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Physical Activity and Cognitive Function in Adults with Multiple Sclerosis: An Integrative Review

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Abstract

Purpose—To identify and synthesize the research evidence concerning (1) the relationship between physical activity and cognitive performance in persons with multiple sclerosis (MS) and (2) to review the reported effects of physical activity interventions on neurocognitive performance conducted in this population.

Methods—Relevant peer-reviewed journal articles were identified by searching PubMed, PsychINFO, and SPORTDiscus through May 2016. Full-text articles meeting the inclusion criteria were evaluated for quality using tools developed by the National Institutes of Health. Studies deemed to be of poor quality were excluded from the review.

Results—Nineteen studies meeting the inclusion/exclusion criteria were analyzed. Nine studies reported significant relationships between higher levels of physical activity or cardiorespiratory fitness and measures of cognitive function. Data extracted from 10 physical activity intervention studies reported mixed results on the effectiveness of physical activity to improve selected domains of cognitive function in persons with MS.

Conclusion—Although correlational studies provide evidence to support a linkage between physical activity and cognitive function in persons with MS, this linkage is confounded by factors that may have influenced the studies' results. Evidence derived from intervention studies that could support a positive effect of physical activity on cognition in persons with MS is equivocal.

Keywords

multiple sclerosis; cognition; cognitive function; exercise; physical activity; review

Introduction

Multiple sclerosis (MS) is estimated to affect about 2.3 million persons worldwide and roughly 450,000 people in the U.S.; but these estimates are inexact, because most

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governments, including that of the U.S., do not require MS reporting [1,2]. MS, the most common neurodegenerative disorder of young adults,[3] is an immune-mediated disease characterized by unpredictable heterogeneous neurologic symptoms, encompassing physical, emotional, communicative, social, and cognitive domains. Over half of those diagnosed with MS experience significant cognitive impairment and subsequent disability related to MS pathology in the central nervous system [4]. This cognitive impairment has profound deleterious effects on health-related quality of life, social relationships, driving ability, and employment [5,6]. Unemployment is arguably the most devastating consequence of MS among working age adults.

Regrettably, cognitive impairment in MS has traditionally been underdiagnosed and undermanaged, with few therapeutic options available [4,7]. Research investigating pharmacologic therapies for cognitive impairment in MS has been generally disappointing,[8] and currently, there are no approved medical therapies to treat cognitive symptoms in MS. Although considerable evidence supports the use of disease-modifying drugs (DMDs) to stabilize and/or slow the progression of MS (e.g., by reducing annualized relapse rates and lesion progression), little is known about their potential effects on cognitive function, which was not assessed as a primary outcome in the pivotal DMD clinical trials [9]. Results from cognitive rehabilitation studies in persons with MS have been mixed,[10] with computer-assisted cognitive rehabilitation programs showing cautious potential [11–13]. Finally, based on evidence of positive effects of physical activity on cognitive function among elderly and cognitively impaired adults, there is growing enthusiasm for pursuing such research in persons with MS [14].

The purpose of this integrative review is to (1) examine the literature describing the relationship between physical activity and cognitive function in persons with MS, and (2) review the evidence concerning the effects of physical activity interventions on cognitive function in persons with MS. This review's ultimate aim is to determine whether there is adequate evidence to support a physical activity intervention to promote cognitive function in persons with MS who experience cognitive problems.

Methods

Search strategy

The electronic databases PubMed, PsycINFO and SportDISCUS were searched for potentially relevant primary source articles published in English prior to May 2016. Full-text articles were retrieved from those screened as potentially relevant through review of titles and abstracts. Ancestral searches were conducted using the reference lists in articles deemed relevant to the review.

Inclusion and exclusion criteria

Studies included in this review were those conducted using samples diagnosed with MS at age 18 or older and that addressed both physical activity and cognitive function. Physical activity was broadly defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" including measured exercise and fitness [15]. Cognitive

function domains included attention, memory, processing speed, executive function, and problem solving. Studies that used scores derived from standardized neuropsychological tests were included, whereas those that used self-report measures, such as the Perceived Deficits Questionnaire [16], were excluded. Although patients' perceptions of cognitive deficits are integral to clinical assessment, self-reports of cognitive impairment are apt to overstate cognitive impairment in those who are depressed and may go unnoticed in those with significant cognitive impairment [17,18]. Dissertations, theses, literature reviews, editorials, qualitative design studies, and discussion articles were also excluded.

Selection of studies

The PubMed, SportDISCUS, and PsycINFO databases were searched using the following key words and phrases: "multiple sclerosis" AND "cognition OR cognitive function OR cognitive impairment" and "physical activity OR exercise." This search, shown in Figure 1, identified 234 potentially relevant primary sources. Of these, 25 were duplicates, 13 were not available in English or included nonhuman subjects, and 179 did not meet inclusion criteria. Seventeen articles remained. Reference lists of these 17 articles were hand searched, yielding 4 more. Two were finally excluded because of methodological concerns following assessment for risk of bias, resulting in 19 full-text articles for this integrative review.

Appraisal of study quality

Quality assessment of the included articles was performed using tools developed by the National Heart, Lung, and Blood Institute at the National Institutes of Health [19]. Three of six available tools were chosen to do this, depending on the research designs of the 19 selected studies: Quality Assessment of Controlled Intervention Studies, Quality Assessment of Before-After (Pre-Post) Studies, and Quality Assessment of Observational Cohort and Cross-Sectional Studies. These tools are intended to facilitate appraisal of a study's internal validity, so that one can judge the study's quality as "good," "fair," or "poor." Potential sources of bias include power, randomization methods, and intention-to-treat analysis in experimental studies, and blinding of assessors, use of valid/reliable measures, and adjustment of results for potential confounds in correlational studies.

Two reviewers separately evaluated and rated each article for potential sources of bias. Disagreement between ratings by the two reviewers was resolved by a third expert reviewer, who also assessed the article and then enabled a final consensus decision. Articles of good or fair quality were included in the review; articles of poor quality were excluded, owing to high risk of bias.

Results

Study Characteristics

Data were extracted from 19 primary sources presenting studies conducted between 2004 and 2016 (N = 1,007 participants). Information included study design, sample characteristics, physical activity measures (correlational studies) or physical activity interventions (experimental studies), cognitive domains identified, and instruments used to measure the domains. Table 1 shows the nine correlational studies with cross-sectional

designs [20–28]. One of these was a cohort study that used a post-hoc correlational design [26]. Table 2 shows the remaining 10 studies with experimental designs: two single-group, pretest-posttest designs [29,30], three randomized counterbalanced treatment designs [31–33], one randomized prospective study [34], and four RCTs [35–38].

The nine correlational studies included 596 individuals; most participants (67% to 100%) were female and had a relapsing-remitting course of MS [20–28]. The 411 participants in the 10 experimental studies were similar to those in the correlational studies in gender (mostly female) and MS type (primarily relapsing-remitting) [29–38]. Kurtzke's Expanded Disability Status Scale (EDSS) [39] was used to describe neurologic function and impairment in five of the correlational [20–23,28] and nine of the experimental [29–37] studies reviewed. EDSS scores are based on seven functional systems: pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, cerebral, and ambulation. EDSS scores range from 0 (*normal neurologic function*) to 10.0 (*death attributable to MS*), increasing in increments of 0.5 [40]. Scores less than 4.0 are considered to reflect mild MS; scores between 4 and 5.5, moderate MS; and scores of 6.0 and above, severe MS [41]. The total EDSS score is heavily weighted on the ability to ambulate and the need of assistive devices (e.g., canes, walkers, wheelchairs). EDSS scores varied from mild (0 to 3.5) to severe (6.0 to 8.0) in the correlational studies reporting these scores. Most participants in the experimental studies had mild to moderate MS (EDSS <6.0); yet participants in Briken et al. [35] had progressive forms of MS with more severe impairment (EDSS >6.0), and 53% of the participants in Sandroff et al. [38] had moderate disability assessed via Patient-Determined Disease Steps [42], a self-report measure. Notably, the study from Slovenia by Velikonja et al. [34] did not report participant gender or intervention group size.

Physical Activity

Physical activity was measured using objective methods in eight of the nine correlational studies. Four of the correlational studies measured aerobic capacity as peak oxygen consumption (VO_{2peak}), using a cycle ergometer or recumbent stepper [20,22,24,28]; three measured steps/day using an accelerometer [23,25,27]; and one used a cycle ergometry protocol to measure aerobic fitness [26]. Vanner et al. [21] quantified physical activity using a self-report measure, the Physical Activity Disability Scale (PADS) [43].

Exercise interventions in the 10 experimental studies varied considerably. The mode of exercise included resistance training, aerobic training (treadmill walking, cycling, rowing, sport climbing, and arm ergometry), and yoga, as well as participation in a web-based physical activity behavior program. Intervention duration ranged from 8 weeks to 6 months. Exercise session length ranged from 30 to 90 min, and the frequency of sessions varied from once to three times a week. Exercise intensity (% of heart rate reserve or one repetition maximum, 1RM) was defined in four studies [30–33].

Cognitive Function

Cognitive impairment affects over 50% of those with MS; it is incapacitating and poorly managed, and it lacks effective treatment [4,5]. Domains of cognition commonly affected in persons with MS include sustained and complex attention, concentration, working and

secondary memory, information processing speed, visuospatial skills, verbal fluency, and executive function—planning, organization, judgment, reasoning, problem solving [4,44–46]. Impaired information processing speed, learning, and memory are widely recognized as the cognitive domains most commonly impaired in persons with MS [45]. The cognitive domains that have been investigated and the neurocognitive tests used to assess them vary widely, as the reviewed studies show. Information processing speed and the ability to attend to stimuli were investigated in all but three of the studies. The Paced Auditory Serial Addition Test (PASAT) [47], a test of auditory processing speed, cognitive flexibility, and numeracy, was used alone in four of the studies [26,29,36,37]; in six studies [20,22–25,27], it was given along with the Symbol Digit Modality Test (SDMT) [48]. The SDMT, commonly used to evaluate cognitive processing speed in persons with MS, has been promoted as being faster and easier to administer and less objectionable to patients than the PASAT. The SDMT was used as a single measure of processing speed in five of the studies [21,28,30,35,38]. Several types of memory (e.g., episodic, relational, working, retrospective, and prospective) were evaluated in nine of the studies [20–23,28,30,35–37] using instruments specific to the type of memory under investigation. Six studies examined executive functioning [26,31–35].

Cognitive function was measured as the primary outcome in eight of the 10 intervention studies [30–36,38]. Two studies [29,37] were not specifically aimed at investigating cognitive outcomes but did include PASAT scores as a consequence of using the Multiple Sclerosis Functional Composite (MSFC) [49] to quantify MS-related functional impairment. The MSFC comprises three instruments: the Timed 25-Foot Walk Test, the Nine-Hole Peg Test, and the 3-sec version of the PASAT.

Discussion

Summary of overall findings

Physical activity has been positively related with improved cognition in aging adults, persons with schizophrenia, and stroke [50–53]. In addition, a review of the literature on exercise and brain health has suggested that physical activity might promote brain health through changes in neuroreactive proteins, immune factors, and stress hormones, which reduce long-term disability through neuroprotection, neuroplasticity, and neuroregeneration [54,55]. Therefore, physical activity is an attractive, modifiable behavioral correlate for improving cognitive functioning in persons with MS.

Evidence supporting a linkage between increased physical activity and improved cognitive function in persons with MS is limited but expanding. Cross-sectional studies exploring the relationship between physical activity and cognitive function have demonstrated positive correlations between physical activity (objective and self-reported) and cognitive processing speed [21,23,25,27] as well as increased verbal learning and memory [21]. Improved physical fitness has been positively related with executive function scores [26] and processing speed [20,22,24,28].

The evidence supporting the effectiveness of physical activity interventions on cognitive function is limited, and the few studies that have so far been published offer conflicting

results. Two of the nine intervention studies in this review found no significant changes in cognitive function after 6 months of yoga or aerobic exercise [36] or after a 6-month program combining 3 weeks of inpatient rehabilitation followed by 22 weeks of home-based resistance training [37]. Eight more recent studies reported positive cognitive outcomes in various cognitive domains (learning, memory, attention/processing speed, and executive function), using widely diverse exercise prescriptions (mode, intensity, time, frequency, and duration) as well as a web-based physical activity behavior intervention [29–35,38]. One research group has been doing key foundational work examining the effects of short bouts of moderate-to-vigorous exercise on a measure of executive function [31–33]. The lack of positive results in the early studies has been attributed to poor methodological rigor, related specifically to insufficient exercise intensity, frequency, supervision, and a lack of physical fitness testing [14,56].

Strengths and weaknesses of the studies

A feature of all of the studies in this review was a wellness perspective toward physical activity rather than an illness perspective, which may be inferred whenever physical activity (e.g., physical or rehabilitation therapy) is prescribed to treat MS symptoms. Physical activity is a key component of health promotion, and evidence suggests that it may have positive impacts on functional impairment and quality of life in persons with MS [57]. Until recently, physical activity was believed to increase MS symptom progression, and patients were instructed to rest [58,59]. Notably, interventions in the reviewed studies were well tolerated by the participants, and no adverse effects attributable to the physical activity interventions were reported. Similar findings for the safety of exercise training in persons with MS have been reported in a systematic review [60].

Evidence supporting the associations between physical activity and cognitive function in persons with MS, while critical as foundational work, fails to establish causation or the direction of any effect in this population. It is equally plausible that cognitive function could affect physical activity or that physical activity could affect cognitive function. It is also possible that other factors, specifically disability status and the ability to ambulate, might have influenced the relationships observed in the studies [56]. Motl et al. [14] suggest conducting further cross-sectional studies to investigate potential relationships between cognitive function and different modes of physical activity (e.g., strength, aerobic, and balance) to inform future RCTs.

High-quality experimental designs measure significant differences ascribed to the manipulation of experimental conditions. This means that studies with such designs must have sample sizes large enough to avoid system-wide error. Yet many of the reviewed intervention studies had relatively small sample sizes (ranging from 20 to 95). Attrition of participants was also a serious threat to quality in a number of the intervention studies. Rates of attrition, when reported, varied considerably—from 4% to 17%. Several studies did not report participant withdrawals or dropouts [29,31–34].

In addition, each component of any physical activity intervention protocol (mode, intensity, frequency, and duration) must be rigorous enough to exert an effect on the outcome variable and must be described in sufficient detail to permit replication by other researchers. There

was considerable variety in the mode (type of exercise), frequency, and duration of physical activity interventions reviewed. Intervention protocols varied from single bouts of acute exercise lasting 20 min [32] to exercise programs that met once a week for 90 min for 6 months [36]. Notably, only four recently published papers documented the intensity of the exercise that participants did. [30–33] Sandroff and colleagues [31–33] have conducted a series of studies investigating the immediate (acute) effect of exercise on executive function. In those studies, treadmill walking yielded robust effects on executive control in ambulatory adults with MS, even in participants whose MS symptoms were worsened by increased body temperature (thermosensitivity). Although this represents foundational work, a critical overarching question about the ecological validity of neuropsychological tests remains: Does improvement in any cognitive function (e.g., executive control) measured using clinical cognitive tests translate into better everyday cognitive function? Does improved performance on one or more clinical cognitive tests increase crucial everyday functions such as driving or employment?

Instrument validity and/or reliability were not consistently well documented in the studies reviewed. Clinical neuropsychological tests, although widely accepted for diagnostic purposes, may lack sensitivity to modest change, especially over a short period of time [61]. The PASAT, used in 10 of the reviewed studies, has shown practice effects in which improved scores might be attributable to repeated test exposure rather than better participant performance [62]. In response to this criticism, the SDMT, used in 11 of the studies reviewed, has been adopted by The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) [63] as the preferred and more easily administered instrument to assess information processing speed in studies of persons with MS [18]. Objective (i.e., accelerometry) and self-report measures of physical activity have been validated in persons with MS [64]. Regrettably, problems with accelerometer accuracy can arise, depending on the participant's mode of physical activity and where the device is worn (e.g., the device is worn on the waist while the participant rides a recumbent bike). Motl et al. [64] have therefore endorsed measuring physical activity more comprehensively, using both objective and self-report measures.

Depression and fatigue are highly prevalent coexisting conditions in MS [65,66]. But their features (e.g., attention, lethargy, poor concentration) confound performance on cognitive assessments, raising concerns about construct validity [18,67]. Yet even though the nature of the interrelationships between depression, fatigue, and cognitive function is indefinite, inclusion of depression and fatigue as study variables is still merited. Distinguishing the contributions that depression and fatigue may have on cognitive impairment is critical despite substantial intra-individual differences and shared construct characteristics.

Recommendations for future research

Appropriately powered randomized clinical trials are needed to determine the feasibility and effectiveness of physical activity interventions for improving cognitive function in persons with MS. Researchers will need to assess and control for baseline levels of cognitive function, disability (EDSS scores), depression, and fatigue, because each may potentially moderate intervention effects. The mode, intensity, frequency, and duration of the physical

activity intervention should be modeled on work done in other populations, such as the elderly, in whom physical activity interventions have supported improvement in cognitive function [50,53]. Motl et al. [14] recommend “a 6-month period of moderate-intensity, aerobic exercise training performed for upwards of 45 minutes on 3–4 days per week using a supervised exercise leader.” Recently, a consensus panel of experts developed physical activity guidelines for adults with MS that are available online through The Canadian Society for Exercise Physiology, using a rigorous process based on an extensive systematic review of the literature [68–70]. The guidelines promote fitness benefits for adults with MS who have mild to moderate disability through “30 minutes of moderate intensity aerobic activity 2 times per week and strength training exercises for major muscle groups 2 times per week.” [70]. Although postintervention assessments up to 1 year would be ideal, the cost of in-person testing can be prohibitive, so perhaps self-report measures collected via the Internet could be implemented. Pilot studies establishing effect sizes for physical activity interventions are needed so that subsequent studies can conduct a priori power analyses to determine necessary sample size. Self-report measures of cognitive function and newer measures of neurocognitive function in everyday life used in conjunction with clinical neuropsychological testing may serve in complementary roles and better reflect changes in cognitive function after experimental manipulation.

Limitations of the review

This review excluded unpublished studies, which might increase the risk of bias, and only 19 studies were ultimately included. In addition, the reviews’ results depend on information in published journal articles, which can sometimes be limited. The decision to limit this review to studies with neurocognitive performance tests means that the results cannot be generalized to studies that have assessed cognitive performance in other ways (e.g., using self-report measures).

Recommendations for clinical practice

A majority of persons with MS experience cognitive impairment, yet there is little to offer them in the way of therapy. Physical activity may present a feasible way to protect or improve cognition, but strong scientific evidence for its usefulness in this population is lacking. Health care providers need evidence to illuminate the most effective mode(s), intensity, frequency, and duration of physical activity for protecting or improving cognitive function. Nevertheless, until more is known about the potential benefits of physical activity for cognitive impairment, promotion of physical activity in this population does offer meaningful benefits (increased strength, mobility, balance, along with decreased fatigue and depression) that warrant the clinician’s endorsement and encouragement [69,71]. Health care providers can offer specific guidance and community resource referrals to increase physical activity and maximize wellness for this population of individuals living with a chronic disabling condition.

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- Physical activity has numerous benefits for persons with multiple sclerosis (MS) including improvements in balance, ambulation, depression, fatigue and quality of life.
- Structured physical activity programs may contribute to cognitive function stability or improvement in persons with MS.

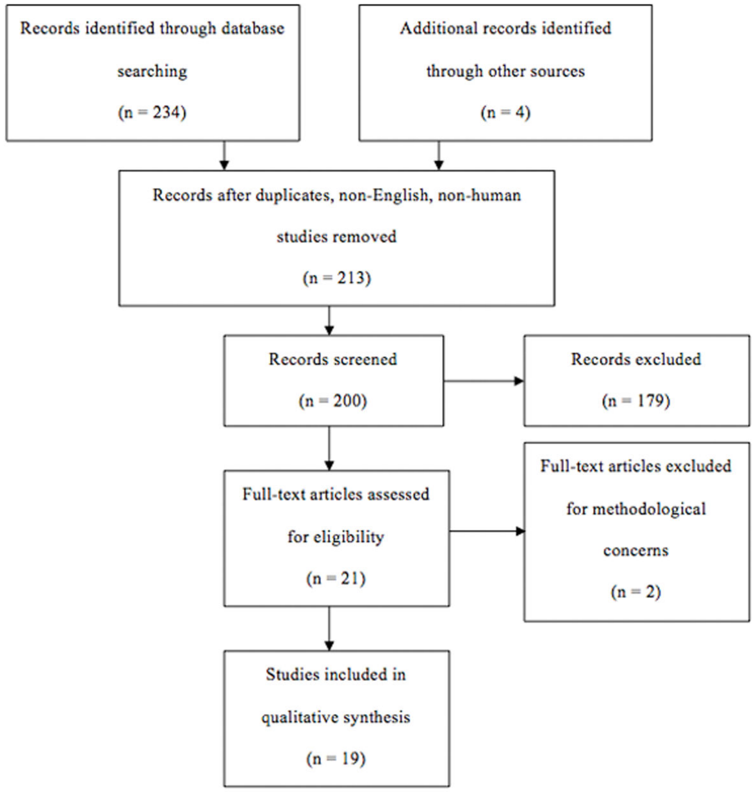

Figure 1.
Selected studies flow diagram

Table 1

Correlational Studies of Physical Activity and Cognition in Persons with MS

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Findings
Prakash et al. [20] 2007	• Cross-sectional • *N*=24	• 100% female • Definite RRMS • EDSS≤6.0	Cardiorespiratory Fitness • VO_{2peak} (cycle ergometer)	• Attention • Memory • Verbal learning and fluency • Delayed recall • Visuospatial learning • Sustained attention • Working memory • IPS	• PASAT • K-Bit • WCST • SRT • Spatial Reminding Test • SDMT • WLG	Significant relationship between level of cardiorespiratory fitness (VO_{2peak}) and information processing speed, sustained attention and working memory [PASAT] (r=0.42) after controlling for age, education and MS duration
Vanner et al. [21] 2008	• Cross-sectional • *N*=43	• 72% female • MS diagnosis • EDSS≤8.0	Physical activity • PADS	• Learning • Memory • Sustained attention • IPS	• RAVLT • SDMT	Significant relationships between PADS and - Verbal learning and memory [RAVLT] (r= −0.349) - Sustained attention and IPS [SDMT] (r= −0.524)
Prakash et al. [22] 2010	• Cross-sectional • *N*=21	• 100% female • RRMS • EDSS≤6.0	Cardiorespiratory Fitness • VO_{2peak} (cycle ergometer)	• Sustained attention • Working memory • IPS • Verbal learning and fluency • Delayed recall • Visuospatial learning	• SDMT • PASAT • WLG • SRT • Spatial Recall Test	Higher levels of cardiorespiratory fitness (VO_{2peak}) were associated with higher scores on composite measure of IPS (SDMT+PSAT +WLG) after controlling for age (r=<0.46)
Motl et al. [23] 2011	• Cross-sectional • *N*=33	• 66.7% female • Definite MS • Ambulatory • EDSS ≤ 7.0	Physical activity • Steps/day (Step Activity Monitor - accelerometer)	• Sustained attention • Processing Speed • Episodic memory • Learning • Visuospatial memory	• PASAT • SDMT • SRT • BVMT-R	Physical activity (steps/day) significantly associated with composite cognitive processing speed score [SDMT+PASAT] (r=0.39), which remained significant after controlling for age, education, gender, and MS duration (r=0.35)
Sandroff & Motl [24] 2012	• Cross-sectional • *N*=31	• 87.1% female • Physician diagnosed MS	Aerobic capacity	• Sustained attention • IPS	• PASAT • SDMT	Aerobic capacity (VO_{2peak}) was significantly associated with composite cognitive

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Findings
		• Ambulatory (with or without assistive device)	• VO_{2peak} (cycle ergometer)			processing speed scores [SDMT+PASAT] (*r*=0.442)
Sandroff et al. [25] 2013	• Prospective • *N*=82	• 76% female • Physician verified MS • Ambulatory (with or without assistive device)	Physical activity • Steps/day (ActiGraph accelerometer)	• Sustained attention • IPS	• PASAT • SDMT - oral and written	• Physical activity (steps/day) was strongly associated with attention and IPS [oral and written SDMT] (*r*=0.45 and .51, respectively) and moderately associated with attention and IPS [PASAT] (*r*=0.23) • Controlling for age and disability, the oral and written versions of the SDMT remained significant (*r*=0.25 and 0.29 respectively), while the relationship with the PASAT became non-significant
Beier et al. [26] 2014	• Longitudinal • Post-hoc correlational analysis • *N*=88	• 80.5% female • Clinically confirmed MS	Physical fitness • Bicycle ergometer protocol	• Processing speed • Flexibility • Calculation ability • Divided attention • Working memory • Executive function	• PASAT • TMT	Significant time x group interaction between improved physical fitness and improved executive function scores (TMT-A, *p*=.05; TMT-BA, *p*=.02) after controlling for age, sex, ethnicity, education, disease activity and MS duration
Sandroff et al. [27] 2014	• Cross-sectional • *N*=212	• 80% female • Clinically definite MS	Physical activity • Steps/day (ActiGraph accelerometer)	• IPS	• PASAT • SDMT • Composite IPS	• Physical activity (steps/day) was associated with SDMT (*r*=0.42), PASAT (*r*=0.27), and composite IPS (*r*=0.39) scores. • Controlling for age, gender and education, the relationship between physical activity and composite IPS (*r*=0.26) scores remained significant • Controlling for age, gender, education, and Timed 25 foot Walk Test scores the relationship between physical activity and composite IPS (*r*=0.13) scores remained significant

Reference	Design	Participant Characteristics	Physical Activity Measure	Cognitive Variables	Cognitive Outcome Measures	Findings
Sandroff et al. [28] 2015	• Cross-sectional • *N*=62	• 72.6% female • Clinically definite MS • Mild (EDSS 0–3.5), *n*=20 • Moderate (EDSS 4.0–5.5), *n*=21 • Severe (EDSS 6.0–6.5), *n*=21	Aerobic capacity • VO_{2peak} (Nustep recumbent step machine)	• IPS • Verbal learning and memory • Visual learning and memory	• SDMT - oral • CVLT-II • BVMT-R	• Aerobic capacity (VO_{2peak}) was significantly associated with IPS [SDMT] (*r*=0.41) • Aerobic capacity (VO_{2peak}) was significantly associated with IPS [SDMT] (*r*=0.42) in the mildly affected group but not the moderate or severely affected groups

BVMT-R = Brief Visuospatial Memory Test-Revised; CVLT-II = California Verbal Learning Test-2nd edition; EDSS = Expanded Disability Status Scale; IPS = Information Processing Speed; PADS = Physical Activity Disability Scale; PASAT = Paced Auditory Serial Addition Test; RAVLT = Rey Auditory-Verbal Learning Test; SDMT = Symbol Digit Modalities Test; SRT = Selective Reminding Test; TMT = Trail Making Test; VO_{2peak} = Peak oxygen consumption; WCST = Wisconsin Card Sorting Test; WLG = Word List Generation

Table 2

Experimental Studies of Physical Activity and Cognition in Persons with MS

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Oken et al. [36] 2004	• RCT • Wait-list control group • *N*=57 (22 yoga/15 aerobic exercise/20 wait list) • 24-week attrition=17%	• 93% female • Clinically definite MS • EDSS≤6.0	• Type – Supervised group programs: Iyengar yoga or aerobic exercise (stationary cycling) • Intensity – Cycling: light to moderate (RPE 2–3) • Time – 90 minutes • Frequency – Once/ week+ home practice • Duration – 24 weeks	• Attention • Alertness • IPS	• Stroop Color and Word Test • Covert orienting of spatial attention task • Attentional shifting task • Modified Useful Field of View task • Simple visual reaction time • PASAT • Weschler Memory Scales III Logical Memory • Weschler Adult Intelligence Scale III Similarities	No statistically significant time x group effects for yoga or aerobic exercise on measures of cognitive function compared to control group
Romberg et al. [37] 2005	• RCT • Control group received no intervention • *N*=95 (47 intervention /48 control) • 6-month attrition=4%	• 64% female • Clinical or laboratory defined MS • EDSS≤5.5	• Type – Week 1–3: Supervised group inpatient rehab program Week 4–26: Unsupervised home program • Intensity – NR • Time – NR • Frequency – Week 1–3: 5 sessions resistance training + 5 sessions aerobic exerciseWeek 4–26: Resistance training 3–4 times/week + aerobic training 1 time/week • Duration – 26 weeks	• Attention • Memory • IPS	• PASAT	No statistically significant time x group interaction on the measure of attention and memory (PASAT)

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
Filipi et al. [29] 2010	• One group pretest/posttest • *N*=33 • 24-week attrition - NR	• 67% female • Laboratory supported MS • EDSS≤6.5	• Type – Supervised individual resistance training • Intensity – NR • Time – 50 minutes • Frequency – 2 times/ week • Duration – 24 weeks	• Attention • Memory	• PASAT	Significant improvement in measure of attention and memory (p<.01) [PASAT]
Velikonja et al. [34] 2010	• Randomized prospective study • *N*=20 (group *n* – NR) • 10-week attrition – NR	• Gender - NR • Relapsing-remitting or progressive MS • EDSS≤6.0	• Type – Supervised group programs: Sports climbing or Hatha yoga • Intensity – NR • Time – NR • Frequency – 1 time/ week • Duration – 10 weeks	• Selective attention • Executive function	• Mazes subtest of Executive module from the Neuropsychological assessment battery • Tower of London Test • Brickenkamp d2 test	Significant improvement on selective attention after yoga (p=.005) compared to sports climbing
Briken et al. [35] 2014	• RCT • Wait-list control group • Intention-to-treat analysis • *N*=42 (10 arm ergometry/11 rowing/11 bicycle ergometry/10 control) • 8–10 week attrition=10.6%	• 57% female • 73.8% SPMS • 2.4% PPMS • EDSS≤6.1	• Type – Individual exercise training programs: Arm ergometry, rowing, or bicycle ergometry • Intensity – Mean Borg Scale = 4.6 • Time – NR • Frequency – 2 to 3 times/week • Duration – 8 to 10 weeks	• Attention • Processing speed • Long-term memory • Executive function	• SDMT • Verbal Learning and Memory Test • Test Battery of Attention • Achievement Testing System • Regensburg Verbal Fluency Test	Significant time x group interaction for • Verbal learning and delayed recall for all exercise groups (p=.011) • Tonic alertness for the bicycle group (p<.001) • Shift of attention for arm (p=.026) and bicycle (p=.002) ergometry groups
Sandroff et al. [38] 2014	• RCT • Wait-list control group • *N*=82 (37 intervention/ 39 control) • 24-week attrition = 7.3%	• 83.3% female • RRMS = 78.9% • Progressive MS = 21.1% • PDDS 0–2 (mild disability) = 47.4% • PDDS 3–6 (moderate	• Type – Internet delivered program promoting physical activity • Intensity – NR • Time – NR • Frequency – NR • Duration – 24 weeks	• IPS	• SDMT	• Significant time x condition (intervention versus control) x disability group effect on processing speed ($F_{1,66}$=5.68, p=0.02) moderate effect size (η^2_p=0.08) • Within the intervention condition, those with

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
		disability) = 52.6%				mild disability had a moderate increase in SDMT scores (d=0.41), while those with moderate disability had a minimal decrease (d= −0.12)
Sandroff et al. [31] 2015	• Randomized counterbalanced within-subjects • N=24	• Ambulatory • 95.8% female • Intact CPS • EDSS median=3.0, range=2.0–6.0	• Type – Supervised treadmill walking at 60% HRR, cycle ergometry at 60% HRR, or yoga monitored by HR and RPE • Time – 30 minutes • Frequency and Duration – single bout of acute exercise	• Executive control	• Modified Flanker Task	• Significant condition x time effects for treadmill walking, cycle ergometry and yoga compared to quiet rest (p=.01, p=<.01, and p=.01, respectively) indicating faster reaction times • Significant condition x time effect for treadmill walking compared to quiet rest (p=.04) reflecting reduced impact of interfering stimuli
Kierkegaard et al. [30] 2016	• One group pretest/posttest • N=20 • 12-week attrition = 15%	• 100% female • RRMS = 100% • EDSS≤4	• Type – Supervised group high-intensity resistance training • Intensity – 80% 1RM • Time – 60 minutes • Frequency – 2 times/ week • Duration – 12 weeks	• IPS	• SDMT	• Significant improvement in the number of correct responses on SDMT reflecting improved processing speed. • Mean score difference pre-post = 4, 95% confidence interval = 0.2 – 7, p=0.04
Sandroff et al. [32] 2016	• Randomized counterbalanced within-subjects • N=24	• Ambulatory • 96% female • EDSS median=3.0, range=1.5–4.0 • 100% RRMS • SDMT raw score > 43 Mean=63.1 SD=10.3	• Type – Supervised treadmill walking at 30%, 50%, and 70% HRR • Time – 20 minutes • Frequency and Duration – single bout of acute exercise	• Executive control	• Modified Flanker Task	• 3-way ANOVA - condition (light, moderate, vigorous) x time (pre, post) x congruency (congruent, incongruent) indicated: – Acute treadmill walking resulted in a reduced toll of incongruent stimuli on reaction time over quiet rest (F(3,69) =

Reference	Design	Participant Characteristics	Physical Activity Characteristics	Cognitive Variables	Cognitive Outcome Measures	Main Findings
						4.27, $p = .01$, $\eta_\rho^2 = .16$) – Light, moderate, and vigorous treadmill walking produced similar reductions in the toll of incongruent stimuli on reaction time over quiet rest ($F(2,46) = 0.88$, $p = .42$, $\eta_\rho^2 = .04$) – Acute treadmill walking had a non-significant effect on response accuracy ($F(3,69) = 1.03$, $p = .38$, $\eta_\rho^2 = .04$)
Sandroff, Motl et al. [33] 2016	• Randomized counterbalanced within-subjects • *N*=14	• Ambulatory • Thermosensitive • 100% female • EDSS median=3.0, range=1.5–4.0 • 100% RRMS	• Type – Supervised vigorous treadmill walking at 70% HRR • Time – 20 minutes • Frequency and Duration – single bout of acute exercise	• Executive control	• Modified Flanker Task	• Significant condition x time interaction ($F(1,13) = 83.13$, $p = 0.01$, $\eta_\rho^2 = 0.87$) indicating vigorous treadmill walking elevated core body temperature over quiet rest • Significant condition x time x congruency interaction ($F(1,13) = 5.25$, $p = 0.04$, $\eta_\rho^2 = 0.29$) indicating vigorous treadmill walking reduced toll of incongruent stimuli on reaction time over quiet rest despite elevated core body temperature

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CPS = Cognitive Processing Speed; EDSS = Expanded Disability Status Scale; HR = Heart Rate; HRR, Heart Rate Reserve; IPS = Information processing speed; NR = not reported; PASAT = Paced Auditory Serial Addition Test; PDDS = Patient-Determined Disease Steps; PPMS = Primary Progressive Multiple Sclerosis; RCT = Randomized controlled trial; RM = Repetition Maximum; RPE = Rating of Perceived Exertion; RRMS, Relapsing-Remitting Multiple Sclerosis; SDMT = Symbol Digit Modality Test; SPMS, Secondary Progressive Multiple Sclerosis