

Exercise as a Countermeasure to Declining Central Nervous System Function in Multiple Sclerosis

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ABSTRACT

Purpose: The decline of central nervous system (CNS) function is a hallmark characteristic of multiple sclerosis (MS) that can manifest as cognitive impairment. We believe that exercise represents a potential behavioral approach for counteracting the declines in CNS structure and associated function among persons with MS (ie, exercise as a countermeasure of CNS decline). This theory is important because disease-modifying drugs represent a first-line approach for modifying the immune system and its effects on the CNS, but these drugs do not generally demonstrate robust improvements in cognitive performance.

Methods: To the best of our knowledge, this article presents the first argument positioning exercise as a countermeasure for CNS decline in MS.

Finding: The reviewed research indicates a proliferating body of evidence describing physical fitness, physical activity, and exercise effects on cognitive performance and neuroimaging outcomes (ie, CNS functioning) in MS, with the consistent and strong association between cognitive performance and neuroimaging outcomes in this population as a backdrop.

Implications: We further present a framework and future research directions for better positioning exercise as a possible neuroprotective behavior against declining CNS function in MS. (*Clin Ther.* 2017;■:■■■-■■■) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: cognition, exercise, multiple sclerosis, neuroimaging, neuroprotection.

eventually becomes neurodegenerative and results in irreversible damage of white matter and gray matter in the CNS.² This CNS damage presents as brain atrophy on magnetic resonance imaging (MRI) and typically manifests as declines in physical and cognitive performance. Cognitive performance has been identified as a particularly relevant and obvious neuro-performance marker of CNS functioning in persons with MS.³ The consideration of cognitive performance as a marker of CNS functioning is, in part, based on its consistent and strong association with brain neuroimaging outcomes,^{4,5} as well as its origins in the CNS and minimal non-CNS (ie, peripheral body system) influences on measurement compared with physical performance outcomes. Cognitive performance can be readily measured by using neuropsychological and computerized testing wherein the outcome reflects performance primarily based on CNS function. Collectively, this makes the combination of cognitive performance and MRI a pair of complementary outcomes for understanding influences on CNS decline in MS.

We believe that exercise represents a potential behavioral approach for counteracting the declines in CNS structure and function among persons with MS (ie, exercise as a countermeasure of CNS decline). This theory is important because disease-modifying drugs represent a first-line approach for modifying the immune system and its effects on the CNS, but these drugs do not generally result in robust improvements in cognitive performance.⁶ Cognitive rehabilitation has been inconsistently associated with improvements in cognitive performance (ie, some studies report clinically meaningful results, whereas others report null results),⁷ and there are few

INTRODUCTION

Multiple sclerosis (MS) is a common neurologic disease that is initially characterized by acute, inflammatory processes and focal demyelination and transection of axons in the central nervous system (CNS), particularly in the cerebral white matter.¹ The disease

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investigations of co-occurring effects on the CNS structure using MRI in MS.⁸ The proposal that exercise represents a promising approach for influencing both brain structure and cognitive function in MS is based largely on the wealth of evidence in gerontology⁹ and emerging evidence in neurologic disease and conditions,¹⁰ as proposed in a Topical Review.¹¹ The argument for exercise as a countermeasure for CNS decline in MS complements previous reviews on exercise as a disease-modifying therapy¹² and an approach for symptomatic/function rehabilitation¹³ in this population.

To our knowledge, the present article offers the first argument for exercise as a countermeasure for CNS decline in MS. To do so, the initial focus is on evidence describing dysfunction of cognitive performance and its neural correlates based on neuropsychological and neuroimaging outcomes as markers of declining CNS function in MS. We then review research on physical fitness, physical activity, and exercise effects on cognitive performance and neuroimaging outcomes (ie, CNS functioning) in MS; this represents the collective body of evidence supporting exercise as a possible countermeasure for CNS decline in MS. The last section of this article provides future research directions for better positioning exercise as a possibly neuroprotective behavior against declining CNS function in MS.

MARKERS OF DECLINING CNS FUNCTION IN MS

Between 45% and 70% of persons with MS experience some degree of impairment in cognitive performance based on results of objective neuropsychological testing.^{4,14} The prevalence of impairment in cognitive performance varies based on the clinical course of MS,¹⁵ whereby those with progressive presentations of MS exhibit more widespread and severe cognitive impairment than those with relapsing-remitting MS (RRMS).^{14,16} Studies have reported cognitive impairment in ~35% of patients with RRMS based on scores at least 1 SD below the normative value on 2 separate neuropsychological tests and ~60% when considering both relapsing and progressive presentations of MS.¹⁷ Cognitive impairment is observed at the earliest stages of the disease, even before a definite MS diagnosis, and often occurs independently of physical disability.¹⁵ Of note, although such cognitive impairments do occur early

in the disease process, performance on neuropsychological tests worsens as the disease progresses.¹⁴ Regardless of clinical disease course, MS-related cognitive dysfunction (ie, poor neuropsychological test performance), typically presents as slowed cognitive processing speed and impairments in learning and memory, as well as executive dysfunction.^{18–20} This pattern of MS-related cognitive dysfunction has been consistently and strongly linked with structural and functional neuroimaging outcomes.^{5,21}

Regarding structural imaging, persons with MS who are cognitively impaired generally have greater numbers of lesions and overall lesion volume than cognitively preserved persons with MS.²² Several studies have reported that whole-brain white matter atrophy is associated with worse cognitive processing speed and working memory, whereas whole-brain gray matter atrophy seemingly reflects worse verbal memory, euphoria, and disinhibition.²³ Others have examined atrophy of specific brain regions and relationships with specific cognitive functions. The 2 most prominent regions of interest are the thalamus and hippocampus. For example, thalamic atrophy has been associated with cognitive impairment (particularly slowed cognitive processing speed, as well as learning and memory, verbal fluency, and spatial perception) and decline in both cross-sectional and longitudinal research in MS samples.^{24–27} Hippocampal lesions and atrophy have been associated with MS-related memory impairment.^{28,29}

Other data indicate that persons with MS have worse white matter integrity (ie, fractional anisotropy) and greater diffusivity (ie, mean diffusivity, radial diffusivity) compared with healthy control subjects.^{30,31} By comparison, cognitively impaired persons with MS have worse white matter integrity and less diffusivity compared with cognitively preserved persons with MS. Focal white matter damage is considered a stronger predictor of cognitive impairment in patients with MS than global lesion burden and white matter integrity.³² Collectively, this information suggests that CNS decline in MS can be characterized by cognitive performance and neuroimaging outcomes.

EXERCISE AND THE CNS IN MS

Exercise training and participation in physical activity are generally accepted as favorable approaches for

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