo this type of training. This is of utmost importance given the limited therapeutic interventions for many neurodegenerative diseases.

Funding:

This work was funded at least in part by a Thomas Rumble Graduate Fellowship by Wayne State University to ALS, by NIH R01 AG059683 to RJW, by R21 NS121276 to RJW and SVT, and by R01 NS086778 to SVT.

List of abbreviations from Tables 1 & 2

1RM	Maximal Strength of Knee Extensor Muscles
6-MWT	6-Minute Walking Time
9HPT	9-Hole Peg Board Test
ABC	Activities Specific Balance Scale
ADAM10	A Disintegrin and Metalloproteinase Domain-Containing Protein
ADLs	Barthel Index of Activities of Daily Living
AE	Aerobic
AKT	Serine/Threonine Kinase Akt
ALS-SS	ALS Severity Scale
ALSFRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
ALSFRS-R	Revised ALSFRS-Respiratory
AMAT	Adult Myopathic Assessment Tool
Apoε4	Apolipoprotein E4
BACE1	β-Site Amyloid Precursor Protein Cleaving Enzyme 1
BADL	Basic Instrumental Activities of Daily Living
BAX	Bcl2-Like Protein 4

BB	Balance Beam
BBS	Berg Balance Scale
BCL2	Bcl2 Apoptosis Regulator
BDNF	Brain Derived Eurotrophic Factor
BECN1	Beclin 1
BEST	Balance Evaluation Systems Test Efficacy Scale
BMI	Body Mass Index
BMT	Barnes Maze Task
BP	Blood Pressure
BW	Body Weight
BWST	Body Weight Supported Treadmill Training
CAMCOG	Cambridge Cognitive Examination
CD36	Cluster of Differentiation 36
CDK5	Cyclin Dependent Kinase 5
CIC	Capicua
CK	Creatine Kinase
CPET	Cardiopulmonary Exercise Test
CS	Citrate Synthase
DA	Dopamine
DAD	Disability Assessment for Dementia
DAT	Dopamine Uptake Transporter
DGI	Dynamic Gait Index
DRS-2	Dementia Rating Scale 2
DJ-1	Protein Deglycase DJ-1
DSBW	Digit Span Backward Walking
DSFW	Digit Span Forward Walking
DT	Dityrosine
ECG	Electrocardiogram
EFAP	Emory Functional Ambulation Profile

EGF	Epidermal Growth Factor Receptor
EMG	Electromyography
F-NT	Finger-to-Nose Test
FAS	Fatty Acid Synthase
FIM	Functional Independence Measure
FRDA	Friedreich's Ataxia
FSS	Fatigue Severity Scale
fx	Function
GAPDH	Glyceraldehyde 3-Phosphate Dehydrogenase
GAS	Goal Attainment Score
GDNF	Glial Cell Line Derived Neurotrophic Factor
GET	Gas Exchange Threshold
GLUT4	Glucose Transport Protein 4
GPx	Glutathione Peroxidase
GR	Glutathione Reductase
GSK3	Glycogen Synthase Kinase 3
GT	Glucose Transport
GTT	Glucose Tolerance Test
H-ST	Heel-to-Shin Test
HIT	High-Intensity Training
HIIT	High-Intensity Interval Training
HSP70	Heat Shock Protein 70 kD
HVLT-R	Hopkins Verbal Learning Test-Revised
IADL	Instrumental Activities of Daily Living
ICARS	International Cooperative Ataxia Rating Scale
IL-10	Interleukin 10
INAS	Inventory of Non-Ataxia Symptoms
JNK	c-JUN N-Terminal kinase
Katz ADL	Katz Index of Independence in Activities of Daily Living

KI	Knock-In
L-	Lactate
LC3	Microtubule-Associated Protein Light Chain 3
LC3B	Microtubule-Associated Proteins 1A/1B Light Chain 3B
LCII/III	Microtubule-Associated Protein 1A/1 B-Light Chain 3 Flu
LPH	Lipid Hydroperoxides
LS	Lifespan
LV	Left Ventricular
mATPase	Myofibrillar Adenosine Triphosphatase
MDA	Malondialdehyde
MDS-UPDRS-III	Movement Disorders Society Unified Parkinson Disease Rating Scale-III
MFES	Modified Falls Efficacy Scale
MMSE	Mini-Mental State Examination
mOxPhos	Mitochondrial Oxidative Phosphorylation Complex
MPTP	Methyl-4-Phenyl-1 2 3 6-Tetrahydropyridine
MRCSS	Medical Research Council Sum Score
mtDNA	Mitochondrial DNA
MIT	Moderate-Intensity Training
MWMT	Morris Water Maze Test
NAD+/NADH	Oxidized/Reduced Nicotinamide Adenine Dinucleotide
NO	Nitric Oxide
NOR	Novel Object Recognition
NPI	Neuropsychiatric Inventory
NRF2	Nuclear Factor Erythroid 2-Related Factor 2
P-APP668	Phospho-Amyloid Precursor Protein 998
P62	Ubiquitin Binding Protein P62
PASE	Physical Activity Scale for the Elderly
PDH	Pyruvate Dehydrogenase

PDQ-39	Parkinson Disease Questionnaire-39
POMA	Performance Oriented Mobility Assessment
PON-I	Paraoxonase
PP	Peak Power
PPT	Physical Performance Test
PS1	Presenilin
QOL	McGill Quality of Life Survey
RCR	Respiratory Control Ratio
RHR	Resting Heart Rate
ROM	Range of Motion
rpS6	Ribosomal Protein S6
RUD	Resource Utilization for Dementia
SAOA	Sporadic Adult-Onset Ataxia
SARA	Scale for Assessment and Rating of Ataxia
SCCR	Succinate Cytochrome C Reductase
SDMT	Single Digit Modalities Test
SNpc	Substantial Nigra Pars Compact
SOD	Mn superoxide dismutase
SPPB	Short Physical Performance Battery
ST	Stretching and Toning
STS	Sit to Stand Test
TAG	Triacylglycerol
TEM	Transmission Electron Microscopy
TFEB	Transcription Factor EB
TG	Transglutaminase
TH	Tyrosine Hydroxylase
TMS	Transcranial Magnetic Stimulation
TMTA	Trail Making Test A
TNFα	Tumor Necrosis Factor Alpha

TSH	Thyroid Stimulating Hormone
TUGT	Timed Up and Go Test
Ub	Ubiquitin
UCP3	Uncoupling Protein 3
UHRDS	Unified Huntington Disease Rating Scale
VCO2	Carbon Dioxide Production
VLDLR	Very Low-Density Lipoprotein Receptor
VMSBW	Visual Memory Span Backward
VMSFW	Visual Memory Span Forward
VO2	Oxygen Consumption ml/min/kg
VO2max	Maximal Oxygen Uptake
VO2peak	Peak O2 Uptake
Wmax	Maximum Workload

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Highlights

- Studies from invertebrate and rodent models, and in patient populations with various stages of symptomology, indicate that exercise can be a highly effective therapeutic for age-related neurodegeneration.
- Exercise activates a number of molecular mechanisms that benefit Alzheimer's, Parkinson's, Huntington's, and various inherited ataxia diseases, as well as Amyotrophic Lateral Sclerosis and Kennedy's Disease.
- The precise type of exercise, stage of intervention, and mechanisms underlying benefits vary and may well require personalized programs to harness the most benefits and not worsen motor activities in patients.

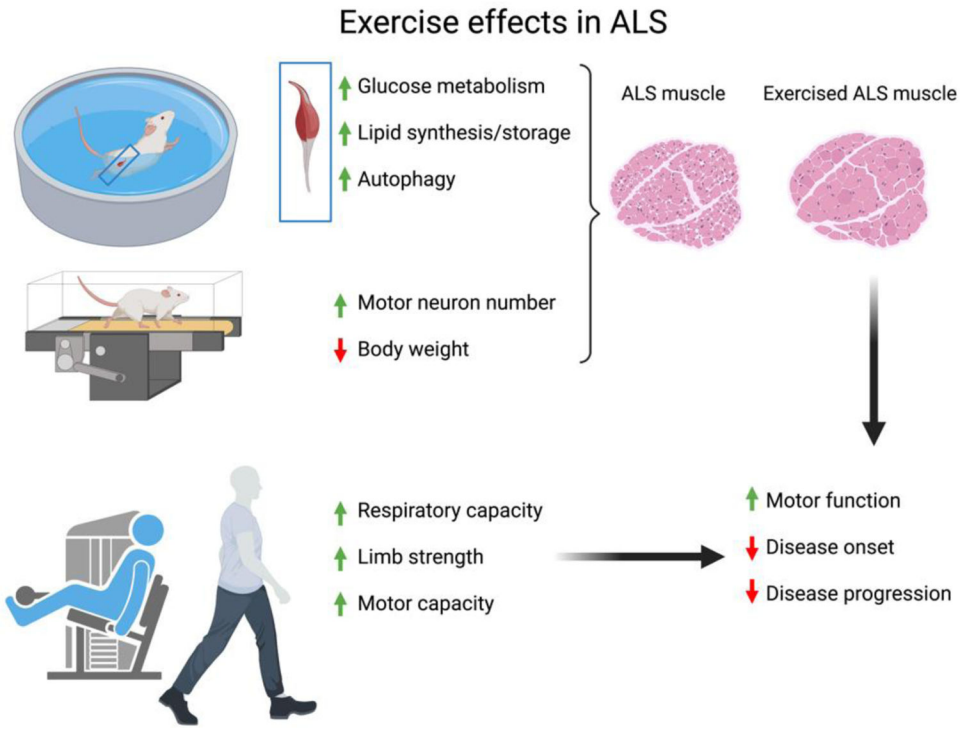


Fig 1: Summary of exercise effects on ALS.

Detailed description of data from animal models is in Table 1. Detailed description of data from human studies is in Table 2.

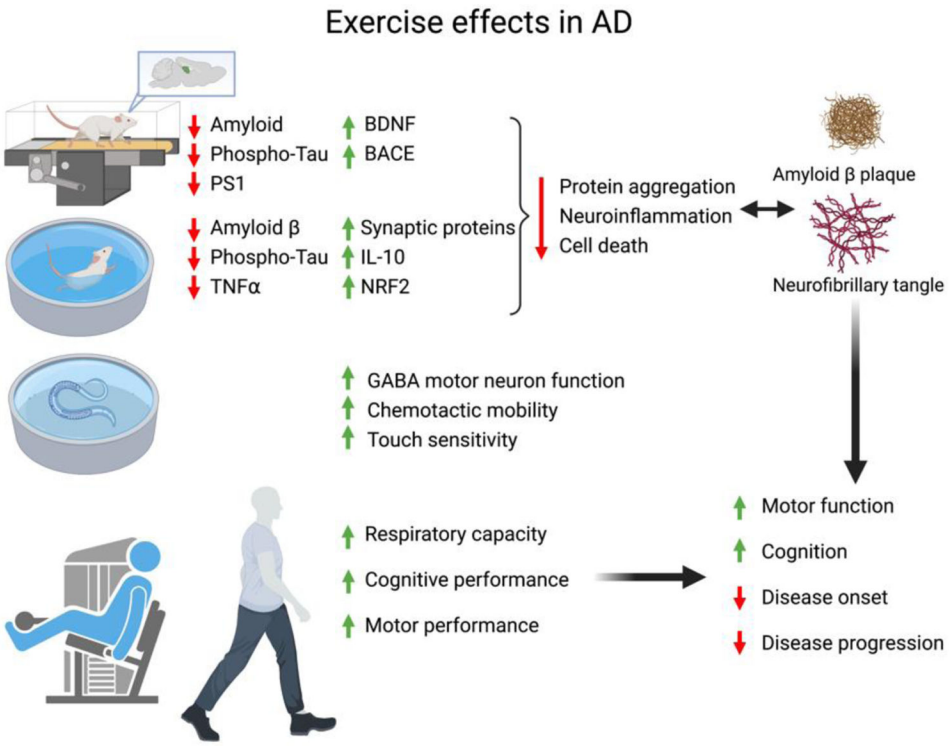


Fig 2: Summary of exercise effects on AD.

Detailed description of data from animal models is in Table 1. Detailed description of data from human studies is in Table 2. Abbreviations: BDNF-brain derived neurotrophic factor, DA-dopamine, DAT-dopamine uptake transporter, DJ-1-protein deglycase DJ-1, GDNF-glial derived neurotrophic factor, Hsp70-Heat shock protein 70kD, TNFα-tumor necrosis factor alpha, SOD-superoxide dismutase.

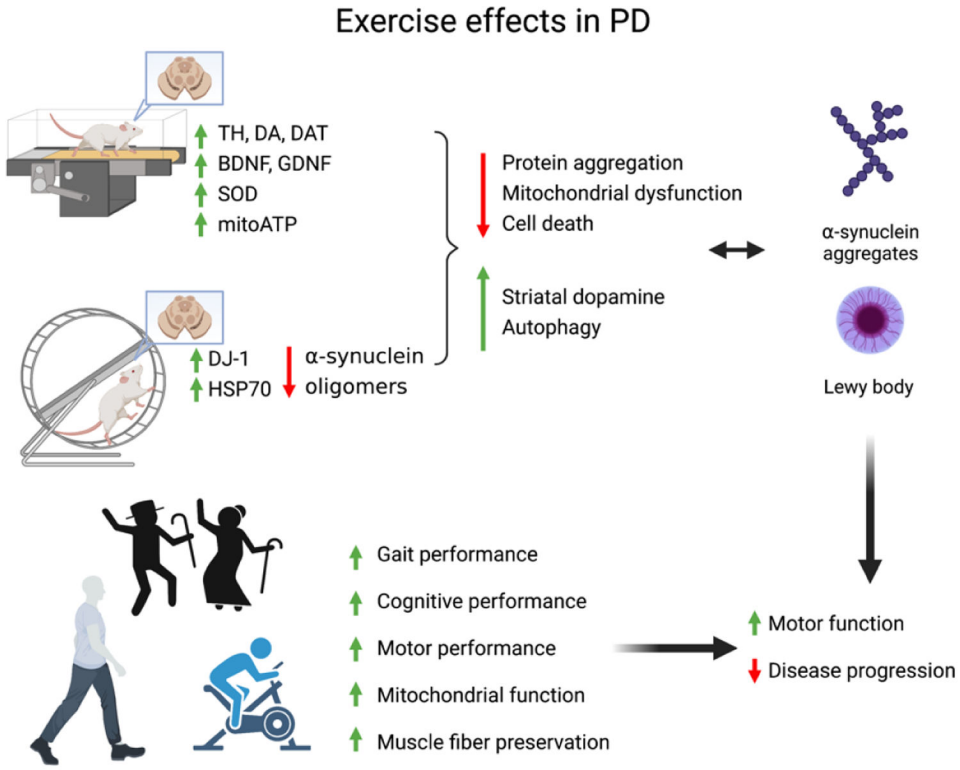


Fig 3: Summary of exercise effects on PD.

Detailed description of data from animal models is in Table 1. Detailed description of data from human studies is in Table 2. Abbreviations: BACE-β-site amyloid precursor protein cleaving enzyme 1, BDNF-brain derived neurotrophic factor, IL-10-interleukin 10, Nrf2-nuclear factor erythroid 2–related factor 2, TNFα-tumor necrosis factor alpha.

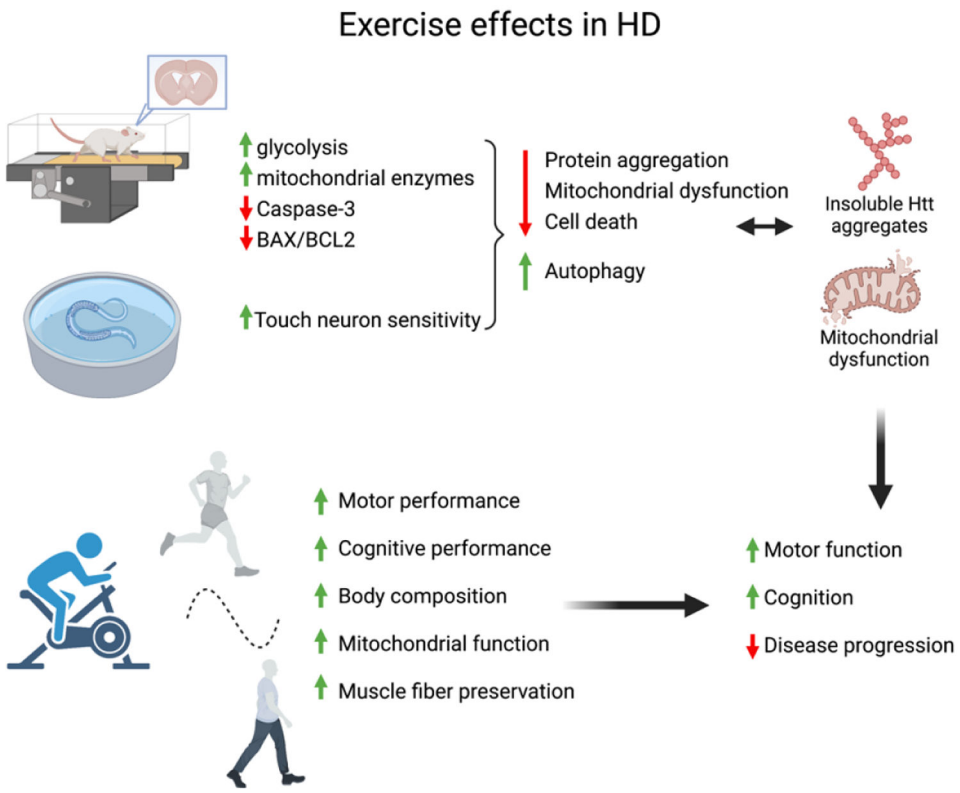


Fig 4: Summary of exercise effects on HD.

Detailed description of data from animal models is in Table 1. Detailed description of data from human studies is in Table 2. Abbreviations: Bax-Bcl-like protein 4, Bcl-2-B cell lymphoma protein 2.

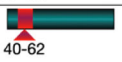
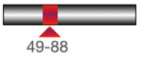
PolyQ Disease	Disease Protein	Relative protein size, polyQ position and polyQ repeat range in disease	Protein function
SCA1	Ataxin-1		Transcriptional regulation
SCA2	Ataxin-2		RNA processing, Translational regulation
SCA3	Ataxin-3		Deubiquitinating enzyme
SCA6	α1A-CT		Transcription factor
SCA7	Ataxin-7		Transcriptional regulation
SCA17	TATA-box-binding protein		Transcriptional regulation
HD	Huntingtin		Possible scaffolding protein
SBMA	Androgen Receptor		Testosterone-activated steroid receptor
DRPLA	Atrophin-1		Transcriptional regulation

Fig 5: The polyQ family of neurodegenerative diseases.

The nine known polyQ diseases are listed along with their causative proteins, the protein's relative size compared to other polyQ disease proteins and their putative functions. Boxed region in SCA6 indicates transcription factor encoded by α1A-CT. Red bars represent the relative location of the polyQ repeat in each protein, and red arrows indicate the range of repeat lengths associated with disease. Whereas CAG/polyQ repeat length is generally stable in an individual (with modest somatic mosaicism), repeat length often changes size in successive generations of a family (Williams and Paulson, 2008).

Abbreviations: DRPLA = dentatorubral-pallidoluysian atrophy; HD = Huntington's disease; SBMA = spinobulbar muscular atrophy; SCA = spinocerebellar ataxia.

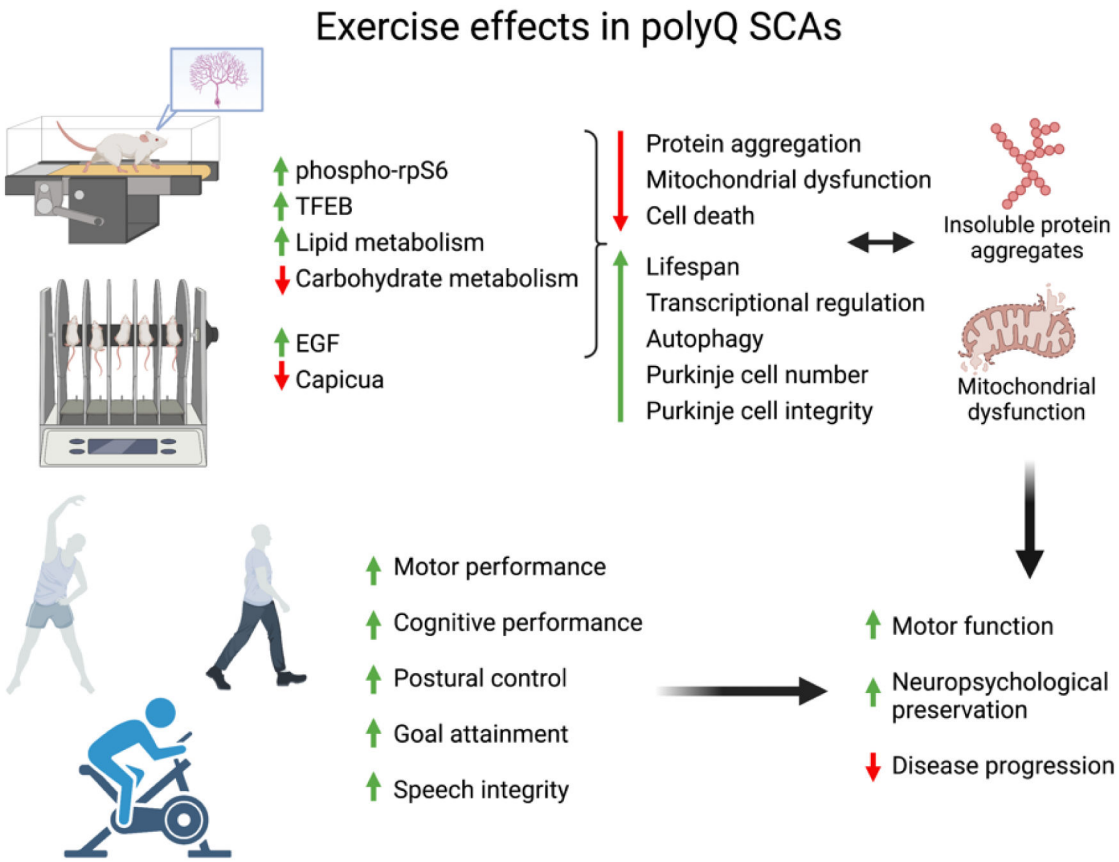


Fig 6: Summary of exercise effects on polyQ SCAs.

Detailed description of data from animal models is in Table 1. Detailed description of data from human studies is in Table 2.

Abbreviations: EGF-epidermal growth factor receptor, phosphor-rpS6-phophorylated ribosomal protein S6, TFEB-transcription factor EB.

Figures 1–4, 6 created with BioRender.com

Table 1.

Exercise Effects in Neurodegenerative Disease: Animal Models

Author, year	Disease	Model system	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
Desseille et al. 2017	ALS	SOD1^{G93A} mouse	Swim exercise, Tread mill	45 days	30min/day 5 days/week	GTT, L^{-} ,GLUT4, GAPDH, PDH, Becn1, P62, LC3B, CD36, VLDLR, FAS, UCP3, TAG	Swim EX: ▲GT, muscle GLUT4, glycolysis, glucose uptake, autophagy, FA transport, storage
Veldink et al. 2003	ALS	Low- and high-copy SOD1^{G93A} mouse	Tread mill	To exhaustion 15 days	45 min/day 5 days/week	Hind paw extension reflex, balance beam, histology, survival	♀ □ EX low copy▲ survival, ▼ disease onset
Carrer as et al. 2010	ALS	SOD1^{G93A} mouse	Tread mill	Until motor symptom onset	MIT/HIT: 30/60 min/day 3/5 days/week	Body weight, motor performance, cervical, thoracic, lumber spinal cord motor neuron count	MIT: ▼body weight, ▲ rotarod performance , lumber motor neuron count day 95, 120 HIT: ▼body weight, ▲ lumber motor neuron count day 120
Liu et al. 2011	AD	APP/PS1 mouse	Tread mill	5 months	30 minutes/day 5 days/week	MWMT, Electrophysiol ogy, BDNF expression	▲ spatial learning, memory on MWMT ▲ hippocam pal BDNF, LTP
Liu, Zhao et al. 2013	AD	APP/PS1 mouse	Tread mill	5 months	30 minutes/day 5 days/week	Hippocampal Aβ, p-Tau, P-APP668, PS1, ADAM10, BACE1, p-CDK5, P-GSK	▼Aβ, p-Tau, P-APP668, PS1 ≠ GSK3
Zhang et al. 2019	AD	APP/PS1 mouse	Tread mill	12 weeks	45 min/day 5 days/week	Hippocampal Aβ, ADAM10, BACE1, flotilla 1, cholesterol	▼ Hippocam pal Aβ, BACE, flotilla 1 cholesterol ▲ Hippocam pal ADAM10
Laranj eiro et al. 2019	AD, HD	C. elegans: smg-*1(cc546ts)Ps nb-1Aβ1– 42::long 3′- UTR, P_{rab-3}F3ΔK280; P_{aex-3}h4R1N**Tau** V 337M; P_{unc-25}GFP, Pmec-3**htt**57Q128*	Swim exercise	4 days, 90 minute sessions	3+3 (Aβ) 3+3+2+2 (Tau, Htt)	Chemotaxis based, mobility, motor neuron morphology, Touch sensitivity,	▲ chemotaxis, mobility, touch sensitivity GABAergic motor neuron integrity
Wu et al. 2018	AD	STZ-induced sporadic AD mouse	Swim exercise	4 weeks	60 minutes/day	BMT, NOR, Hippocampal Aβ, p-Tau, synaptophysin , spinophillin, IL-10, TNFα, NRF2DNA binding, spatial memory	▲ spatial learning, memory on BMT, NOR ▲ synaptophysin, spinophillin, IL-10 NRF2 DNA binding ▼Aβ, p-Tau, TNFα
Lau et al. 2011	PD	1-MPTP-induced PD mouse	Tread mill	18 weeks	40 minutes/day 5 days/week	SNpc anti-TH IHC, mitochondrial respiration, mitoATP, SOD, DAT, BDNF, GDNF, balance beam	▲ striatal TH, DA, DAT, GDNF ▲ SNpc BDNF ▲ MnSOD, Cu-Zn Sod, RCR, mitoATP ▼ balance beam foot slip, latency to fall

Author, year	Disease	Model system	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
Al-Jarrah et al. 2007	PD	1-MPTP-induced PD mouse	Tread mill	4 weeks	40 minutes/day 5 days/week	SNpc anti-TH IHC, ECG, calorimetry, CS activity, open field	Striatal TH unchanged vs untrained MPD controls ▼ RHR, VO_2, VCO_2▲CS, LV mass ▼ amphetam ine-stimulated locomotion
Pothakos et al. 2009	PD	1-MPTP-induced PD mouse	Tread mill	18 weeks	40 minutes/day 5 days/week	SNpc anti-TH IHC, step length, gait analysis, MWMT, BB, open field, spontaneous activity, total distance	Striatal TH unchanged vs untrained MPD controls ▲ balance, coordination ▼ amphetamine-stimulated locomotion
Zhou et al. 2017	PD	α-synuclein (Y39C) PD mouse	Running wheel	2 weeks	Free access	Rotarod, MWMT, DJ-1, HSP70, BDNF, α-synuclein	▲ Rotarod, MWMT performance ▲ brain, muscle, plasma DJ-1 ▲ brain HSP70 ▼ brain α-synuclein oligomers, ▲ plasma α-synuclein
van Dellen et al. 2008	HD	R6/1 HD mouse	Running wheel	4 months	Free access	Hind paw extension reflex, static horizontal rod, Rotarod, open field, BW, brain weight, Ub+ aggregates	▲ static horizontal rod coordination ▼ onset rear paw clasping
Herbst and Holloway 2015	HD	R6/1 HD mouse	Tread mill	20 weeks	60 minutes/day 5 days/week	Hind paw extension reflex, mtDNA, mitochondrial respirometry, pyruvate, glutamate	▲ mitochond rial complex I, III, complex I respiration ▼ onset individual rear paw clasping Clasping phenotype precedes mitochondria I changes
Caldw ell et al. 2020	HD	CAG140 knock-in HD mouse	Tread mill	12 weeks	40 minutes/day 3 days/week	Rotarod, NO, TG, PDH, NAD+/ NADH, aconitase, JNK, AKT	▲ NO, aconitase activity, TCA reducing equivalents ▲ mOxPhos activity, glycolysis, PDH ▼ TG activity
Ji et al. 2015	HD	Quinolinic acid induced HD rat	Tread mill	14 days	30 minutes/day	BCL2, caspase-3, BAX, radial 8-arm maze, Rotarod	▲ spatial learning in radial maze, Rotarod performance ▼ dentate gyrus caspase-3,BAX/ BCL2
Fryer et al. 2011	SCA1	ATXN1154Q, ATXN1154Q; CIC-L+/−mice	Fixed-speed Rotarod	4 weeks	5 days/week	Lifespan, EGF, CIC expression, open field, dowel, Rotarod, conditioned fear, IHC, BW	EX ATXN1154Q : ▲LS, brainstem EGF, ▼CIC ATXN1154Q ;CIC-L+/ − : ▲ LS, BW, motor fx, learning, memory, Purkinje cell number, integrity,
Chuang et al. 2019	SCA1	SCA1(82Q) mouse	Tread mill	4 weeks	50 minutes/day	Rotarod, IHC, rpS6, p62, LC3	▲ motor performance , cerebellar phospho-rpS6 ▼ Purkinje cell loss
Giorge tti et al. 2016	SBMA	ARQ113 mouse	Tread mill	6 weeks	30 minutes/day 5 days/week	RNAseq, soleus muscle TEM, mitochondrial copy no., metabolic rate/ substrate utilization, muscle histology, grip strength, lifespan	▼ carbohydrate metabolism genes, grip strength, mitochondria I number/inte grity, muscle fiber size, Type I, II fibers ▲ lipid metabolism genes

Author, year	Disease	Model system	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
Chua et al. 2013	SBMA	ARQ113 mouse	Tread mill	3 days	Increasing time/ intensity, 80 minutes cumulative	TFEB expression, LC-3II/III-GFP	▲ TFEB expression, baseline muscle autophagy, exercise-induced increase in muscle autophagy

Abbreviations: EX: exercised, GTT: glucose tolerance test, L-: lactate ,GLUT4: glucose transport protein 4, GAPDH: Glyceraldehyde 3-phosphate dehydrogenase, PDH: pyruvate dehydrogenase, Becn1: Beclin 1, P62, LC3B, CD36, VLDLR: very low density lipoprotein receptor, FAS: fatty acid synthase, UCP3: uncoupling protein 3, TAG: triacylglycerol, GT: glucose transport, ADAM10: a disintegrin and metalloproteinase domain-containing protein, BACE1: β-site amyloid precursor protein cleaving enzyme 1, P-APP668: phospho-amyloid precursor protein 998, PS1 Presenilin: , CDK5: cyclin dependent kinase 5, GSK3: glycogen synthase kinase 3, MWMT: Morris water maze test, BDNF: brain derived neurotrophic factor, BMT: Barnes maze task, NOR: Novel object recognition, MPTP: methyl-4-phenyl-1,2,3,6-tetrahydropyridine, SNpc: substantial nigra pars compact, TH: tyrosine hydroxylase, DA: dopamine, SOD: Mn superoxide dismutase, DAT: dopamine uptake transporter, GDNF: glial cell line derived neurotrophic factor, RCR: respiratory control ratio, BB: balance beam, VO2: oxygen consumption, VCO2: carbon dioxide production, LV: left ventricular, CS: citrate synthase, BW: body weight, Ub: ubiquitin, mtDNA: mitochondrial DNA, NO: nitric oxide, TG: transglutaminase, NAD+/NADH: oxidized/reduced nicotinamide adenine dinucleotide, JNK: c-JUN N-Terminal kinase, AKT: serine/threonine kinase 1, mOxPhos: mitochondrial oxidative phosphorylation complex, KI: knock-in, CIC: Capicua, LS: lifespan fx: function, rpS6: ribosomal protein S6, LC3: and microtubule-associated protein light chain 3 , TEM: transmission electron microscopy, TFEB: transcription factor EB, LCII/III: Microtubule-associated protein 1A/1B-light chain 3

Table 2.

Exercise Effects in Neurodegenerative Disease: Human Studies

Author, year	Disease	Participants	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
Park et al. 2020	ALS	94 experimental 159 control	Five randomized controlled trials: muscle endurance, resistance, treadmill, intensive endurance, home-based functional training	6–24 months	2–5 days/ week	ALSFRS, ALSFRS-R ALSFRS-Respiratory, ALSFRS-R-Limb	▼ALSFRS,ALSFRS-R ALSFRS-Respiratory =ALSFRS-R-Limb
Merico et al. 2018	ALS	23 exercised 15 control	Submaximal isometric muscle contraction and 65% Max HR aerobic cycling or treadmill endurance	5 weeks	Resistance: 3 Reps Endurance: 20 minutes	RHR, VO_2, 6MWT, MRC_{ss} FIM, FSS, muscle dynometry	▲ FIM, FSS, MRC_{ss}, bicep muscle strength ▼VO_2
Ferri et al. 2019	ALS	8 trained 8 untrained control	Combined strength and endurance program tailored to participant aerobic capacity, strength and function	12 weeks	3 days/ week	PP, VO_{2peak}, GET, CPET, 1RM, TUGT, 6MWT, ALSFRS-R, ALS-SS, QOL	▼ALSFRS-R, ALS-SS, TUGT
Vidoni et al. 2021	AD	78 exercised 39 education control	Aerobic exercise at 60–75% max HR	52 weeks	150 minutes/ week	18F-AV45 PET imaging, MRI, executive function tests, verbal memory domain tests, visuospatial domain tests, VO_{2peak}	▲ VO_{2peak}
Vidoni et al. 2019	AD	33 (AE) exercised 32 (ST) control	Aerobic exercise at 60–75% max HR	26 weeks	150 minutes/ week	DAD, BADL, IADL, RUD	ST: ▼DAD IADL , DAD performance AE: =DAD IADL , DAD performance
Ventur elli et al. 2011	AD	12 walking group (WG) 12 control (CG)	Moderate Intensity Walking	24 weeks	30 minutes/day	BP, BMI, POMA, PPT, MMSE, 6MWT, ADLs	CG: ▼MMSE, =ADLs WG: =MMSE, ▼ADLs
Arcove rde et al. 2014	AD	20 exercise group 10 control group	Treadmill walking at 60% max HR	16 weeks	2 days/ week	CAMCOG, verbal fluency test, digit span test, Trail Making Test A, Stroop Test, BBS, TUGT, STS, ECG	▲ CAMCOG, BBS ▼functional reach, TUGT
Jensen et al. 2019	AD	107 intervention 93 control	Aerobic exercise at 70–80% max HR	16 weeks	3 days/ week	Apoε genotyping, NPI, SDMT, TUGT, Timed 10-m walk test, Timed 400-m walk test, dual task performance test, VO_{2max}	EX Apoε4 carriers:=SDMT ▲NPI, TUGT, 10-m, 400-m walk, VO_{2max} EX Apoε4 noncarriers: ▼SDMT, ▲ VO_{2max}
Sanders et al. 2020	AD	39 intervention 30 control	Walking and lower limb strength Low-intensity: 5763% max hR High-intensity: 83–89% max HR	12 weeks low- +12 weeks high-intensity	3 days/ week	Apoε genotyping, 6MWT, SPPB, 6-m walking speed test, static balance, MMSE, TMTA,	▲Gait speed No significant effect of Apoε carriership

Author, year	Disease	Participants	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
						DSFW, DSBW, VMSFW, VMSBW, Stroop Test	
Rawson et al. 2019	PD	29 Tread mill 36 Tango 23 Stretching	Treadmill Tango Stretching	12 weeks	3 days/ week	MMSE, MDS-UPDRS-III, PASE, forward/ backwa rd walking velocity, 6MWT, PDQ-39	Treadmill group ▲forward/ backward walking velocity
Fisher et al. 2008	PD	10 BWST 10 Low-Intensity 10 Zero-Intensity	High-intensity, PBWS Treadmill Low-intensity Aerobic Zero-Intensity	8 weeks	24 sessions	UPDRS, STS, TMS, gait speed, stride/ step length, joint excursion, gait velocity, ROM, STS	High-intensity BWST ▲all motor performance parameters ▼ corticomot or excitability
Mueller et al. 2017	HD	13 HD patients 11 healthy controls	10 weeks constant load cycling 8 weeks HIIT 6 weeks interval/constant load cycling	26 weeks	3 days/ week	UHDRS, Stroop Test, skeletal muscle biopsy: CS, mitochondrial respirometry, mATPase, muscle fiber type distribution	Exercised HD patients and controls: ▲CS acitivity, complex III, V, SCCR, capillary-to-fiber ratio
Mueller et al. 2019	HD	10 HD patients 9 healthy controls	10 weeks constant load cycling 8 weeks HIIT 6 weeks interval/constant load cycling	26 weeks	3 days/ week	MyHC cross sectional area, myonuclear cell count, satellite cell count	Exercise HD: = MyHC c.s.area, myonuclear, satellite cell ct. Healthy: ▲ MyHCc.s. area, myonuclear, satellite cell ct.
Frese et al. 2017	HD	12 HD patients 12 healthy controls	10 weeks cycling at 65% VO2peak 8 weeks HIiT cycling 90% VO2peak 6 weeks cycling 50% VO2peak	26 weeks	3 days/ week	UHRDS-motor, HVLT-R, DRS-2, Symbol-Digit modalities test, Stroop Tests, TMTA and B, category fluency task, L-, glucose, HbA1c, TSH, CK, VO2peak	EX HD: lower scores than healthy controls on all motor and neuropsycho logical assessments ▲ VO2peak, improve body composition
Velazquez-Perez et al. 2019	SCA2	15 rehab 14 control	Neurorehabilitation	12 weeks	4 hours/day 5 days/ week	5-m tandem gait on floor/ mattress, time upholding tandem position on floor/ matress/s eesaw, F-NT, H-ST, 9HPT, SARA, INAS	▲time upholding stance over mattress, seesaw ▼ 5-m tandem gait on floor/mattres s, F-NT, H-ST
Leonar di et al. 2017	SCA1 SCA2 SCA3 FRDA	SCA1: 1 SCA2: 3 SCA3: 2 FRDA: 5	Physical rehabilitation+proprioceptive stabilizer	6 weeks	180 minutes/day 5 days/ week	SARA, PATA dysarthria, 6MWT, 9HPT, cadence, length cycle, support R/L/cycle, support R/L/ cycle, flight R/L/cycle, single/double	▲ PATA, 6MWT, cadence, all gait parameters except step length ▼SARA, 9HPT dominant hand

Author, year	Disease	Participants	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
						support R/L/ cycle	
de Oliveira et al. 2018	SCA2 SCA3 SCA7	SCA2: 1 SCA3: 6 SCA7: 1	PBWS Treadmill Training Stage 1: gait/conditioning Stage 2: dynamic balance	8–10 weeks/ stage	50 minutes/day 2 days/we ek	CPET, VO2peak, VO2max, VCO2, treadmill inclination, BBS, DGI, SARA, Katz ADL	▲ CPET, treadmill inclination, DGI, BBS
de Oliveir a et al. 2015	SCA2 SCA3 SCA7	SCA2: 2 SCA3: 8 SCA7: 1	Static and Dynamic Balance Exercises 3 groups of exercises 10 repetitions of each exercise	4 weeks	<60 minutes/day 2 days/ week	BBS	▲BBS
Tabba ssum et al. 2013	SCA1 SCA2 SCA3	10 Group A 10 Group B	Core Stability Training Group (A) Conventional Balance Training Group (B)	4 weeks	60 minutes/day 3 days/ week	BEST, MFES	Group A: ▲ ▲BEST Group B: ▲BEST
Wang et al. 2018	SCA3	5 Exergaming 4 Control	Exergaming Training and balance Control	4 weeks	40 minute sessions, 9 total	MMSE, SARA, 9HPT, walking speed	Both groups: ▼SARA Exergaming: ▼ SARA gait-posture subscore
IIg et al. 2009	SCA6 Afferent ataxia	SCA6: 10 Afferent ataxia: 6	Intensive coordinative training Intra-patient controls	4 weeks inpatient+ 4 weeks at-home	60 minutes/day 3 days/ week	SARA-gait, posture, speech, limb-kinetic subscores, ICARS, BBS, GAS, high speed motion capture motor analysis	Both groups: ▼SARA, ▲ ICARS, BBS, GAS SCA6: ▼SARA, ▲ ICARS BBS, GAS retention at-home ▲ gait velocity, step length, limb coordination
IIg et al. 2010	SCA6 Afferent ataxia	SCA6: 10 Afferent ataxia: 6	Intensive coordinative training Intra-patient controls	4 weeks inpatient+ 4 weeks at-home	60 minutes/day 3 days/ week	Longitudinal study of same participants from Ilg et al. 2009	Disease progression related▲Ove rall SARA, ▼ ICARS SCA6: ▼SARA, ICARS compared to 2009 baseline ▲BBS, GAS (stable or improved)
Fonteyn et al. 2013	SCA3 SCA6 SAOA	SCA3: 1 SCA6: 2 SAOA: 7	Gait adaptability treadmill training	5 weeks	60 minutes/day 2 days/ week	SARA, 10-m walking test, TUGT, BBS, EFAP, ABC, obstacle avoidance on treadmill, gait analysis, obstacle	▲Obstacle avoidance on treadmill, gait efficiency, EFAP
Tercero-Perez et al. 2019	SCA7	6 ITG 6MTG 6UC	Neurorehabilitation: Intensive Training Group (ITG) Moderate Training Group (MTG) Untrained Control (UC)	24 weeks	120 minutes/day 3–5 days/ week	SARA-gait, posture, dysarthria, dysmetria, tremor, stance subscores, INAS, ADLs, DT, LPH, MDA, GR, GPx, PONI	ITG: ▼SARA, ▼INAS, DT, MDA, LPH▲ ADLs MTG: ▼SARA, INAS, DT , MDA, LPH▲ ADLs

Author, year	Disease	Participants	Exercise Modality	Duration	Frequency	Evaluated Criteria	Significant Outcomes
Schrader et al. 2015	SBMA	24 exercised 26 control	Low-intensity exercise Stretching control	6 weeks	3 sets/ exercise 3 times/ week	AMAT, total activity, muscle strength, balance, TUGT, STS, QOL, CK, IGF-1	No significant differences Post-hoc analysis, low-functioning subgroup:▲ AMAT total activity sub score
Preisler et al. 2009	SBMA	8 SBMA particip ants	Cycling at 65%-70% VO2max	12 weeks	30 minutes/day 4 days/ week	VO2max, Wmax, ADL, muscle morphology, CK, CS, body composition, EMG, static strength, lung function	Training not well tolerated, no significant effects
Heje et al. 2019	SBMA	5 HIIT 5 control	HIIT (cycling)	16 weeks	10 minutes/day 3 days/ week	VO2max, Wmax, CK, self-rated muscle pain, muscle fatigue, activity level	▲VO2max, Wmax

Abbreviations: ST: stretching and toning, AE: aerobic, ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale, ALSFRS-R: revised ALSFRS-Respiratory, ALSFRS-R-Limb, RHR: resting heart rate, VO2: oxygen consumption, ml/min/kg, 6MWT: 6 minute walk time, MRCSS: medical research council sum score, FIM: functional independence measure, FSS: fatigue severity scale, PP: Peak power, VO2peak: peak O2 uptake, GET: gas exchange threshold, CPET: cardiopulmonary exercise test, 1RM: maximal strength of knee extensor muscles, TUGT: timed up and go test, ALSSS: ALS severity scale, QOL: McGill quality of life survey, BMI: body mass index, BP, blood pressure, POMA: performance oriented mobility assessment, PPT: physical performance test, MMSE: Mini-mental state examination, ADLs: Barthel index of activities of daily living, BADL: basic instrumental activities of daily living, DAD: Disability Assessment for Dementia, IADL: instrumental activities of daily living, RUD: Resource Utilization for Dementia, CAMCOG: Cambridge Cognitive Examination, STS: sit to stand test, ECG: electrocardiogram, Apoε4: , NPI: Neuropsychiatric Inventory, SDMT: Single Digit Modalities Test, VO2max: maximal oxygen uptake, SPPB: short physical performance battery, TMTA: Trail Making Test A, DSFW: digit span forward walking, DSBW: backward, VMSFW: visual memory span forward, VMSBW: backward, MDS-UPDRS-III: Movement Disorders Society Unified Parkinson Disease Rating Scale-III, PASE: Physical Activity Scale for the Elderly, PDQ-39: Parkinson Disease Questionnaire-39, BWST: Body weight supported treadmill training, TMS: transcranial magnetic stimulation, ROM: range of motion, CS: citrate synthase, UHDRS: unified Huntington Disease Rating Scale, HIIT: high intensity interval training, mATPase: myofibrillar adenosine triphosphatase, SCCR: succinate cytochrome c reductase, UHRDS-Unified Huntington Disease Rating Scale, HVLT-R: Hopkins Verbal Learning Test-Revised, DRS-2: dementia rating scale 2, CK: creatine kinase, TSH: thyroid stimulating hormone, F-NT: finger-to-nose test, H-ST: heel-to-shin test, 9HPT: 9-hole peg board test, SARA: Scale for Assessment and Rating of Ataxia, INAS: Inventory of Non-Ataxia Symptoms, FRDA: Friedreich's ataxia, 6-MWT: 6 minute walking time, BBS: Berg Balance Scale, DGI: Dynamic Gait Index, Katz ADL: Katz index of independence in activities of daily living, BEST: Balance Evaluation Systems Test Efficacy Scale , MFES: Modified Falls Efficacy Scale, ICARS: international cooperative ataxia rating scale, GAS: Goal attainment score, EFAP: emory functional ambulation profile, SAOA: sporadic adult onset ataxia, ABC: activities specific balance scale, DT: dityrosine, LPH: lipid hydroperoxides, MDA: malondialdehyde, GR: glutathione reductase, GPx: glutathione peroxidase, PON-I: Paraoxonase, AMAT: Adult myopathic assessment tool, Wmax: Maximum workload, EMG: Electromyography