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Correlates of Processing Speed Change With Combined Cognitive Rehabilitation and Exercise in Progressive MS: Secondary Analysis of the CogEx Trial

Brian M. Sandroff, PhD[1,2], Robert W. Motl, PhD[3], Roberto S. Hernandez, PhD[4], Maria Pia Amato, MD[5,6], Giampaolo Brichetto, MD[7,8], Jeremy Chataway, MD[9,10], Nancy D. Chiaravalloti, PhD[1,2], Gary R. Cutter, PhD[11], Ulrik Dalgas, PhD[12], John DeLuca, PhD[1,2], Rachel Farrell, MD[9], Peter Feys, PhD[13], Massimo Filippi, MD[14], Jennifer Freeman, PhD[15], Matilde Inglese, MD[16,17], Cecilia Meza, MA[18], Maria A. Rocca, MD[14], Amber Salter, PhD[4], and Anthony Feinstein, MD[18]; On Behalf of the CogEx Study Team

Abstract

Background. Cognitive rehabilitation and exercise training are promising approaches for improving cognition in persons with progressive multiple sclerosis (MS). Identifying heterogeneity of change and factors that influence the effects of cognitive rehabilitation and/or exercise training on cognitive outcomes at the individual level have direct relevance for developing tailored and optimized rehabilitation interventions for improving cognition in progressive MS. *Objective*. This study involved a secondary data analysis from the CogEx trial in progressive MS. This study first described heterogeneity of change in cognitive processing speed (CPS) across the intervention conditions and then identified possible adherence/compliance, baseline performance, and demographic/clinical variables as correlates of rehabilitation-related CPS changes. *Methods*. A total of 311 persons with progressive MS who were pre-screened for impaired CPS completed 12 weeks of combined cognitive rehabilitation (or sham) and exercise training (or sham). CPS was measured before and after the 12-week period. As potential correlates of CPS changes, we measured adherence/compliance (ie, treatment exposure), performance outcomes at baseline, as well as demographic and clinical characteristics at baseline. *Results*. There was heterogeneity of change in CPS across the 4 intervention conditions. We further identified baseline learning and memory impairment and premorbid intelligence quotient (IQ), but not adherence/compliance, other baseline performance outcomes, or demographic/clinical characteristics as significant correlates of CPS changes across the 4 intervention conditions. *Conclusions*. The overall pattern of results suggests that future trials in this area might account for impaired learning and memory and/or premorbid IQ as potential covariates, or more carefully consider the role of reserve within rehabilitation interventions in progressive MS.

Keywords

cognitive rehabilitation, exercise, cognition, multiple sclerosis, response heterogeneity

Introduction

Cognitive functioning is compromised as a result of the multiple sclerosis (MS) disease process, particularly among those with progressive clinical courses.[1] Indeed, recent data suggest that cognitive impairment occurs in upwards of 79% of persons with primary or secondary progressive MS.[1] Progressive MS-related cognitive dysfunction is highly debilitating and is poorly treated with pharmacological agents.[2] We recently performed a 4-arm, randomized, double-blinded, sham-controlled trial of cognitive rehabilitation and aerobic exercise training along with respective sham conditions on cognitive processing speed (CPS) in a large, international sample of persons with progressive MS (ie, the CogEx trial[3];). The CogEx trial reported a non-significant, group by time interaction on Symbol Digit Modalities Test (SDMT) scores as a primary measure of CPS (all 4 conditions improved from baseline to 12 weeks).[4] We *post-hoc* hypothesized that the non-significant group by time interaction on SDMT scores may have been associated with the lack of a true control condition (ie, passive/waitlist control that accounted for passage of time and afforded the

opportunity to isolate potential learning effects on SDMT scores in the trial). That hypothesis was based on all 4 intervention conditions involving active components that may have resulted in large improvements on the SDMT,[4] but was not directly testable within the CogEx trial dataset. Herein, we were interested in further examination of correlates of changes in SDMT scores with cognitive rehabilitation and/or exercise training among individuals with progressive MS within the 4 conditions (ie, the present study). Indeed, such an exploratory analysis from a large clinical trial is critical for understanding heterogeneity of treatment effects and possible correlates of heterogeneity that may inform future research and clinical practice.[5]

The study of heterogeneity of change with rehabilitation in progressive MS is important for precision medicine. The identification of heterogeneity of change and factors that influence the effects of cognitive rehabilitation and/or exercise training on cognitive outcomes in MS[6,7] at the individual level have direct relevance for developing tailored and optimized rehabilitation interventions for improving cognition in progressive MS. Individual responses to rehabilitation may differ based on the actual amount of rehabilitation completed (ie, adherence and compliance) relative to the prescription, baseline levels of physiological and functional outcomes, and/or demographic/clinical characteristics. Such an examination could provide critical information on the development of targeted rehabilitation interventions for optimally improving cognition among progressive MS subgroups.

This study involved a secondary analysis of data from the CogEx trial in 311 persons with progressive MS[3,4] and focused on understanding possible individual level variability and correlates of changes in SDMT scores. We focus on changes in SDMT scores as the original CogEx trial reported overall improvements in this outcome, but no overall improvements on California Verbal Learning Test-II (CVLT-II) or Brief Visuospatial Memory Test-Revised (BVMT-R) scores as secondary cognitive outcomes of learning and memory.[4] To that end, the present study involved a largely data-driven approach and aimed to: (a) describe heterogeneity of change in SDMT scores as a measure of CPS overall and within the intervention conditions of the CogEx trial; (b) identify possible adherence/compliance, baseline performance, and demographic/clinical variables as correlates of rehabilitation-related changes (or lack thereof) on SDMT scores within the intervention conditions; and (c) determine the strongest correlates of SDMT changes within the intervention conditions. Although this secondary analysis was largely exploratory, we operationalized adherence/compliance, baseline performance, and demographic/clinical variables as potential correlates based on a published model for examining response heterogeneity with rehabilitation in MS.[13]

Methods

Trial Description

The CogEx trial was a randomized, double-blind, and sham-controlled trial of the comparative and combined effects of cognitive rehabilitation and aerobic exercise training on cognitive outcomes in persons with progressive MS that involved 11 sites across 6 different countries (Canada [1 site], USA [2 sites], United Kingdom [2 sites], Denmark

[1]Kessler Foundation, West Orange, NJ, USA
[2]Department of Physical Medicine & Rehabilitation, Rutgers NJ Medical School, Newark, NJ, USA
[3]Department of Kinesiology and Nutrition, University of Illinois Chicago, Chicago, IL, USA
[4]Department of Neurology, Section on Statistical Planning and Analysis, University of Texas Southwestern Medical Center, Dallas, TX, USA
[5]Department NEUROFARBA, Section Neurosciences, University of Florence, Florence, Italy
[6]IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy
[7]Scientific Research Area, Italian Multiple Sclerosis Foundation (FISM), Genoa, Italy
[8]AISM Rehabilitation Service, Italian Multiple Sclerosis Society, Genoa, Italy
[9]Queen Square MS Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK
[10]National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, London, UK
[11]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA
[12]Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark
[13]REVAL, Faculty of Rehabilitation Sciences, Hasselt University, Diepenbeek, Belgium
[14]Neuroimaging Research Unit, Division of Neuroscience, Neurology Unit, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy
[15]Faculty of Health, University of Plymouth, Plymouth, Devon, UK
[16]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy
[17]IRCCS Ospedale Policlinico San Martino, Genova, Italy
[18]Department of Psychiatry, University of Toronto and Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Corresponding Author:
Brian M. Sandroff, Kessler Foundation, 1199 Pleasant Valley Way, West Orange, NJ 07052, USA.
Email: bsandroff@kesslerfoundation.org

[1 site], Belgium [1 site], and Italy [4 sites]).[3] Briefly, following the completion of baseline assessments, participants were randomized into 1 of 4, 12-week conditions (cognitive rehabilitation [CR] + exercise training [EX], CR + sham-exercise training [EX-S], sham-cognitive rehabilitation [CR-S] + EX, or CR-S + EX-S). Following the completion of the 12-week study period, participants underwent follow-up assessments by a treatment-blinded outcome assessor. Alternate, equivalent forms were applied wherever possible for follow-up cognitive assessments to minimize potential practice effects.[3]

This paper first focuses on changes in SDMT scores for the overall sample, and then changes in SDMT scores within the separate, pooled conditions (ie, CR vs CR-S collapsed across exercise conditions, and EX vs EX-S collapsed across cognitive rehabilitation conditions). This is appropriate considering the non-significant group by time interactions on SDMT scores that indicated overall improvements in SDMT scores that were similar across the 4 experimental conditions that are reported in the primary CogEx outcomes paper.[4] Such an approach increases statistical power to better understand what drove the SDMT improvements within each condition of the CogEx trial.

Participants

The full inclusion/exclusion criteria are reported elsewhere,[3,4] as these are the same as for the overall CogEx trial. Briefly, participants had a neurologist-confirmed diagnosis of primary or secondary progressive MS, were between the ages of 18 and 70 years, ambulatory with or without assistance, had minimal contraindications for exercise training, and were insufficiently physically active based on a Godin Leisure-Time Exercise Questionnaire Health Contribution Score of <24.[8] Given the primary study outcome of the CogEx trial, participants further had impaired CPS, defined as a score of at least 1.282 standard deviations below published, country-specific normative data (10th percentile) on the SDMT; we note that this was an inclusion criterion for the original CogEx trial.

Intervention Conditions

Overview. As reported in the protocol and primary outcomes papers,[3,4] participants were randomly assigned to 1 of 4 intervention groups consisting of cognitive rehabilitation (or sham) combined with exercise training (or sham). All 4 interventions occurred over 2 sessions per week over a 12-week period. Within each session, participants first undertook ~1 hour of cognitive rehabilitation (or sham) that was immediately followed by ~1 hour of exercise training (or sham). The intervention conditions were manualized and progressed in terms of duration and intensity across the 12-week study period. Full details are reported in the protocol and primary outcomes papers.[3,4]

Cognitive Rehabilitation. The CogEx CR condition involved administration of the computerized Rehacom program.[9] For the CogEx trial, Rehacom modules included divided attention 1 and 2, attention and concentration, vigilance 2 and sustained attention that are integral to processing speed. Each session involved completing 2 prescribed modules. Participants began at level 1 on each RehaCom module and advanced through the program based on their performance, under the guidance of the research assistant. Thus, progression was individualized based on module success. Complete details on the CR condition can be found in the Supplemental Materials of the primary outcomes paper.[4]

Sham Cognitive Rehabilitation. The CogEx CR-S condition involved administration of Internet training; this has been used as an active control condition for cognitive rehabilitation trials in MS.[10] The Internet training consisted of completing several activities associated with computer and Internet use (eg, keyboard/mouse overview and search engine use). Complete details on the CR-S condition can be found in the Supplemental Materials of the primary outcomes paper.[4] Of note, the CR-S condition matched the CR condition on duration throughout the 12-week study period.

Aerobic Exercise Training. The CogEx EX condition involved supervised aerobic exercise training on a recumbent arm-leg stepper (Nustep T5XR, Nustep Inc, Ann Arbor, MI, USA). Briefly, EX consisted of bouts of continuous, moderate-intensity exercise along with high-intensity interval training (HIIT) performed on alternating days, 2 times per week for 12 weeks. The continuous bouts progressed from 10 minutes of moderate-intensity exercise toward 30 minutes of moderate-to-vigorous intensity exercise in Week 12. The HIIT bouts progressed from 5, 1-minute intervals at a work rate associated with 80% to 90% of peak oxygen consumption (VO_{2peak}) interspersed with 1-minute rest periods (ie, lightly exercising at 15 W) in Week 1 toward 10, 2-minute intervals at a work rate associated with 90% VO_{2peak} interspersed with 2-minute rest periods in Week 12. Complete details on the EX condition can be found in the Supplemental Materials of the primary outcomes paper.[4]

Sham Exercise Training. The sham exercise condition consisted of supervised stretching and balance that were performed 2 times per week, based on the physiotherapy program published by Barrett et al.[11] The EX-S condition prescription involved completing up to 3 sets of 6 different exercises per session that were performed in different

positions (eg, prone, supine, and crook lying). Complete details on the EX-S condition can be found in the Supplemental Materials of the primary outcomes paper.[4]

Outcomes

We provide brief descriptions on the outcomes included in this secondary analysis below; complete details on the outcomes are reported in the protocol and primary outcomes papers.[3,4] We note that all outcomes were collected using the same procedures with similar equipment across sites.

Cognitive Processing Speed. Cognitive processing speed represented the primary CogEx outcome and was measured using the oral version of the SDMT.[12] The primary SDMT outcome was the raw score (ie, total number of correctly provided symbol-digit pairs in 90 seconds).

Correlates of Change

Based on the overall mean improvements on SDMT scores, but non-significant group by time interaction on this measure that was reported in the CogEx primary outcomes paper,[4] we examined adherence/compliance, baseline performance outcomes, and baseline demographic/clinical characteristics as correlates of heterogeneity of change on the SDMT. We considered adherence and compliance as potential correlates of change to address the question of whether or not engaging in more of the intervention conditions resulted in disproportionate improvements in the outcomes; this provides a more nuanced test of the overall CogEx hypotheses.[3,4] We further considered baseline performance and demographic/clinical characteristics as potential correlates of SDMT changes, respectively, based on a published model for examining response heterogeneity with rehabilitation in MS.[13]

Adherence/Compliance. Adherence was defined as attending and undertaking the intervention sessions,[3] and expressed as a percentage of the 24 total intervention sessions. Compliance was defined as undertaking and completing the sessions consistent with the prescription,[3] and expressed as a percentage of the 24 total intervention sessions. For CR and CR-S, compliance was operationalized based on completing the prescribed modules within a given session. For EX, compliance was operationalized based on exercising within 5 W of the prescribed work rate for at least 90% of the session for the continuous bout of exercise, and exercising within 5 W of the prescribed work rate for at least n − 1 intervals for the weekly HIIT session. For example, if a participant exercised at the prescribed intensity for 4 of 5 possible intervals in week 1, that session was rated as compliant, whereas if they exercised at the prescribed intensity for 4 of 6 possible intervals in Week 2, the session was rated as non-compliant. For EX-S, compliance was operationalized based on completing at least n − 1 prescribed stretching/balance exercises per session. Across all conditions, failure to attend a session was recorded as non-adherent/compliant for that session. We note that these characterizations of adherence and compliance are consistent with recent recommendations for moving rehabilitation research forward in MS.[14]

Mobility. The 6-Minute Walk Test (6MWT) characterized walking performance based on walking endurance.[15] The 6MWT is associated with strong psychometric properties in MS.[15] The 6MWT was administered using standard instructions for MS.[15] The primary 6MWT outcome was the total distance walked over the 6-minute period in meters.

Baseline Cognitive Impairment. We included baseline cognitive impairment as a potential predictor of cognitive changes based on previous research.[7,8] We focus on impairment as opposed to continuous raw scores given that identifying cognitively impaired/unimpaired persons with MS who may have improved more on the SDMT provides more easily interpretable information regarding the potential target population for a subsequent trial. Baseline cognitive performance was assessed using the SDMT, CVLT-II, and BVMT-R (ie, BICAMS neuropsychological battery). Verbal learning and memory was measured using the CVLT-II.[16] The primary CVLT-II outcome was the total learning score across 5 trials. The BVMT-R is a neuropsychological test of visuospatial learning and memory.[17] The primary BVMT-R outcome is the total learning score across 3 trials. Information on the SDMT is described above.[12] We characterized impairment on the CVLT-II and BVMT-R based on scores at least 1.282 SD units below the age-, sex-, education-, and language-specific normative scores (ie, 10th percentile). We further characterized impairment on the BICAMS based on the number of impaired tests. Of note, all participants were impaired on the SDMT as a trial inclusion criterion.

Cardiorespiratory Fitness. Cardiorespiratory fitness, operationalized as VO_{2peak} and W_{peak}, was recorded using a maximal, incremental exercise test on a recumbent arm-leg stepper (Nustep T5XR, Nustep Inc, Ann Arbor, MI, USA) with respiratory gases analyzed using calibrated, open circuit spirometry. The standardized protocol and criteria for an interpretable test result have been described and validated for delivery across the disability spectrum in MS.[18]

Moderate-to-Vigorous Physical Activity (MVPA). MVPA was measured via accelerometry using ActiGraph model GT3X+ accelerometers (Actigraph Corporation, Pensacola, FL, USA). Participants wore the accelerometer around the waist during the waking hours of the day for a 7-day period. Only data from valid days (wear time ≥600 minutes) were

processed in ActiLife (Actigraph Corporation) using MS cut-points for MVPA for inclusion in the analyses.[19] Of note, MVPA is expressed in minutes per day.

Demographic/Clinical Characteristics. The demographic characteristics included age, sex, marital status, primary language, total years of schooling, highest level of education, premorbid intelligence quotient (IQ), and current employment status. The clinical characteristics included disease duration and type of progressive MS.

Disability Status. The Expanded Disability Status Scale (EDSS) was provided by the participant's treating neurologist and ranges between 0 (normal neurological examination) through 10 (death caused from MS).[20]

Patient Reported Outcome Measures (PROMs). PROMs of fatigue (Modified Fatigue Impact Scale [MFIS]),[21] subjective cognitive deficits (20-item Perceived Deficits Questionnaire),[22] walking impairment (12-item Multiple Sclerosis Walking Scale),[23] mood (Beck Depression Inventory[24] and Hospital Anxiety and Depression Scale[25]), MS-related quality of life (Multiple Sclerosis Impact Scale-29[26]), and global function (Functional Assessment of Multiple Sclerosis)[27] were included using total scores per measure.

Data Analysis

All statistical analyses were performed independently for each outcome variable and were conducted in SAS (version 9.4, Cary, NC, USA). The analyses included participants who were randomized, began the intervention, and had adherence/compliance data for the different intervention conditions. If all sessions were missing for a specific participant, that participant was excluded from the analyses. We created waterfall plots to allow for visual inspection of the distributions and potential heterogeneity of change in SDMT scores overall and within the 4 individual conditions (ie, CR, CR-S, EX, and EX-S).

We evaluated associations between correlates and change in SDMT scores in the overall sample using bivariate methods. We then evaluated associations among the variables that were significantly correlated with changes in SDMT scores in the overall sample and within the 4 individual conditions. The bivariate correlations involved Pearson product–moment correlations (r) for continuous variables, point-biserial correlations (r_{pb}) for dichotomous variables, and Spearman rank-order correlations (ρ) for multi-level categorical variables between potential correlates and change in SDMT. Cohen's guidelines of 0.1, 0.3, and 0.5 indicated small, moderate, and strong correlations, respectively.[28] Then to examine the relative strength of potential correlates of SDMT changes within the conditions, we performed 4 independent multivariable linear regressions that regressed SDMT change on variables that were significantly associated (at $P < .2$) with SDMT change based on bivariate correlations using direct entry. A false discovery rate correction[29] was applied to correct for multiple comparisons where the adjusted significance level for all tests conducted in the analysis was $P < .021$. Of note, we did not perform a sample size calculation prior to conducting analyses for this study as the sample size was limited to existing data. While potentially limited in the ability to detect small associations in this analysis, Austin and Steyerberg[30] show that for linear regression, 2 subjects per variable in linear regression accurately estimated the standard errors of the regression coefficients, the estimated confidence intervals had approximately the expected coverage rates, and the adjusted R^2 estimates behaved well. Thus, the current sample size likely was sufficient for the number of predictors included in the regression models.

Results

Descriptive Characteristics and Changes in Outcomes

Of the 311 randomized participants, 306 began the intervention. Two participants were excluded from the EX/EX-S analysis due to missing exercise logs. The characteristics for the overall sample (n = 306 for CR/CR-S and n = 304 for EX/EX-S) and the subsamples who completed the CR (n = 155) and CR-S (n = 151), irrespective of the exercise conditions, and who completed the EX (n = 152),and EX-S (n = 152) conditions, irrespective of the cognitive rehabilitation conditions, are provided in Table 1. There were no baseline differences between the intervention conditions for all included characteristics. There were significant differences in adherence and compliance ($P < .001$ and $< .001$, respectively) in the EX/EX-S conditions, and non-significant differences in adherence and compliance ($P = .990$ and .985, respectively) in the CR/CR-S conditions. As we previously reported, there was a non-significant group * time interaction on SDMT scores overall.[4] There further were non-significant group * time interactions on SDMT scores for the CR/CR-S comparison ($P = .635$, $d = 0.052$, 95% CI = −0.181, 0.285) as well as for the EX/EX-S comparison ($P = .053$, $d = -0.236$, 95% CI = −0.470, −0.001). Such data and associated interpretations are provided in the primary outcomes manuscript.[4]

The waterfall plots for change in SDMT scores for the overall sample, and 12-week intervention conditions are provided in Figure 1. Of note, based on visual inspection, there was substantial heterogeneity of change in SDMT scores overall. This did not seemingly vary as a function of the individual conditions, based on a non-significant Levene's test for differences in variance for change in SDMT score ($P = .137$).

Table 1. Demographic Characteristics of the Overall Sample, in the Cognitive Rehabilitation (CR) and Sham Cognitive Rehabilitation (CR-S) Conditions Regardless of Exercise Training Group Assignment, and in the Exercise Training (EX) and Sham Exercise Training (EX-S) Conditions Regardless of Cognitive Rehabilitation Group Assignment.

Variable	Overall CR sample (n = 306)	CR condition (n = 155)	CR-S condition (n = 151)	Overall EX sample (n = 304)	EX condition (n = 152)	EX-S condition (n = 152)
Age; mean (SD)	52.5 (7.11)	52.7 (7.29)	52.4 (6.93)	52.5 (7.12)	52.0 (7.38)	53.0 (6.84)
Sex[a]; n (%)						
Female	190 (62.1)	95 (61.3)	95 (62.9)	188 (61.8)	99 (65.1)	89 (58.6)
Male	116 (37.9)	60 (38.7)	56 (37.1)	116 (38.2)	53 (34.9)	63 (41.4)
School; mean (SD) y	13.9 (3.33)	13.9 (3.40)	13.9 (3.27)	13.9 (3.34)	13.9 (3.32)	14.0 (3.36)
Highest level of education completed; n (%)						
Primary	25 (8.2)	11 (7.1)	14 (9.3)	24 (7.9)	12 (7.9)	12 (7.9)
Secondary (high school)	145 (47.4)	78 (50.3)	67 (44.4)	144 (47.4)	71 (46.7)	73 (48.0)
College/university	136 (44.4)	66 (42.6)	70 (46.4)	136 (44.7)	69 (45.4)	67 (44.1)
Premorbid IQ; mean (SD)	109.5 (9.11)	109.2 (9.60)	109.9 (8.57)	109.5 (9.12)	109.6 (8.56)	109.4 (9.67)
EDSS; median (IQR)	6.0 (4.5; 6.5)	6.0 (4.5; 6.5)	5.8 (4.0; 6.5)	6.0 (4.5; 6.5)	5.5 (4.0; 6.0)	6.0 (4.5; 6.5)
Type of MS; n (%)						
Primary progressive	82 (26.8)	45 (29.0)	37 (24.5)	82 (27.0)	43 (28.3)	39 (25.7)
Secondary progressive	224 (73.2)	110 (71.0)	114 (75.5)	222 (73.0)	109 (71.7)	113 (74.3)
Duration of MS; mean (SD) y	14.5 (9.60)	14.2 (9.60)	14.9 (9.61)	14.5 (9.63)	14.1 (9.44)	15.0 (9.82)
Primary language; n (%)[b]						
English	112 (36.7)	58 (37.7)	54 (35.8)	112 (37.0)	55 (36.2)	57 (37.7)
Italian	150 (49.2)	77 (50.0)	73 (48.3)	150 (49.5)	74 (48.7)	76 (50.3)
Dutch	20 (6.6)	10 (6.5)	10 (6.6)	18 (5.9)	10 (6.6)	8 (5.3)
Danish	17 (5.6)	7 (4.5)	10 (6.6)	17 (5.6)	9 (5.9)	8 (5.3)
French	1 (0.3)	0 (0.0)	1 (0.7)	1 (0.3)	1 (0.7)	0 (0.0)
Other	5 (1.6)	2 (1.3)	3 (2.0)	5 (1.7)	3 (2.0)	2 (1.3)
Marital status; dichotomized; n (%)						
Single	103 (33.7)	45 (29.0)	58 (38.4)	103 (33.9)	48 (31.6)	55 (36.2)
Partnered	203 (66.3)	110 (71.0)	93 (61.6)	201 (66.1)	104 (68.4)	97 (63.8)
Currently working; n (%)[c]	112 (36.8)	48 (31.4)	64 (42.4)	112 (37.1)	62 (40.8)	50 (33.3)

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; School, total years of schooling.
$P < .05$; 2-sample *t*-test between CR conditions ($P = .047$ (Currently working)).
[a]Self-identified sex.
[b]n = 303.
[c]n = 302.

Bivariate Correlates of SDMT Changes

The bivariate analyses are provided in Tables 2 to 4. In the overall sample, only baseline CVLT-II impairment, baseline BVMT-R impairment, number of impaired baseline BICAMS tests, MFIS total score, and premorbid IQ were significantly associated with changes in SDMT scores. To address the possibility of collinearity among the significant cognitive correlates of SDMT change, we performed a bivariate correlation analysis among baseline SDMT scores and baseline impairment on the CVLT-II, BVMT-R, and BICAMS. Baseline SDMT scores were significantly associated with baseline CVLT-II impairment ($r = -.268$, $P < .001$), BVMT-R impairment ($r = -.219$, $P < .001$), and number of impaired baseline BICAMS tests ($r = -.296$, $P < .001$). As such correlations were statistically significant, we further performed collinearity tests within the regressions (described below).

We then performed bivariate correlations among baseline CVLT-II impairment, baseline BVMT-R impairment, number of impaired BICAMS tests, MFIS total score, premorbid IQ, and change in SDMT score within the intervention conditions. For the CR condition, baseline CVLT-II impairment ($r = -.21$, $P = .01$), BVMT-R impairment ($r = -.28$, $P < .01$), number of impaired BICAMS tests ($r = -.29$, $P < .01$), and premorbid IQ ($r = .28$, $P < .01$) were identified as significant correlates of change ($P < .05$). For the CR-S condition, baseline CVLT-II impairment ($r = -.21$, $P = .02$), BVMT-R impairment ($r = -.34$, $P < .01$), number of impaired BICAMS tests ($r = -.34$, $P < .01$), and MFIS total score ($r = .20$, $P = .02$) were identified as significant correlates of SDMT change. For the EX condition, baseline CVLT-II impairment ($r = -.22$, $P = .01$), BVMT-R impairment ($r = -.32$, $P < .01$), and number of impaired BICAMS tests ($r = -.34$, $P < .01$) were identified as significant correlates of SDMT change. For the EX-S condition, baseline

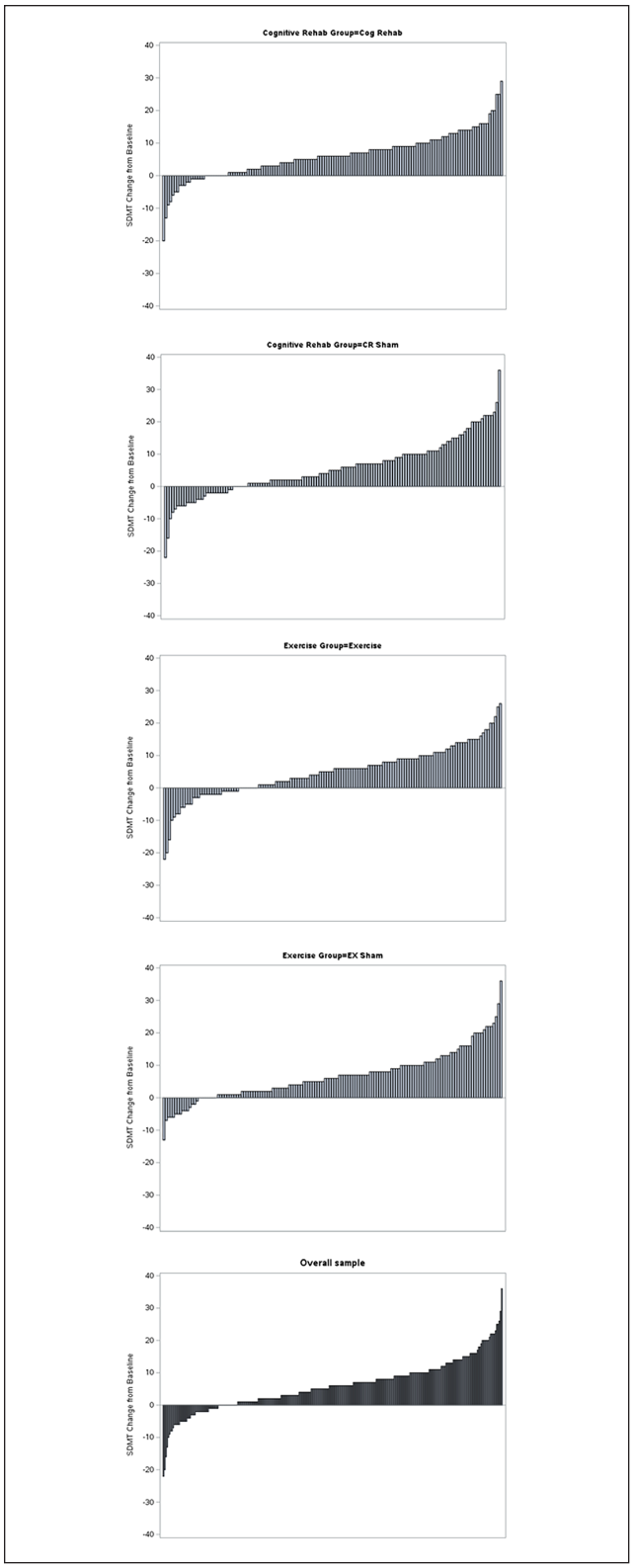

Figure 1. Waterfall plots for change in SDMT in the cognitive rehabilitation condition; sham cognitive rehabilitation condition; exercise training; sham exercise training; and overall sample.

CVLT-II impairment ($r=-.20$, $P=.02$), BVMT-R impairment ($r=-.32$, $P<.01$), number of impaired BICAMS tests ($r=-.30$, $P<.01$), and premorbid IQ ($r=.31$, $P<.01$) were identified as significant correlates of SDMT change. Thus, across all 4 conditions, having in-tact (ie, unimpaired) verbal and visuospatial learning and memory were associated with larger improvements in SDMT score. The scatter plots depicting those correlations are provided in Figures 2 and 3.

Regressions

Based on the pattern of bivariate correlations above, we performed multivariable regressions with direct entry to examine the relative strength of the correlates of SDMT changes within the 4 separate conditions (Table 5). Of note, for each of the regressions, we did not include number of impaired tests on the baseline BICAMS due to collinearity with CVLT-II and BVMT-R impairment, respectively. Overall, there was low collinearity among the included predictors within the regressions, based on all variable inflation factor values falling between 1.08 and 2.30 and all condition indices falling below 30. Within the CR condition, the variability in change in SDMT scores was not explained by any factors considered at the adjusted significance level (ie, $P<.021$). Within the CR-S condition, BVMT-R impairment (Estimate=−4.35, SE=1.64, $P=.009$) and MFIS total (Estimate=0.10, SE=0.04, $P=.014$), but not CVLT-II impairment, explained a statistically significant portion of variance in change in SDMT scores ($R^2=.11$). Within the EX condition, BVMT-R impairment (Estimate=−3.79, SE=1.52, $P=.014$), but not CVLT-II impairment, explained a statistically significant portion of variance in change in SDMT scores ($R^2=.06$). Finally, within the EX-S condition, premorbid IQ (Estimate=0.19, SE=0.07, $P=.007$) and BVMT-R impairment (Estimate=−3.81, SE=1.56, $P=.016$), but not CVLT-II impairment, explained a statistically significant portion of variance in change in SDMT scores ($R^2=.15$).

Discussion

The current paper sought to identify potential correlates of changes in SDMT scores to better understand possible individual level variability and correlates of changes in CPS in response to rehabilitation among a large international sample of persons with progressive MS. Such an effort was a data-driven approach to better understand the primary results from the CogEx trial that reported non-significant group-by-time interactions on SDMT scores whereby there were similar improvements in CPS across each of the 4 conditions.[4] The primary pattern of results identified that overall, in-tact learning and memory, fewer impaired BICAMS tests, higher premorbid IQ, and less fatigue, but not adherence and compliance (ie, treatment

Table 2. Adherence, Compliance, and Baseline Performance Characteristics of the Overall Sample, in the Cognitive Rehabilitation (CR) and Sham Cognitive Rehabilitation (CR-S) Conditions Regardless of Exercise Training Group Assignment, and in the Exercise Training (EX) and Sham Exercise Training (EX-S) Conditions Regardless of Cognitive Rehabilitation Group Assignment.

Variable	Overall CR sample (n = 306)	CR condition (n = 155)	CR-S condition (n = 151)	Overall EX sample (n = 304)	EX condition (n = 152)	EX-S condition (n = 152)
Average adherence (%); median (IQR)**	100.0% (91.7; 100.0)	100.0% (91.7; 100.0)	100.0% (91.7; 100.0)	100.0% (100.0; 100.0)	100.0% (91.7; 100.0)	100.0% (100.0; 100.0)
Average compliance (%); median (IQR)**	100.0% (83.3; 100.0)	100.0 % (91.7; 100.0)	100.0% (83.3; 100.0)	83.3% (58.3; 100.0)	75.0% (41.7; 91.7)	91.7% (83.3; 100.0)
FAMS total; mean (SD)*	103.4 (28.74)	99.9 (29.42)	107.1 (27.66)	103.5 (28.78)	105.7 (27.93)	103.5 (28.78)
MSWS total; mean (SD)	63.5 (26.52)	65.7 (25.98)	61.2 (26.95)	63.5 (26.60)	63.5 (27.47)	63.5 (26.60)
PDQ total; mean (SD)	28.5 (17.31)	29.8 (17.63)	27.2 (16.94)	28.4 (17.29)	28.4 (18.43)	28.4 (17.29)
MFIS total; mean (SD)	44.2 (17.23)	46.1 (17.14)	42.3 (17.16)	44.2 (17.27)	43.5 (17.79)	44.2 (17.27)
HADS anxiety; mean (SD)	6.5 (4.49)	6.7 (4.78)	6.4 (4.19)	6.5 (4.46)	6.4 (4.43)	6.6 (4.49)
HADS depression; mean (SD)	6.2 (4.01)	6.5 (4.23)	5.9 (3.77)	6.2 (4.02)	5.9 (3.87)	6.4 (4.15)
MSIS physical; mean (SD)*	57.7 (18.35)	60.1 (18.44)	55.3 (17.99)	57.7 (18.40)	58.0 (18.28)	57.3 (18.58)
MSIS mental; mean (SD)	22.4 (8.68)	23.0 (8.84)	21.8 (8.51)	22.4 (8.70)	22.4 (8.58)	22.3 (8.84)
Avg total min/d MVPA; mean (SD)	13.1 (18.05)	12.7 (19.47)	13.5 (16.51)	13.1 (18.10)	14.7 (19.24)	13.1 (18.10)
6MWT total distance; mean (SD)	265.8 (140.15)	251.4 (138.80)	280.6 (140.44)	265.6 (140.59)	273.4 (141.49)	265.6 (140.59)
VO_{2peak}; mean (SD)*	17.5 (6.34)	16.8 (5.60)	18.2 (6.97)	17.5 (6.36)	17.5 (6.27)	17.5 (6.36)
W_{peak}; mean (SD)*	81.1 (33.82)	76.9 (30.60)	85.4 (36.41)	81.4 (33.72)	82.0 (34.27)	81.4 (33.72)
Baseline CVLT-II impairment; n (%)	121 (39.5)	64 (41.3)	57 (37.7)	121 (39.5)	59 (38.3)	62 (40.8)
Baseline BVMT-R impairment; n (%)	90 (29.6)	44 (28.6)	46 (30.7)	90 (29.6)	42 (27.5)	48 (31.8)
BICAMS impairment; n (%)						
SDMT only; n (%)	155 (50.7)	77 (49.7)	78 (51.7)	154 (50.7)	79 (52.0)	75 (49.3)
2 BICAMS tests; n (%)	91 (29.7)	48 (31.0)	43 (28.5)	90 (29.6)	46 (30.3)	44 (28.9)
3 BICAMS tests; n (%)	60 (19.6)	30 (19.4)	30 (19.9)	60 (19.7)	27 (17.8)	33 (21.7)

IQR, interquartile range.

All participants demonstrated impairment on the SDMT at baseline based on at least 1.282 SD units below the age-; sex-; education-; and language-adjusted normative mean.

*$P < .05$; Kruskal–Wallis test between CR conditions. ($P = .036$ (FAMS); $P = .021$ (MSIS physical) $P = .048$ (VO_{2peak}); $P = .029$ (W_{peak})).

**$P < .001$; Kruskal–Wallis test between EX conditions. ($P < .001$ (Average adherence); $P < .001$ (Average compliance)).

Table 3. Correlations Among Adherence/Compliance, Baseline Performance, Demographic/Clinical Characteristics, and Change in SDMT as a Continuous Variable in the Overall Sample.

Variable	Sample size (n)	Correlation with SDMT change (*r*)	*P*-value
Avg adherence	282	.099	.097
Avg compliance	282	.072	.227
CVLT-II impairment	**282**	**−.188**	**.002**
BVMT-R impairment	**282**	**−.261**	**<.001**
BICAMS impairment (number of tests)	**282**	**−.269**	**<.001**
MFIS total	**279**	**.143**	**.017**
PDQ total	281	.114	.055
FAMS total	258	−.024	.696
MSWS total	279	.016	.786
Avg total min/d MVPA	261	.032	.610
6MWT total distance	282	.005	.929
VO_{2peak}	282	−.053	.371
W_{peak}	281	−.015	.804
HADS anxiety	281	.060	.320
HADS depression	281	.098	.102
MSIS physical	282	.046	.440
MSIS mental	282	.051	.397
Premorbid IQ	**246**	**.201**	**.001**
Age	282	.070	.242
Gender	282	.027	.648
Marital status	282	.007	.902
Language	281	.013	.826
Total years of school	282	.035	.559
Type of MS	282	−.059	.321
Duration of MS	280	−.010	.867
Currently working	281	.039	.515
EDSS score	281	−.013	.827

*$P < .021$ are bolded.

exposure), other baseline performance measures, or demographic/clinical characteristics were significantly correlated with SDMT changes in persons with progressive MS. Interestingly, the pattern of correlations were relatively similar within the 4 conditions wherein having in-tact learning and memory and fewer impaired BICAMS tests were associated with larger changes in SDMT scores in each of the 4 conditions. However, when applying multivariable regression analyses, no single variable was consistently and significantly associated with SDMT changes across each of the CR, CR-S, EX, and EX-S conditions. Thus, the results underscore the importance of considering baseline learning and memory impairment and premorbid IQ, in particular, as potential covariates in future rehabilitation research endeavors aimed at improving processing speed in persons with progressive MS.

The CogEx trial applied alternate, equivalent forms of the SDMT at baseline and 12-week follow-up to minimize the potential effect of practice/learning on SDMT performance; however, it is unlikely that such an effect was completely eliminated. However, we do note that the SDMT improvements observed in the CogEx trial were larger than those that represent practice effects with repeated SDMT administration in progressive MS.[31] There are no pure measures of CPS (or any cognitive domain[32];), and the SDMT is no exception. From a task-demand perspective, successful completion of the SDMT does require visuospatial elements to rapidly scan between the symbol-digit pairs in the key and the stimuli (ie, symbols) to orally pair with single-digit numbers. The SDMT further involves a learning and memory component such that being able to quickly memorize the symbol/digit pairs in the key is likely conducive to better test performance. To that end, it is intuitive that demonstrating better/in-tact learning and memory, perhaps in the visuospatial domain, might predict potential improvements from repeated exposure to the SDMT. In the present study, baseline CVLT-II and BVMT-R impairment were significantly associated with SDMT changes overall and within the 4 conditions. Such a finding further aligns with reports on the importance of immediate and/or incidental visual

Table 4. Correlation Analysis for SDMT Change in the Separate Conditions.

	CR		CR-S		EX		EX-S	
Variable	Correlation (*r*)	*P*-value	Correlation (*r*)	*P*-value	Correlation (*r*)	*P*-value	Correlation (*r*)	*P*-value
CVLT-II impairment	**−.207**	**.012**	**−.206**	**.016**	**−.218**	**.010**	**−.198**	**.018**
BVMT-R impairment	**−.280**	**<.001**	**−.344**	**<.001**	**−.324**	**<.001**	**−.318**	**<.001**
BICAMS impairment (number of tests)	**−.292**	**<.001**	**−.338**	**<.001**	**−.343**	**<.001**	**−.301**	**<.001**
MFIS total	.072	.392	**.200**	**.020**	.152	.077	.126	.134
Premorbid IQ	**.284**	**.001**	.137	.139	.090	.332	**.306**	**<.001**

Abbreviations: CR, cognitive rehabilitation; CR-S, sham cognitive rehabilitation; EX, exercise; EX-S, sham exercise.
Correlation analysis only involves variables that were significantly associated with SDMT change in the overall sample (Table 3).
*$P < .021$ are bolded.

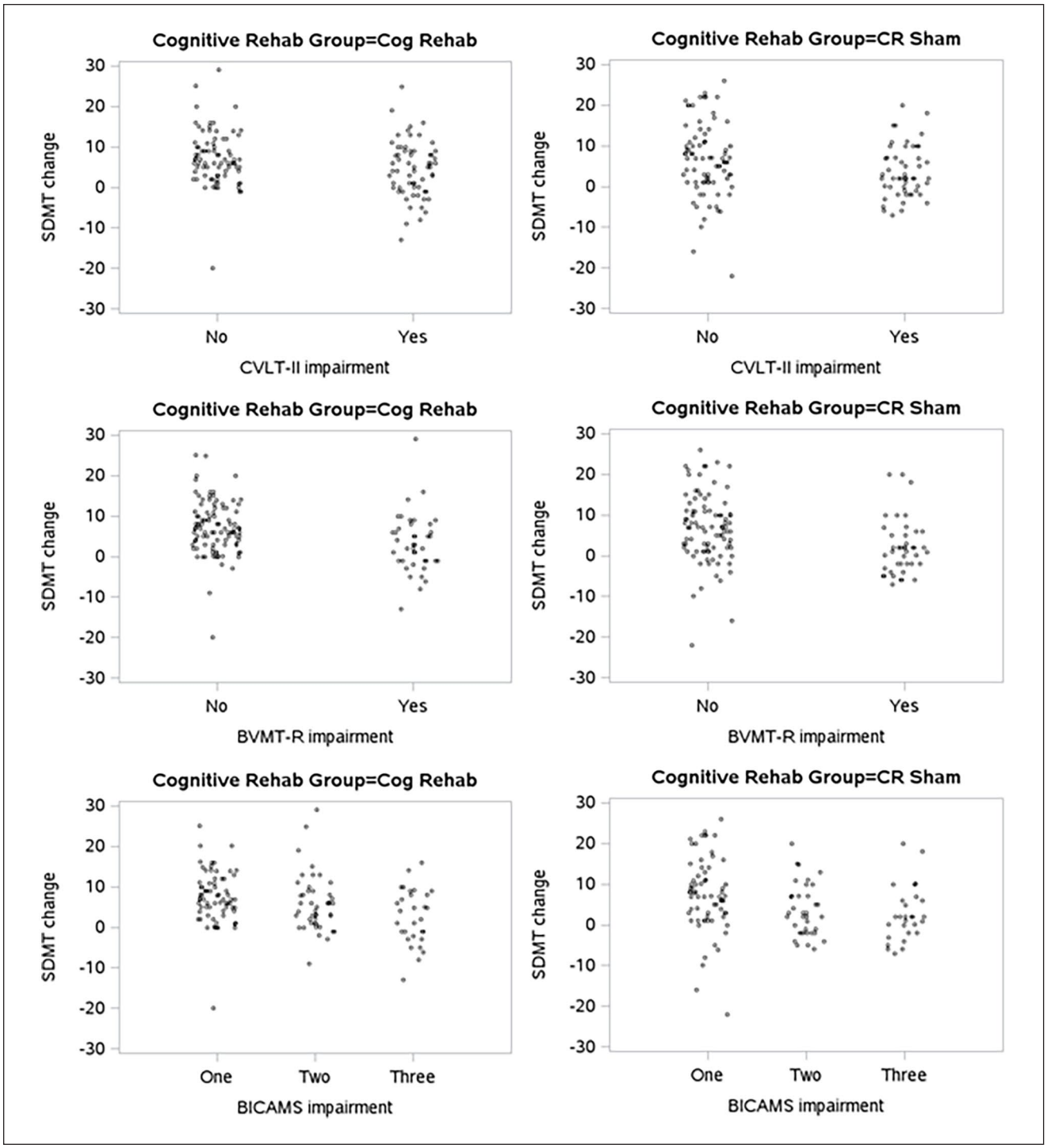

Figure 2. Scatter plots for change in SDMT and BICAMS variables by cognitive group (CR vs CR-S).

memory when completing the SDMT in persons with MS, wherein BVMT-R scores explained a significant portion of variance in SDMT performance.[33]

However, it was not expected that the correlation between baseline learning and memory impairment and change in SDMT scores would be qualitatively larger than the potential association of treatment exposure based on adherence and compliance. Indeed, neither adherence nor compliance were significantly associated with changes in SDMT scores overall or in any of the 4 conditions. This result was especially surprising, as we considered adherence and compliance as a likely correlate of SDMT changes based

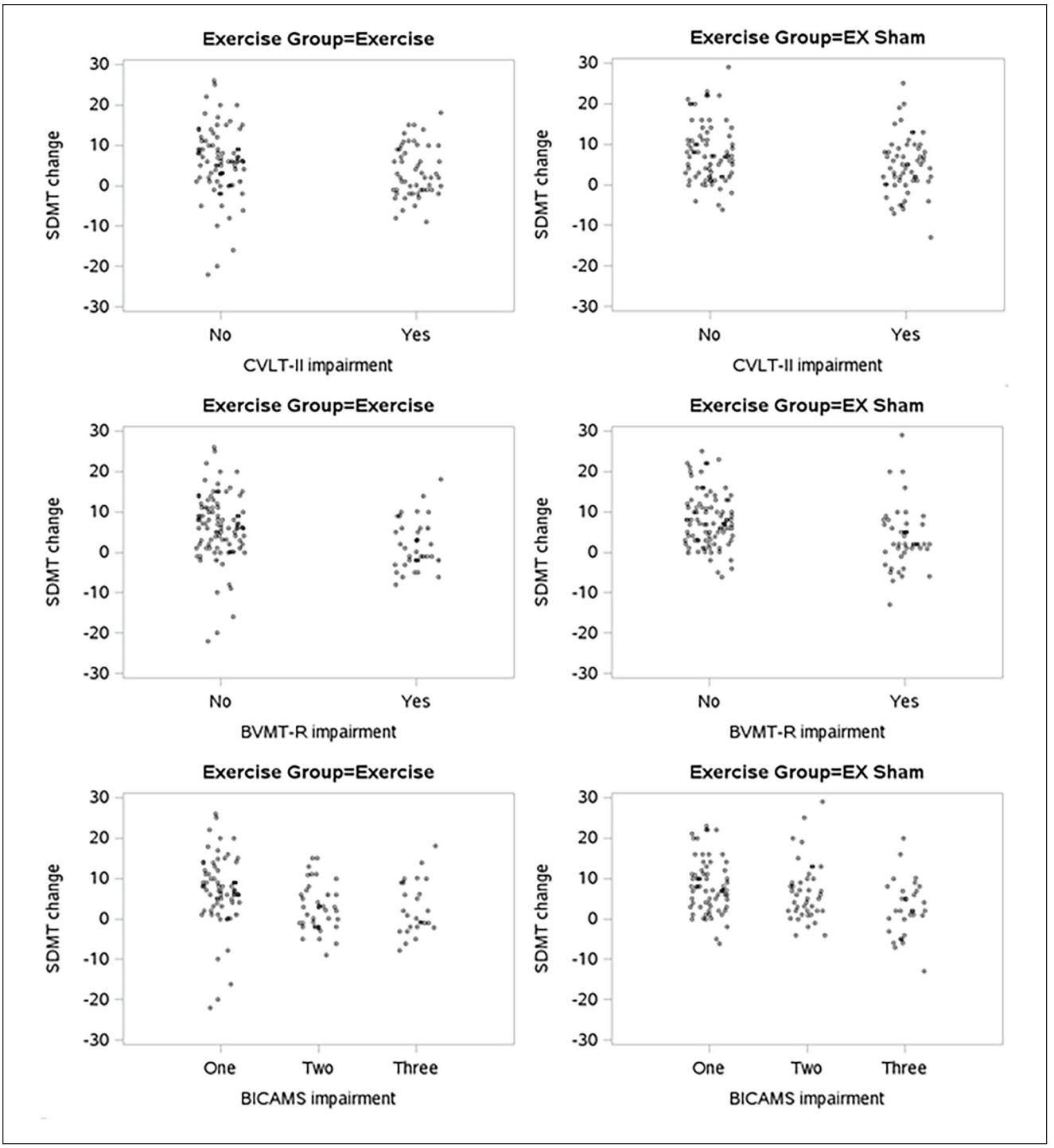

Figure 3. Scatter plots for change in SDMT and BICAMS variables by exercise group (EX vs EX-S).

on our overall trial hypothesis on the potential benefits of cognitive rehabilitation and aerobic exercise training on CPS impairment in persons with progressive MS.[3,4] The CogEx trial was designed to test the comparative and combined effects of cognitive rehabilitation and aerobic exercise training as 2 rehabilitative approaches to improve CPS among persons with progressive MS who demonstrated impairments in CPS. Despite the overall and within-group cognitive improvements reported in the primary outcomes paper,[4] engaging in more of the active interventions was

Table 5. Regression Analysis for SDMT Change With Significant Correlates ($P < .2$) by Condition.

Condition	Predictor	Estimate	Standard error	*P*-value	Model R^2 (adjusted)
CR					.11
	Premorbid IQ	0.15	0.07	.026	
	BVMT-R impairment				
	Yes	−2.60	1.48	.081	
	No		reference		
	CVLT-II impairment				
	Yes	−1.86	1.32	.160	
	No		reference		
CR-S					.11
	BVMT-R impairment				
	Yes	−4.35	1.64	.009	
	No		reference		
	MFIS total	0.10	0.04	.014	
	CVLT-II impairment				
	Yes	−1.75	1.56	.264	
	No		reference		
EX					.06
	BVMT-R impairment				
	Yes	−3.79	1.52	.014	
	No		reference		
	CVLT-II impairment				
	Yes	−1.39	1.40	.323	
	No		reference		
EX-S					.15
	Premorbid IQ	0.19	0.07	.007	
	BVMT-R impairment				
	Yes	−3.81	1.56	.016	
	No		reference		
	CVLT-II impairment				
	Yes	−1.59	1.44	.273	
	No		reference		

Note. * denotes $p < .021$.

seemingly not associated with such cognitive improvements. This too was the case for other baseline performance outcomes and demographic/clinical characteristics outcomes as potential correlates of SDMT changes. Of note, though demographic/clinical characteristics such as age and EDSS score have predicted SDMT decline over 10-years in persons with MS,[34] these variables were not associated with SDMT changes in response to rehabilitation among persons with progressive MS.

One interpretation of the overall pattern of results is that perhaps having in-tact learning and memory represents a proxy of reserve in progressive MS, wherein those who demonstrated higher reserve (ie, in-tact learning and memory) improved more on the SDMT in response to rehabilitation than those with depleted reserve (ie, impaired learning and memory). As the importance of reserve in MS is well-established,[35] such a construct could have been more influential than treatment exposure or demographic/clinical characteristics for explaining SDMT improvements in the CogEx trial. Such an interpretation aligns with the observed significant correlation between higher premorbid IQ and larger SDMT changes in the CR condition. Indeed, there is the possibility that high reserve represents a marker of better overall central nervous system integrity among persons with progressive MS, and this may allow for greater neural adaptations (ie, neuroplasticity) with physical and/or cognitive interventions.[36] This underscores the importance of focusing on reserve as a potential variable that reflects the capacity for rehabilitation adaptations in progressive MS in future interventions.[37] For example, future research efforts might consider testing multifocal interventions that build reserve as an approach to improve CPS in this population. In addition, future research efforts in this area might consider designing trials that pre-screen participants for high/low reserve a priori as a precision medicine approach. This could involve the consideration of multiple proxies beyond

those included in this study such as occupational attainment or cognitive leisure.

Another potential interpretation of the observed pattern of null results regarding adherence/compliance is that the irreversible, neurodegenerative disease processes associated with progressive MS might overwhelm the capacity for 12-weeks of cognitive rehabilitation and exercise training to directly improve impairments in CPS.[38] However, as the correlations among adherence, compliance, and SDMT change were small, non-statistically significant, but still non-zero, we do not believe that cognitive rehabilitation and exercise training are inert for CPS change in progressive MS. Future research on the effects of rehabilitation and reserve on CPS in progressive MS is warranted, given the importance of treating CPS impairment as a highly common and disabling consequence of progressive MS.[1,2] Based on the current pattern of results, such research efforts might consider applying a double-baseline period for further mitigating the practice/learning effect of the SDMT, and/or controlling for baseline learning and memory impairment as a potential covariate. Another future research approach might involve applying additional neurocognitive trial endpoints of CPS that are less sensitive to practice effects (eg, NIH Toolbox) to examine the effect of the intervention(s) on the larger cognitive construct of processing speed.

Another possibility is that perhaps longer intervention durations are necessary for significantly improving processing speed in those with progressive MS who present with substantial disability, whereas similar or shorter interventions have resulted in improvements in cognition those with milder MS disability (eg, Ref. 39-42). Longer intervention periods (and associated measurement intervals) further might be conducive for mitigating potential learning effects on the SDMT. Future research efforts that focus on long-term rehabilitation as an approach to change cognition in this population might consider trial endpoints that reflect changes in rates of neurodegeneration (eg, annualized thalamic atrophy[43]) as a benchmark of success against ongoing progressive disease. At the time of study conception and design, relatively short-duration studies in relapsing-remitting MS largely informed our intervention duration, given the lack of research in progressive MS.[3] There too is the possibility that the RehaCom modules and the recumbent stepping-based exercise training were suboptimal modalities for improving CPS in this population. Perhaps other applications of cognitive rehabilitation paradigms that are more specific for processing speed, exercise modalities that more directly affect brain networks that are critical for CPS, and/or applying acute exercise as an approach to prime the brain prior to cognitive rehabilitation sessions can result in larger improvements relative to control conditions.[44,45]

This study is associated with several limitations. This study represents a secondary analysis of data from a primary randomized controlled trial, and the trial was not designed a priori for measuring individual-level correlates of change in SDMT scores. We further acknowledge that this secondary analysis was largely exploratory. This data-driven approach was important to understand what drove the varying SDMT improvements that were observed in the CogEx trial. Relatedly, we did not control for multiple comparisons within our analytic approach, given the exploratory nature of the analyses. This may have increased the risk of Type I error; however, such analyses are important for encouraging hypothesis generation for future research as well as to encourage further validation of potential correlates of cognitive changes in response to rehabilitation in other progressive MS samples. Additionally, although adherence rates were high for all 4 conditions, compliance rates were nearly 100% for the EX-S condition, which may not be realistic. This may have been a product of imprecise measurement of compliance within the EX-S condition, as this outcome was based on the number of exercises performed, rather than rating the degree to which the stretching and balance exercises were performed relative to how they were designed (ie, proper form and full range-of-motion). We do not believe this to be the case for the CR or EX conditions, as compliance with Rehacom is automatically taken into account when completing each individual session and progressing through the computerized program, and performance during each session of the EX condition was carefully and precisely monitored based on work rate from the console of the recumbent stepper. Finally, there is the possibility of mathematical coupling/collinearity that could have confounded potential associations among baseline cognitive performance and changes in SDMT scores, given significant correlations among baseline SDMT, CVLT-II, and BVMT-R scores. However, we note that the magnitude of correlations among baseline SDMT, CVLT-II, and BVMT-R scores were all small, suggesting a relatively low degree of mathematical coupling/collinearity in the present analyses. Nevertheless, future research efforts in this area should account for collinearity as a potential confound of examining potential cognitive correlates of cognitive changes.

Conclusions

Overall, we report on individual-level correlates of SDMT changes from the international CogEx trial of cognitive rehabilitation and exercise training on CPS impairment in those with progressive MS. The primary pattern of results indicated that the lack of baseline learning and memory impairment and higher premorbid IQ (potentially reflecting reserve) was significantly associated with changes on SDMT scores overall or within the cognitive rehabilitation and exercise training conditions. This result suggests that future trials in this area might account for impaired learning and memory as a potential covariate, or more carefully

consider the role of reserve within rehabilitation interventions among those with progressive MS.

Author Contributions

Brian M. Sandroff: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Writing - original draft; and Writing - review & editing. Robert W. Motl: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; and Writing - review & editing. Roberto S. Hernandez: Formal analysis and Writing - review & editing. Maria Pia Amato: Methodology; Project administration; and Writing - review & editing. Giampaolo Brichetto: Methodology; Project administration; and Writing - review & editing. Jeremy Chataway: Methodology; Project administration; and Writing - review & editing. Nancy D. Chiaravalloti: Methodology; Project administration; and Writing - review & editing. Gary R. Cutter: Methodology; Project administration; and Writing - review & editing. Ulrik Dalgas: Methodology; Project administration; and Writing - review & editing. John DeLuca: Methodology; Project administration; and Writing - review & editing. Rachel Farrell: Methodology; Project administration; and Writing - review & editing. Peter Feys: Methodology; Project administration; and Writing - review & editing. Massimo Filippi: Methodology; Project administration; and Writing - review & editing. Jennifer Freeman: Methodology; Project administration; and Writing - review & editing. Matilde Inglese: Methodology; Project administration; and Writing - review & editing. Cecilia Meza: Methodology; Project administration; and Writing - review & editing. Maria A. Rocca: Methodology; Project administration; and Writing - review & editing. Amber Salter: Conceptualization; Formal analysis; Investigation; Methodology; and Writing - review & editing. Anthony Feinstein: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; and Writing - review & editing.

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ORCID iDs

Brian M. Sandroff https://orcid.org/0000-0002-2013-7632
Nancy D. Chiaravalloti https://orcid.org/0000-0003-2943-7567
Ulrik Dalgas https://orcid.org/0000-0003-4132-2789
Peter Feys https://orcid.org/0000-0002-5680-5495
Massimo Filippi https://orcid.org/0000-0002-5485-0479
Maria A. Rocca https://orcid.org/0000-0003-2358-4320
Amber Salter https://orcid.org/0000-0002-1088-110X

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