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Device-Measured Physical Activity and Cognitive Processing Speed Impairment in a Large Sample of Persons with Multiple Sclerosis

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Abstract

Objective: There is accumulating evidence regarding the beneficial effects of physical activity (PA) on cognitive processing speed in persons with multiple sclerosis (MS). However, one overarching limitation of this research is that researchers have not recruited samples who have the actual problem of being studied (i.e., cognitive processing speed impairment). This study examined associations between device-measured PA and cognitive processing speed in a large sample of persons with MS overall and between those with and without cognitive processing speed impairment. **Method:** Three hundred eighty-five persons with MS underwent the oral Symbol Digit Modalities Test (SDMT) and wore an accelerometer for 7 days for PA measurement. We divided the overall sample into subsamples with ($n = 140$) and without ($n = 245$) cognitive processing speed impairment based on age, sex, and education-adjusted SDMT *Z*-scores. **Results:** After controlling for age and disability status, higher levels of device-measured PA were significantly associated with faster cognitive processing speed overall, and the association was significantly stronger among persons with MS who presented with cognitive processing speed impairment. **Conclusions:** This examination provides initial cross-sectional support for informing the development of PA interventions as a possible approach for managing MS-related cognitive processing speed impairment. This highlights the importance of developing purposefully designed trials involving PA interventions for targeting cognitive processing speed as a primary end point among persons with MS with impaired cognitive processing speed.

Keywords: Multiple sclerosis, Physical activity, Cognition, Exercise, Cognitive processing speed, Symbol Digit Modalities Test

INTRODUCTION

Multiple sclerosis (MS) is a common neurological disease with an estimated prevalence of nearly 1 million adults in the United States (Wallin et al., 2019). The MS disease process is initially characterized by inflammation and demyelination in the central nervous system, followed by eventual neurodegeneration and axonal transection (Trapp & Nave, 2008). This damage results in substantial physical and cognitive dysfunction. Indeed, there is a growing body of evidence indicating that MS-related physical and cognitive dysfunctions co-occur in patients (i.e., cognitive–motor coupling; Benedict et al., 2011). There is further accumulating evidence regarding the beneficial effects of physical activity (PA) behavior on a number of different outcomes, including physical and cognitive functioning in this population (Motl, 2014; Motl et al., 2017). However, one overarching limitation of the overall body of research on PA effects on all outcomes among persons with MS is that researchers often do not recruit samples who have the actual problem of being studied (e.g., MS studies examining the effects of PA on depressive symptoms do not usually include persons with major depression; Motl et al., 2017). This limitation precludes conclusions regarding PA behavior as a possible treatment approach for managing major MS symptoms, this is, especially important for highly burdensome symptoms that further are poorly managed with pharmacology, such as cognitive impairment.

Cognitive dysfunction is a hallmark consequence of MS that has deleterious effects on the lives of those with the disease (Chiaravalloti & DeLuca, 2008). Upward of 50% of patients demonstrate cognitive impairment (particularly slowed cognitive processing speed) based on objective neuropsychological testing, and there are no United States Food and Drug Administration-approved pharmacological therapies for mitigating MS-related cognitive processing speed impairment (Chiaravalloti & DeLuca, 2008). PA has been identified as an alternative behavioral approach for improving cognitive

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performance among persons with MS, partly based on a large corpus of evidence involving older adults of the general population (Motl, Sandroff, & Benedict, 2011). For example, reviews and meta-analyses report on robust associations between measures of PA and neuropsychological test performance among healthy and cognitively impaired (i.e., mild cognitive impairment, dementia, Alzheimer's disease) older adults (Bherer, Erickson, & Liu-Ambrose, 2013; Groot et al., 2016; Sanders, Hortobagyi, la Bastide-van Gemert, van der Zee, & van Heuvelen, 2019). By comparison, the body of evidence in persons with MS is substantially smaller than that of older adults (Motl, Sandroff et al., 2011). There is preliminary evidence of associations between device-measured PA and cognitive processing speed in persons with MS (Sandroff, Motl, Scudder, & DeLuca, 2016) as well as evidence from one randomized controlled trial (RCT) of an Internet-based PA intervention that resulted in improvements in cognitive processing speed among persons with MS (Sandroff, Klaren et al., 2014). However, that RCT did not evaluate PA as a treatment for MS-related cognitive processing speed impairment, given that participants were not prescreened for slow (i.e., impaired) cognitive processing speed. By extension, further it is unknown if PA is even associated with cognitive processing speed among persons with MS who demonstrate impaired cognitive processing speed (Prakash, Patterson, Janssen, Abduljalil, & Boster, 2011).

The initial provision of cross-sectional associations between device-measured PA and cognitive processing speed in persons with MS who demonstrate impaired processing speed could provide an impetus for the subsequent development and implementation of longitudinal PA interventions as possible behavioral treatments for persons with objective MS-related cognitive processing speed impairment (as opposed to merely improving cognitive processing speed performance). Indeed, this is important given that persons with MS who demonstrate slow cognitive processing speed likely have the greatest need for such behavioral interventions that selectively target cognitive processing speed as a primary end point.

The current cross-sectional study sought to examine the association between device-measured PA (i.e., steps/day) and cognitive processing speed in a large sample of persons with MS with and without cognitive processing speed impairment. We focused on device-measured steps/day given that this is the PA outcome that is most commonly associated with cognitive processing speed among persons with MS (Motl, Gappmaier, Nelson, & Benedict, 2011; Sandroff, Pilutti, Dlugonski, & Motl, 2013; Sandroff, Dlugonski et al., 2014; Sandroff, Klaren et al., 2014). Steps/day further represents a valid, accessible, and easily interpretable PA outcome among persons with MS (Dlugonski et al., 2013). We hypothesized that higher values of steps/day would be associated with faster cognitive processing speed overall, and that those associations would be stronger in persons with cognitive processing speed impairment. Such a hypothesis is based upon the concept of cognitive–motor coupling, whereby physical and cognitive dysfunctions tend to co-occur among adults with MS (Benedict et al., 2011) and further aligns with previous cross-sectional reports on associations between physical fitness and cognitive processing speed in persons with MS who have cognitive processing speed impairment (Sandroff, Motl, & DeLuca, 2017).

METHODS

Participants

The present cross-sectional study represents a secondary data analysis of five separate examinations of physical and cognitive functioning among persons with MS (Baird et al., 2019; Goldman et al., 2013; Sandroff & Motl, 2012; Sandroff, Klaren et al., 2014; Sandroff, Bollaert et al., 2017). The studies had common inclusion criteria: (a) definite MS diagnosis; (b) relapse-free for the previous 30 days; (c) ambulatory with or without assistance; (d) ability to read 14-point font; and (e) willingness and ability to wear an accelerometer and complete the oral Symbol Digit Modalities Test (SDMT) as a measure of cognitive processing speed. Of note, study-specific inclusion criteria for age differed across the five studies, resulting in an overall age range between 22 and 78 years, and, as the present study was a secondary data analysis, groups were not recruited *a priori* based on the presence/absence of cognitive processing speed impairment.

Device-Measured PA

PA was measured as steps/day using waist-worn ActiGraph (Actigraph, Inc., Pensacola, FL) model GT3X and GT3X+ accelerometers. Those accelerometers contain a solid state, digital accelerometer that generates an electrical signal proportional to the force acting on it along three axes (i.e., vertical, anterior/posterior, medial/lateral). The raw accelerometer data were downloaded using ActiLife software and processed into 60-s epochs using the low-frequency extension. The low-frequency extension is a filter for enhancing accelerometer sensitivity for capturing PA in slow-moving populations, and this further renders the data compatible across current (i.e., GT3X and GT3X+) and previous ActiGraph models (i.e., 7164). Using ActiLife software, the raw accelerometer data in 60-s epochs were further processed into step counts. The data were then scored for wear time; days consisting of ≥10 h of wear time were considered valid days and cases demonstrating at least two valid days were included in the analyses (Klaren, Hubbard, Zhu, & Motl, 2016; Motl et al., 2007). Total steps were averaged across all valid days and reported as steps/day. Collectively, this procedure provides a reliable estimate of PA behavior among persons with MS using ActiGraph accelerometers (Klaren et al., 2016).

Cognitive Processing Speed

Cognitive processing speed was measured using the oral version of the SDMT (Smith, 1982). The oral SDMT

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demonstrates strong psychometric properties and is highly sensitive to generalized MS-related cognitive impairment (Benedict, Bollaert et al., 2017; Benedict, DeLuca et al., 2017). Scores on the oral SDMT have emerged as the best predictor of future cognitive decline in persons with relapsing–remitting MS (Amato et al., 2010). Briefly, the SDMT involves pairing abstract geometric symbols with single-digit numbers based on a key as quickly and accurately as possible for 90 s. The primary SDMT outcome is the total number of correct responses in the 90-s period (i.e., raw score). We further calculated *Z*-scores on the SDMT, for characterizing impairment in cognitive processing speed using regression-based norms that controlled for age, sex, and education; if education data were not available, we calculated SDMT *Z*-scores that controlled for both age and sex (Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2010). Using those regression-based norms is particularly advantageous as they control for an individual's specific demographic characteristics, as opposed to a general range, as is typical of manualized normative data (Parmenter et al., 2010). We defined cognitive processing speed impairment as SDMT scores that were at least 1.5 *SD* units below the regression-based normative score (after adjustment for demographic characteristics) for healthy controls (i.e., seventh percentile or below). Of note, recent recommendations have adopted this demographically adjusted cut point for determining impairment on a given neuropsychological test in persons with MS (Sumowski et al., 2018).

Disability Status

The Patient-Determined Disease Steps (PDDS) scale (Hadjimichael, Kerns, Rizzo, Cutter, & Vollmer, 2007) was included in this study as a self-report measure of disability status in MS. The PDDS contains a single item for measuring self-reported neurological impairment on an ordinal scale. Scores range from 0 to 8, with higher scores indicative of worse MS-related disability. For example, PDDS scores of 0 reflect minimal disability (i.e., mild symptoms that do not limit activity), scores of 3 reflect onset of ambulatory disability (without requiring an assistive device), scores of 4 and 5 reflect gradations of ambulatory disability requiring single-point assistance, scores of 6 reflect ambulatory disability wherein bilateral support is required, scores of 7 reflect primary reliance on a wheelchair, and scores of 8 reflect being bedridden due to MS. Of note, the PDDS score is a valid measure of disability status among persons with MS based on strong correlations with other measures reflecting MS-related neurologic disability (i.e., Expanded Disease Status Scale) (Learmonth, Motl, Sandroff, Pula, & Cadavid, 2013).

Procedure

The procedures for all five studies were approved by University Institutional Review Boards and all participants provided written informed consent. The research further was completed in accordance with the Helsinki Declaration. All five studies involved in-person and free-living segments. The in-person segment took place in a laboratory setting wherein participants initially provided demographic and clinical information, followed by undergoing SDMT administration in a quiet, sound-dampened room. Participants were then provided with the waist-worn accelerometer, instructions for use, and a logbook. Participants were instructed to wear the accelerometer around the waist on an elastic belt, with the unit centered on the nondominant hip, during the waking hours of the day (except when showering, bathing, and swimming) over a 7-day period. Participants further were instructed to remove the belt while sleeping. Upon completion of the 7-day period, participants returned the accelerometer and logbook through the US Postal Service *via* prestamped and preaddressed envelopes. Participants were remunerated *via* gift card upon returning the materials.

Data Analysis

All data were analyzed using SPSS version 25 (IBM, Inc., Armonk, NY, USA) and are reported as mean (*SD*) unless otherwise noted. As the present study involved a secondary analysis of a combined dataset consisting of five separate studies, there were data missing for some key outcomes. As such, the subsequent analyses were performed in slightly different sample sizes, depending on the outcome of interest. We initially performed bivariate, nonparametric Spearman correlations (r_s) between average steps/day and SDMT raw scores in the overall sample (Rousselet & Pernet, 2012). We then computed SDMT *Z*-scores based on regression-based norms (Parmenter et al., 2010) and identified groups of persons with MS with and without cognitive processing speed impairment based on the SDMT cutoff value (i.e., ≥1.5 *SD*s below the age, sex, and education-adjusted normative score; Sumowski et al., 2018). We applied Levene's test to evaluate possible heterogeneity of variances in steps/day and SDMT scores between the subsamples. We then performed independent samples *t* tests and chi-square difference tests to determine possible differences in demographic and clinical characteristics between the groups based on cognitive processing speed impairment. We performed additional bivariate Spearman correlations between steps/day and SDMT scores in the cognitive processing speed-impaired and noncognitive processing speed-impaired subsamples. This was followed by partial Spearman correlations (pr_s) between steps/day and SDMT scores, controlling for demographic and clinical characteristics that significantly differed between the groups in the overall sample and cognitive processing speed impairment subsamples. Values for the magnitude of correlation coefficients of .1, .3, and .5 were interpreted as small, moderate, and large, respectively (Cohen, 1988). We lastly applied Fisher's *z* test to examine whether the partial correlation coefficients were significantly different in magnitude between the subsamples grouped on the presence/absence of cognitive processing speed impairment.

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Table 1. Descriptive characteristics of 385 persons with MS with and without cognitive processing speed impairment

	Overall ($n = 385$)		Cognitive processing speed impairment ($n = 140$)		No cognitive processing speed impairment ($n = 245$)		
Variable	*n*	Value	*N*	Value	*N*	Value	*p*-Value
Age (years)	385	49.9 (11.6)	140	47.2 (10.9)	245	51.4 (11.8)	<.01*
Sex (*n*, % female)	385	301/385 (78.2%)	140	102/140 (72.9%)	245	199/245 (81.2%)	.06
Education (years)	352	16.1 (2.2)	128	15.9 (2.2)	224	16.2 (2.2)	.30
MS type							
Relapsing–remitting (*n*, %)	344	299/344 (86.9%)	125	103/125 (82.4%)	219	196/219 (89.5%)	.06
Progressive (*n*, %)		45/344 (13.1%)		22/125 (17.6%)		23/219 (10.5%)	
Disease duration (years)	352	12.3 (9.4)	128	11.3 (8.2)	224	12.9 (9.9)	.11
PDDS (median, IQR)	381	2.0 (4.0)	139	3.0 (3.0)	242	1.0 (2.0)	<.01*
SDMT (raw score)	385	49.6 (12.8)	140	39.5 (9.6)	245	55.4 (10.7)	<.01*
SDMT (*Z*-score)	385	−1.1 (1.2)	140	−2.3 (0.6)	245	−0.4 (0.8)	<.01*
Steps/day	385	4840.9 (2714.1)	140	4421.8 (2763.9)	245	5080.4 (2661.4)	.02*

Note: All data are presented as mean (*SD*) unless otherwise noted; * $p < .05$ based on two-tailed test; cognitive processing speed impairment based on SDMT score of 1.5 *SD* units or more below published normative value; MS = multiple sclerosis; PDDS = Patient-Determined Disease Steps; SDMT = Symbol Digit Modalities Test; SDMT *Z*-scores based on regression-based normative values controlling for age, sex, and education.

RESULTS

Descriptive Characteristics

The overall sample included 385 persons with MS who underwent administration of the SDMT and provided at least two valid days of accelerometer data (Klaren et al., 2016; Motl et al., 2007). Demographic and clinical characteristics, SDMT scores, and average steps/day of the overall sample, and cognitive processing speed-impaired/noncognitive processing speed-impaired subsamples are presented in Table 1, along with *p*-values for possible cognitive processing speed impairment group differences in those variables. Briefly, the overall sample was mostly female and highly educated with relapsing–remitting MS. Overall, the sample demonstrated some degree of cognitive processing speed impairment based on a mean SDMT score that was 1.1 *SD* units below the regression-based normative score that controlled for age, sex, and education (i.e., SDMT *Z*-score). On average, the sample was physically inactive based on accelerometer-measured steps/day values; this is consistent with other large samples of persons with MS (Dlugonski et al., 2013; Klaren, Motl, Dlugonski, Sandroff, & Pilutti, 2013; Motl et al., 2013; Sandroff, Dlugonski et al., 2012). Regarding the subsamples, persons with MS who presented with cognitive processing speed impairment were significantly younger ($d = 0.37$), had significantly worse disability (PDDS scores), and took fewer steps/day ($d = 0.24$) than persons with MS who did not present with cognitive processing speed impairment based on chi-square difference tests and independent samples *t* tests. Furthermore, Levene's test confirmed homogeneity of variances in steps/day and SDMT scores between the subsamples ($p > .05$ for both). Of note, age and PDDS scores were jointly and significantly associated with steps/day ($r_s = .31$ and $-.54$, respectively) and SDMT raw scores ($r_s = .40$ and $-.41$, respectively) in the overall sample.

Bivariate Correlations

The scatter plot of the association between steps/day and SDMT scores in the overall sample and subsamples based on cognitive processing speed impairment is presented in Figure 1. Within the overall sample, average steps/day was significantly and moderately associated with SDMT scores ($r_s = .35$, $p < .01$). Average steps/day was significantly associated with SDMT scores in both subsamples. The correlation was moderate to large in magnitude for persons with cognitive processing speed impairment ($r_s = .49$, $p < .01$) and was moderate in magnitude for persons without cognitive processing speed impairment ($r_s = .30$, $p < .01$). The magnitudes of those correlations were significantly different between subsamples based on Fisher's *z* test for ($z = -2.07$, $p = .02$), whereby steps/day was more strongly associated with SDMT scores in persons with MS who presented with cognitive processing speed impairment.

Partial Correlations

Given that age and PDDS scores were jointly associated with both steps/day and SDMT scores in the overall sample and further differed between the subsamples, we performed partial Spearman correlations between steps/day and SDMT scores, controlling for age and PDDS, in the overall sample and cognitive processing speed impairment subsamples. In the overall sample, after controlling for age and PDDS scores, average steps/day was significantly associated with SDMT scores ($pr_s = .11$, $p = .04$); this partial correlation was small in magnitude. However, after accounting for age and PDDS scores, average steps/day was significantly associated with SDMT scores in persons with MS who demonstrated cognitive processing speed impairment ($pr_s = .29$, $p < .01$),

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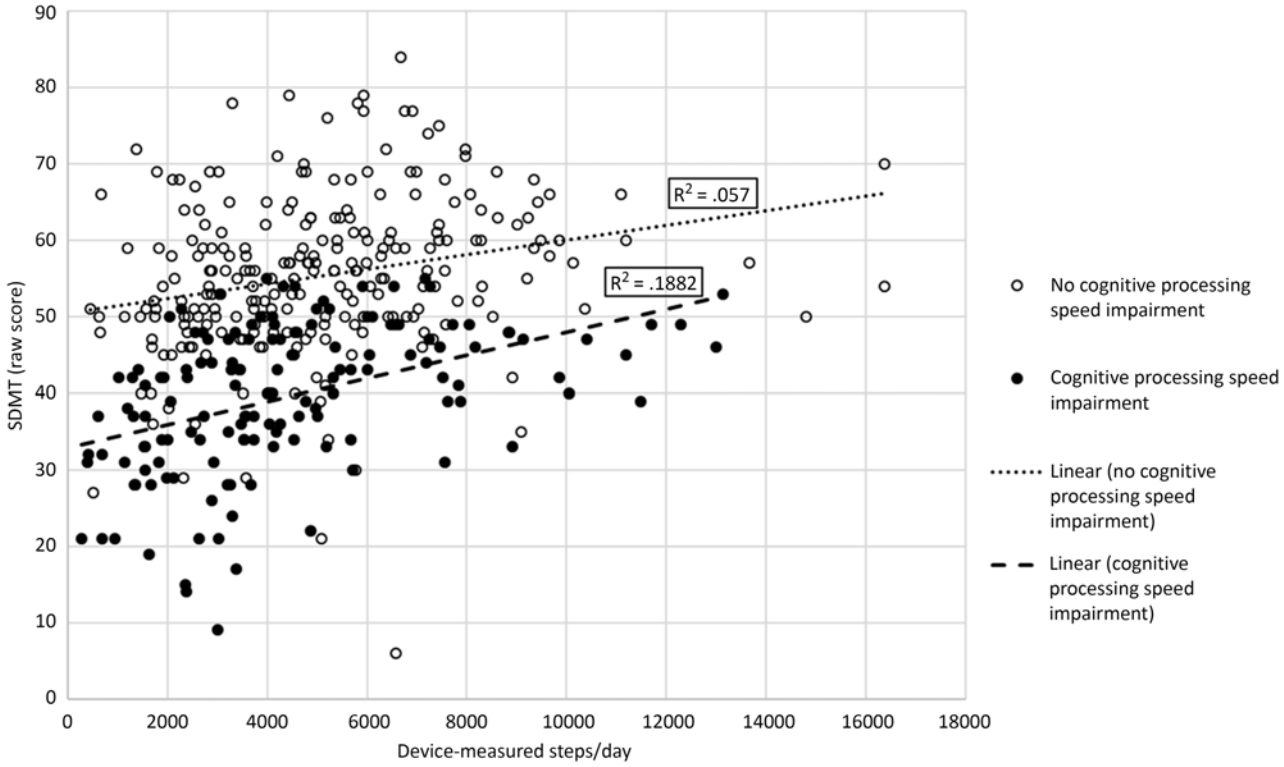

Fig. 1. Scatter plot of device-measured physical activity (i.e., steps/day) and Symbol Digit Modalities Test raw score in 385 persons with MS with and without cognitive processing speed impairment along with lines of best fit.

but not in persons with MS without cognitive processing speed impairment ($pr_s = -.01$, $p = .90$). Importantly, the magnitudes of those correlations were significantly different between subsamples based on Fisher's z test ($z = 2.87$, $p < .01$), such that PA was more strongly associated with SDMT scores, independent of age and disability status, in persons with MS who presented with cognitive processing speed impairment.

DISCUSSION

The current study involved a secondary analysis of data on the associations between device-based measures of PA and cognitive processing speed in a large sample of persons with MS overall and between subsamples with and without cognitive processing speed impairment. The primary results indicated that higher levels of device-measured PA behavior (i.e., steps/day) were moderately and significantly associated with faster cognitive processing speed overall; that association was attenuated, but still statistically significant after controlling for age and disability status as covariates. After controlling for those covariates, the correlation between steps/day and SDMT scores was significantly stronger among persons who presented with cognitive processing speed impairment compared with persons with MS who did not present with cognitive processing speed impairment. This provides preliminary, cross-sectional data supporting PA as a possible behavioral approach for managing MS-related cognitive processing speed impairment (i.e., the most common and debilitating cognitive problem associated with the disease; Chiaravalloti & DeLuca, 2008). The primary results further can inform the development of purposefully designed RCTs involving PA interventions for treating impaired cognitive processing speed in persons with MS. If correct, then future RCTs of PA interventions have the potential to influence cognitive processing speed to an even greater degree than observed in the previous study of noncognitively impaired persons with MS (Sandroff, Klaren et al., 2014).

The primary results equally support cognitive status as an important determinant of PA behavior. Indeed, persons with MS who demonstrated worse cognitive processing speed engaged in less PA behavior, independent of age and disability status. Perhaps impairments in cognitive processing speed present unique barriers for PA participation among persons with MS. Such an observation and hypothesis are consistent with evidence in older adults describing a bidirectional relationship between PA and cognitive performance (Daly, McMinn, & Allan, 2015). Moreover, the current sample of persons with MS who presented with cognitive processing speed impairment was insufficiently physically active relative to normative steps/day data (i.e., Tudor-Locke, Johnson, & Katzmarzyk, 2009). Given the association between PA and cognitive processing speed in the current study, by extension, perhaps cognitive rehabilitation interventions aimed at improving cognitive processing speed could enhance PA behavior among persons with MS who presented with cognitive processing speed impairment (Motl, Sandroff, & DeLuca, 2016).

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This is important given the prevalence and burden of MS-related cognitive processing speed impairment coupled with the well-established observation that persons with MS do not engage in sufficient levels of free-living, health-enhancing PA compared with adults of the general population (e.g., Kinnett-Hopkins, Adamson, Rougeau, & Motl, 2017).

One recent systematic review highlighted that PA is possibly efficacious for improving cognitive processing speed among persons with MS based on convergent evidence from 1 Class II and 3 Class IV studies (Sandroff et al., 2016). However, that systematic review identified a major field-wide limitation that involved the complete lack of prescreening for cognitive processing speed impairment in such research studies; this further has been identified as a limitation of PA research in MS overall (Motl et al., 2017). Accordingly, it was not possible to consider PA as a possible treatment for MS-related cognitive processing speed impairment, given that participants must actually present with the problem being studied in order for an intervention to be considered a treatment (Sandroff et al., 2016). To overcome such a limitation, the present secondary analysis sought to provide initial proof-of-concept data by examining the cross-sectional associations between device-measured steps/day and cognitive processing speed based on the presence/absence of cognitive processing speed impairment among persons with MS. Indeed, after controlling for age and disability status, the correlations among steps/day and cognitive processing speed were significantly stronger among persons with MS who presented with cognitive processing speed impairment. Based on a similar hypothesis involving cardiorespiratory fitness (Sandroff, Motl et al., 2017), such a pattern of results suggests that perhaps there is more room for improving cognitive processing speed with future interventions aimed at enhancing PA among persons with MS who demonstrate impaired cognitive processing speed. The current pattern of results suggests a small, but significant association between PA behavior and cognitive processing speed, independent of age and disability status, in a large sample of persons with MS. This observation is consistent with the concept of cognitive–motor coupling in persons with MS, whereby disease-related neural damage might jointly affect neural substrates that subserve both cognitive and motor functioning (Benedict et al., 2011). Interestingly, the present results provide additional support for such a hypothesis as persons with MS who presented with cognitive processing speed impairment engaged in significantly less PA behavior than the subsample without cognitive processing speed impairment.

The present results both replicate and extend previous reports on cross-sectional associations between PA measures and scores from neuropsychological tests in persons with MS. Within the overall sample, the associations between device-measured PA and cognitive processing speed were statistically significant and moderate in magnitude. Such a pattern of results is consistent with other studies that report on small-to-moderate associations between device-measured steps/day and cognitive processing speed in persons with MS (Motl, Gappmaier et al., 2011; Sandroff et al., 2013; Sandroff, Dlugonski et al., 2014). Of note, none of those cross-sectional studies examined those associations based on the presence/absence of objective cognitive processing speed impairment. The present secondary analysis extends those results by providing the first reports of small-to-moderate correlations between device-measured PA and cognitive processing speed (based on SDMT scores), independent of age and disability status, in persons with MS who presented with impaired cognitive processing speed.

Strengths of the current study include the large overall sample and focal examination of cognitive processing speed impairment (using regression-based norms that accounted for age, sex, and education) as an influence on the PA/cognitive processing speed relationship in persons with MS. Another strength involves the focus on device-measured steps/day, as this outcome is more easily integrated into clinical practice than other device-measured PA outcomes (e.g., activity counts/day). However, there are several noteworthy limitations. This study involved a cross-sectional design that does not permit inferences of causation between engaging in more PA behavior and faster cognitive processing speed. The present study involved a secondary analysis of data from five studies on physical and cognitive functioning among persons with MS; this presented several issues. One problem is that we were not able to prospectively recruit persons with MS based on the presence/absence of cognitive processing speed impairment *a priori*. We further were unable to administer complete neuropsychological batteries to participants to examine whether or not the PA–cognitive processing speed impairment relationship extends into other cognitive domains that are commonly impaired in MS (i.e., learning and memory/executive function). This further limited our ability to classify persons with MS as cognitively impaired or intact based on other criteria (i.e., number of failed neuropsychological tests, poor cognitive performance in multiple domains, generation of a composite cognitive score). We recognize that a universal definition of MS-related cognitive impairment is lacking, and that defining cognitive impairment is a particularly salient issue in cognition research among persons with MS in general (Sumowski et al., 2018). We note that the oral SDMT is not a pure measure of cognitive processing speed, and performance can be influenced by sensorial impairment, oral motor impairment, and/or slow visual search skills (Costa, Genova, DeLuca, & Chiaravalloti, 2017). However, this neuropsychological test is considered a more pure measure of cognitive processing speed than other neuropsychological measures of cognitive processing speed that are common in MS research (e.g., Paced Auditory Serial Addition Test), as it relies less on working memory (i.e., the central executive; Rao et al., 2014). We further did not collect data on possible medical factors (i.e., comorbidities, health history) that might explain the association between PA behavior and cognitive processing speed (beyond the influences of age and disability status) across the five studies. Hence, we were unable to control for those factors, which could have upwardly biased the correlations between steps/day and cognitive processing speed in the

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samples. There were further missing PDDS data, resulting in a slightly smaller sample size for examining partial correlations between steps/day and SDMT scores, that controlled for disability status as a covariate. Due to the nature of the five studies, data on light PA or weekday *versus* weekend accelerometer wear time were not available. However, we do note that the present approach for collecting and processing accelerometer data for capturing device-measured steps/day provides a valid, reliable, and clinically meaningful estimate of free-living PA behavior among persons with MS (Dlugonski et al., 2013; Klaren et al., 2016; Motl et al., 2007). Finally, due to the nature of the five studies, data on cardiorespiratory fitness were not available. This could have afforded the opportunity to examine whether or not free-living PA accounts for additional variance in cognitive processing speed, beyond the influence of cardiorespiratory fitness (Sandroff, Motl et al., 2017). Future research efforts might consider strategically disentangling the relationship among cardiorespiratory fitness, free-living PA, and cognitive processing speed among persons with MS who demonstrate impaired cognitive processing speed.

CONCLUSIONS

Collectively, the present study provides novel evidence of a statistically significant association between device-measured PA behavior and cognitive processing speed, independent of age and disability status, particularly among persons with MS who demonstrate objective impairment in cognitive processing speed. This examination provides initial cross-sectional support for informing the development of PA interventions as an approach for managing MS-related cognitive processing speed impairment, as well as possible cognitive rehabilitation interventions for enhancing free-living PA behavior. This highlights the importance of developing purposefully designed rehabilitative RCTs for specifically targeting cognitive processing speed and PA as primary end points among persons with MS who presented with cognitive processing speed impairment.

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DISCLOSURE

The authors declare no conflicts of interest.

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