The Relationship between Processing Speed and Verbal and Non-Verbal New Learning

and Memory in Progressive Multiple Sclerosis

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Abstract

Objective: Processing speed (PS) deficits are the most common cognitive deficits in MS, followed by learning and memory deficits, and are often an early cognitive problem. It has been argued that impaired PS is a primary consequence of MS, which in-turn decreases learning. The current analysis examined the association between between PS and learning in a large cohort of individuals with progressive MS.

Methods: Baseline data from a randomized clinical trial on rehabilitation taking place at 11 centers across North America and Europe were analyzed. Participants included 275 individuals with clinically definite progressive MS (primary, secondary) consented into the trial.

Results: SDMT significantly correlated with CVLT-II ($r=0.21, p=0.0003$) and BVMT-R ($r=0.516, p<0.0001$). ROC analysis of the SDMT z-score to distinguish between impaired and non-impaired CVLT-II performance demonstrated an AUC of 0.61 (95% CI:0.55-0.68) and a threshold of -1.62. ROC analysis between SDMT and BVMT-R resulted in an AUC of 0.77 (95% CI:0.71-.83) and threshold of -1.75 for the SDMT z-score to predict impaired BVMT-R.

Conclusions: Results indicate little ability beyond chance to predict CVLT-II from SDMT (61%), albeit statistically significant. In contrast, there was a 77% chance that the model could distinguish between impaired and non-impaired BVMT-R. Several potential explanations are discussed.

The Relationship between Processing Speed and Verbal and Non-Verbal New Learning and

Memory in Progressive Multiple Sclerosis

Multiple sclerosis (MS) is characterized by widespread lesions or plaques in the brain, causing motor, psychiatric, and cognitive problems.[1] Prevalence estimates of cognitive dysfunction in MS fall as high as 70%, with attention,[2] new learning and memory,[3] processing speed and working memory,[4] and executive functions[5] impacted. Greater prevalence and severity of cognitive impairment have been seen in both secondary progressive MS (SPMS) and primary progressive MS (PPMS).[6,7] Deficits in information processing speed are the most common cognitive deficit seen in MS across subtype, followed by deficits in verbal and non-verbal learning and memory.[8]

Processing speed (PS) can be defined as the amount of time it takes to process a set amount of information, or the amount of information that can be processed within a unit of time.[9] MS research demonstrates a clear cost for slowed PS in everyday life, such as safety concerns (e.g.,driving[10]) and difficulty performing tasks of daily living.[11] PS deficits also result in occupational problems due to real-world demands.[12] Impaired PS additionally has a significant effect on higher-level cognitive processes, including working memory,[3] executive functions,[9] and learning and memory.[13] It has been argued that impaired PS is a primary consequence of MS, which decreases the acquisition of new information and completion of higher level cognitive functions, such as learning and memory.[7,14] At early disease stages, there is some evidence that there is more impairment in PS than in episodic memory,[15] which supports the idea that slowed PS may arise early in the disease process and contribute to the development of episodic memory disturbance. Much of this work has however been done with largely relapsing-remitting MS (RRMS) samples.

Given that progressive MS (PMS) is marked by worsening of MS symptomatology and that increased severity and prevalence of cognitive deficits are observed in the progressive forms of the disease, the investigation of such relationships in PMS is warranted.

The current analysis was conducted to examine the association between PS impairment and learning impairment in a large cohort of individuals with PMS. It was hypothesized that we would observe a significant predictive relationship between PS impairment and impairment in both verbal and non-verbal learning.

Methods

Data for the current analysis were obtained at baseline of a multi-arm, randomized clinical trial, *CogEx*, collected at 11 sites in 6 countries [Canada (1 site), US (2), England (2), Denmark (1), Belgium (1) and Italy (4)]. See Feinstein et al[16] for study protocol.

Participants: Participants included 275 individuals with clinically definite PMS (primary or secondary) who were enrolled in the clinical trial, completed their baseline assessments at the time of data analysis and had a country-specific Symbol Digit Modalities Test (SDMT) z-score less than -1.282 *SD* units. The current sample thus demonstrated a limited range of SDMT scores, falling 1.282 SD or more below the mean, consistent with the inclusion criteria for the clinical trial. That is, 19.3% of those who passed our initial phone screened did not meet our entry criteria due to the requirement of an impaired SDMT. The mean age of the sample was 52.6(SD=7.1), with a mean education of 13.9 years (SD=3.3); mean disease duration was 14.4(9.5) and mean EDSS was 6.0(min: 1.5, max: 6.5). 62% of the sample was female. See Table 1 for demographics.

Procedure: Patients were recruited via specialized in- and outpatient MS clinics, as well as media advertising. Prior to study enrollment, all potential subjects completed a 2-step screening procedure, including a *pre-screening* examination in-person or via telephone to collect basic information and a detailed face-to-face screening for neurological, psychiatric, cognitive, and medical variables. Participants completed the neuropsychological measures described below, as part of the baseline assessment.

Neuropsychological Measures: Assessments consisted of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS),[17] including the SDMT–oral version, California Verbal Learning Test-II (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMT-R). Measures were administered in English in the US, Canada and England, Italian in Italy, and both Dutch and French in Belgium. Reliability and validity has been established for the BICAMS across these languages.[18–22]

The SDMT–oral version[23] involves the conversion of a set of simple geometric designs into an oral response, requiring the examinee to substitute a number for a randomized presentation of a geometric figure. The appropriate number is shown in a key containing the Arabic numbers 1-9, each with a different geometric figure. The sensitivity of the SDMT to the cognitive effects of numerous neurological illnesses and injuries has been demonstrated, particularly PMS.[24]

The CVLT-II consists of a list of 16 words from 4 semantic categories presented orally over 5 trials, including 20-minute delayed recall and recognition trials; delayed trials are not included

in the BICAMS. The CVLT-II has good reliability and validity.[25] Total learning across the 5 learning trials was the dependent variable (CVLT-II TL).

The BVMT-R measures visual-spatial learning and memory. A matrix of six designs is presented for 10 seconds in each of three consecutive trials. Participants are given as much time as necessary to reproduce the designs on the free recall trial before having the stimulus presented for learning again. Total learning across the 3 trials was the dependent variable, (BVMT-R TL). The BVMT-R has been used successfully with persons with MS[17].

The Beck Depression Inventory-II (BDI-II)[26] was administered to examine depression, given the known impact of depression on cognition.[27] The participants responds to 21-items assessing various aspects of depression (mood, motivation, appetite) confirming one of four statements of graded severity expressing how he/she might think or feel about that aspect of depression. The total score is the sum of all endorsed statements; higher scores indicate greater depression.

The Modified Fatigue Impact Scale (MFIS) is a modified form of the Fatigue Impact Scale[28] that assesses the impact of fatigue on one's life. Fatigue is evaluated along multiple dimensions: physical, cognitive, and psychosocial. This scale has demonstrated high internal consistency and it has been shown to be capable of discriminating fatigue in MS from other medical illnesses.

Analyses: The current analyses utilized only the baseline (pre-treatment) evaluation of all participants who were consented into the study (n=275) as of October 1,2021 and completed the SDMT and the CVLT-II or BMVT-R (two participants did not complete the BMVT-R). The total score on each neuropsychological measure was converted to a z-score using country-specific,

regression-based normative data. All country-specific regression equations account for age, sex and education level. The association between neuropsychological measures was evaluated using Pearson correlation coefficients and linear regression. Assumptions were assessed using residual plots and other diagnostics.

Receiver operating characteristic (ROC) curves were used to examine the ability of the SDMT z-score to distinguish impairment on the CVLT-II TL or BMVT-R TL. Impairment on the CVLT-II TL or BMVT-R TL was defined as a z-score less than -1.5. Logistic regression was conducted to determine the threshold of SDMT z-score which maximized the sensitivity and specificity of predicting impairment on these tests using the Youden's index. The area under the curve (AUC) and its 95% confidence interval are reported for each model. Statistical analyses were performed in SAS, version 9.4.

Results

Neuropsychological Performance

With impairment defined as performance at least 1.5 SD below the mean of normative data, over 50% of the sample was impaired within more than one neuropsychological domain (Table 2). The mean SDMT z-score for the sample was -2.1(0.75) with 81.1% of participants classified as impaired using this definition. The mean CVLT-II TL z-score score was -1.05(1.3) with 34.9% impaired and mean BVMT-R TL z-score was -0.74(1.2) with 26.7% impaired. There were no significant differences in neuropsychological test performance between individuals with PPMS and SPMS (Table 1). The correlation between the BVMT-R TL and CVLT TL was statistically significant and moderate (0.41, p<.0001).

The Relationship between PS and Verbal New Learning and Memory

The Pearson correlation coefficient between the SDMT and CVLT-II TL Score was statistically significant, but weak (r=0.21,p=0.0003). Linear regression analysis was also statistically significant, but again showed a weak relationship between the 2 variables, with an R^2=0.046 (p=0.0003;Figure 1). When adjusting for depression (BDI-II), EDSS, fatigue and disease duration in the regression model, the relationship between the CVLT TL and SDMT persisted. The relationship similarly persisted when adjusting for data collection site and disease subtype (PPMS, SPMS).

ROC analysis of the SDMT z-score to distinguish between impaired and non-impaired CVLT-II TL performance demonstrated an AUC of 0.61 (95% CI:0.54-0.68) and a threshold of -1.71 associated with a sensitivity of 78.9% and specificity of 45.1%.

The Relationship between PS and Non-Verbal New Learning and Memory

Pearson correlation coefficient between the SDMT and BVMT-R TL z Score was statistically significant, and moderate (r=0.516,p<0.0001). Linear regression analysis was also significant, showing that a 1-point increase in SDMT z-score was associated with a 0.86 increase in the BVMT-R z-score, with an R^2=0.27 (p<0.0001;Figure 2). Similar to verbal memory, depression, EDSS, fatigue and disease duration had no impact on the results. The relationship similarly persisted when adjusting for data collection site and disease subtype (PPMS, SPMS).

The ROC analysis between SDMT and the BVMT-R TL resulted in an AUC of 0.77 (95% CI:0.71-.83) and threshold of -2.27 for the SDMT z-score to identify impaired BVMT-R TL with a sensitivity of 69.8% and specificity of 72.6%.

Discussion

Results indicated a statistically significant, moderate correlation between PS and visuospatial learning, with a statistically significant, but weak correlation noted between PS and verbal learning in persons with PMS, in the presence of a significant, moderate correlation between the 2 learning tests. The AUC identified in the ROC analysis of the SDMT and CVLT-II TL indicated only a 61% chance that the model will be able to distinguish between impaired and non-impaired CVLT-II TL performance in those with SDMT z-score less than -1.282. This indicates little ability beyond chance to predict verbal learning from SDMT performance. In contrast, the area under the curve for the BVMT-R TL analysis demonstrated a 77% chance that the model will be able to distinguish between impaired and non-impaired BVMT-R TL utilizing the SDMT. This corroborates the pattern of correlations noted, with the SDMT-BVMT-R TL showing a much stronger correlation than the SDMT-CVLT-II TL. There are several potential explanations for this pattern of results.

The measures utilized in the current study constitute the BICAMS[17], a brief cognitive assessment designed to capture the most common cognitive deficits in MS, while also minimizing redundancy. It is thus not surprising that the correlations between measures would be limited. However, we did observe distinct results for verbal versus non-verbal learning. That is, 6 times greater variance was accounted for by SDMT in predicting BVMT-R TL performance as compared with CVLT TL performance. Pattern analysis, commonly done in clinical neuropsychological assessment,[29] highlights the potential role of task characteristics. That is, the SDMT is visuospatial in nature. By extension, it is more similar to the non-verbal learning test utilized in this study, the BVMT-R, than the verbal learning task, the CVLT-II, specifically in regard to the stimuli presented. Both the SDMT and the BVMT-R utilize line drawings of simple shapes, while the CVLT-II presents the participants with words read aloud to be remembered later utilizing no visual

stimuli. The processed stimuli themselves are thus more similar in the BVMT-R analysis then in

the CVLT-II analysis. Indeed, others have drawn similar conclusions regarding similarity in task

characteristics, such as the reliance of the SDMT on incidental visual memory in test

performance.[30]

An additional consideration is the processes that must be successfully completed for

successful task completion. Theoretically, when the same processes are required for two tasks,

they will be more highly correlated than when the processes differ between two tasks.[29] The SDMT

and BVMT-R are similar in that the patient must scan an 8½x11 sheet of paper and visually process

the information. Thus, both tests require efficient visual scanning for successful completion, an

finding observed by others on the   SDMT .[31]   In contrast the stimuli on the CVLT-II are presented

orally and require auditory processing, not visual processing. One might thus expect the SDMT

and BVMT-R to be more highly correlated than the SDMT and CVLT-II. Other differences

between the learning tests that could potentially have contributed to the difference in relationship

with the SDMT include the mode of responding (oral, written) and the difference in the number of

learning trials provided (CVLT-II =5, BVMT-R =3).

Despite the design of the BICAMS to limit redundancy, the minimal relationship between

PS and verbal learning and memory was somewhat surprising. Several previous studies have in

fact shown PS to account for a significant amount of variance in verbal learning and memory[,3,14]

although not all studies have noted such a relationship[32]; these studies have used various measures

to assess these constructs.   For example, Chiaravalloti and colleagues found PS performance on

Letter Comparison and Pattern Comparison to account for 19.5% of variance in the Open Trial

Selective Reminding Test (OT-SRT)–trials to criterion and WMS-IV Logical Memory (34% of

variance[33]), with a similar relationship noted by Litvan et al[14] utilizing the Rey Verbal Learning

Test and the Paced Auditory Serial Addition Test (PASAT). While not presenting consistent findings regarding the relationship between PS and learning and memory, both DeLuca, 1994[3] and Deluca 1998[32] utilized the PASAT and the OT-SRT. That is, these 2 studies utilized the same tasks to assess PS and memory, but different relationships were found with different samples. Importantly, no previous studies to our knowledge have examined the relationship between PS and *visual versus verbal learning and memory* using only the BICAMS tests (CVLT,BVMT-R,SDMT); thus, the current work represents an important contribution to the literature and more work examining the relationships between these tests is warranted given their wide usage. It is similarly important to note that the current study included only PMS participants; no previous work has examined this question in a strictly PMS sample. Importantly however, the current study was cross-sectional in nature. Thus, a remaining question that cannot be addressed is that the minimal correlation between verbal new learning and processing speed in this progressive MS sample may be a result of more extensive neurodegeneration, potentially also in the hippocampus, that may be expected with PMS. That is, it is possible that verbal memory and processing speed become less related as the disease progresses due to differential neurodegeneration, potentially underlying the variable relationships observed between the constructs in the literature. This important question is best answered empirically through future longitudinal studies.

The clinical implications of the current analyses are important to mention. It is widely recognized that PS deficits are the most common cognitive limitation documented in persons with MS. As such, the SDMT is widely known and administered by clinicians of multiple specialties and is not restricted in use to neuropsychologists alone. The AUC provides a measure of the accuracy of a threshold for a test such as the SDMT; AUCs greater than 0.7 are considered to have utility[34] and this is thus a finding that has clinical significance. The obtained AUC >0.7 thus

indicates that use of the SDMT score, may indicate potential impairment in visuospatial learning as documented on the BVMT-R. This is potentially helpful to clinicians as the SDMT is often used as a screening instrument, and thus may prompt a referral for a full neuropsychological battery to identify potential impact of cognitive deficits on multiple aspects of daily life, beyond processing speed alone.

It is interesting to note that only 40% of the participant sample was impaired on the SDMT alone, with 41% of the sample being impaired on the SDMT and one or both of the memory measures as well. The co-occurrence of cognitive deficits is important to note as such patterns have clinical implications. For example, Chiaravalloti & DeLuca (2015)[24] noted that individuals with MS that were impaired on memory **and** PS showed less benefit from a memory rehabilitation treatment than individuals that were impaired on memory alone. It is not yet known if the opposite is true. However, it is clear that the co-occurrence of cognitive deficits in multiple domains has the potential to result in decreased therapeutic efficacy, a question that can be empirically examined in the forthcoming RCT analyses from *CogEx*.

No study is without its limitations. An important limitation in the current analyses is the selection of participants. That is, the parent study was specifically designed to examine efficacy of treatment for PS deficits. All enrolled individuals thus demonstrated PS impairment as defined by a score on the SDMT falling at least 1.282 standard deviations below the mean. This results in one variable in each analysis, the SDMT, having a restricted range. It is known that a restricted range of one of the variables in a correlation results in a reduced correlation coefficient.[35] In addition, this patient selection factor does limit generalization of findings to individuals with PMS who have impaired processing speed. A second limitation that must be recognized is that the neuropsychological testing was limited to learning; retention was not tested and therefore no

inferences can be made regarding retention of learned information for either recall or recognition. However, it is fairly well accepted that MS patients show greater impairments in learning and memory than recall and recognition[3,32]. Similarly, executive functioning, another higher order cognitive function shown to be impacted by PS deficits and often impaired in persons with MS, was not assessed. Future research should examine this relationship with tests of executive functioning. Finally, the lack of data from healthy controls and patients with RRMS preclude direct the comparison of the relationship of PS to learning with these important comparison other samples. Future research including these different samples would be useful.

Despite the noted limitations, it is important to note the unique study sample composed of 275 individuals with progressive MS and use of only the BICAMS tests. Results of the current study indicate an association between SDMT performance and the BVMT-R TL, which may be helpful to clinicians in identifying individuals potentially at risk for non-verbal learning and memory deficits given their SDMT performance.

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Table and Figure Legends

<u>Table 1.</u> Demographic and Clinical Summary

<u>Table 2.</u> BICAMS Impairment Distribution (Impairment defined as 1.5 SD below the mean of country specific normative data)

<u>Figure 1</u>. Scatter Plot depicting correlation between the SDMT and CVLT-II Total z Score (r=0.21, p=0.0003). Linear regression analysis was also statistically significant (R^2=0.046)

<u>Figure 2</u>.   Scatter Plot depicting correlation between the SDMT and BVMT-R Total z Score (r=0.516, p<0.0001). Linear regression analysis was significant (R^2=0.27)

Table 1. Demographic Variables, Disease Characteristics and Neuropsychological Testing Overall and by Progressive MS Course

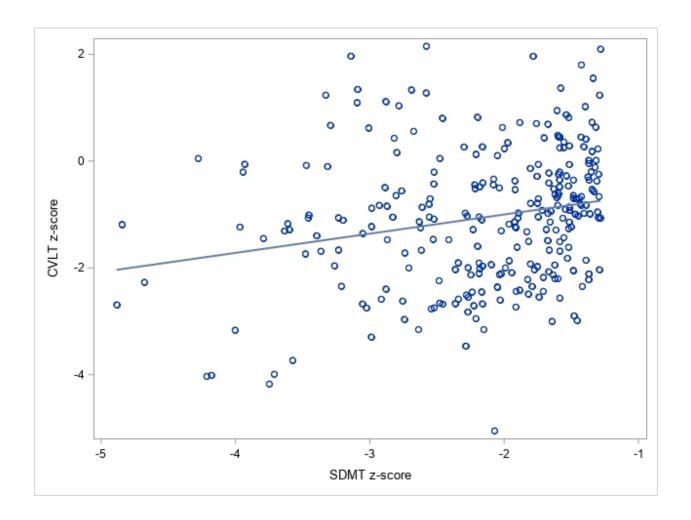|	Total (N=275)	Primary progressive (N=78)	Secondary progressive (N=197)	p-value
Age [years]	52.6(7.1)	52.1(7.4)	52.8(6.9)	0.46[a]
Sex:				*0.011[b]*
Male	105(38.2)	39(50.0)	66(33.5)	
Female	170(61.8)	39(50.0)	131(66.5)	
Marital status:				0.39[b]
Single	53(19.3)	17(21.8)	36(18.3)	
Married	166(60.4)	46(59.0)	120(60.9)	
Divorced	27(9.8)	5(6.4)	22(11.2)	
Widowed	8(2.9)	1(1.3)	7(3.6)	
Common-law	6(2.2)	2(2.6)	4(2.0)	
In a relationship	15(5.5)	7(9.0)	8(4.1)	
Total years of schooling	13.9(3.3)	14.4(3.1)	13.7(3.4)	0.11[a]
Highest level of education completed:				0.49[b]
Primary	22(8.0)	7(9.0)	15(7.6)	
Secondary (high school)	132(48.0)	33(42.3)	99(50.3)	
College/University	121(44.0)	38(48.7)	83(42.1)	
Are you currently working?*				0.95[b]
No	178(65.2)	50(64.9)	128(65.3)	
Yes	95(34.8)	27(35.1)	68(34.7)	
Disease Duration*	14.4(9.5)	7.3(6.8)	17.3(8.9)	*<0.001[a]*
EDSS score*	6.0(1.5,6.5)	6.0(2.5,6.5)	6.0(1.5,6.5)	
Assistive Device				0.75[b]
Bilateral	101(36.7)	26(33.3)	75(38.1)	
None	99(36.0)	29(37.2)	70(35.5)	
Unilateral	75(27.3)	23(29.5)	52(26.4)	
SDMT z-score	-2.1(0.75)	-2.1(0.71)	-2.1(0.77)	0.82[a]
CVLT TL z-score	-1.05(1.3)	-0.88(1.3)	-1.1(1.3)	0.15[a]
BVMT-R TL z-score*	-0.74(1.2)	-0.77(1.2)	-0.72(1.3)	0.79[a]

*Data not available for all subjects. Missing values: Are you currently working?=2, Disease Duration=1, EDSS score=3, BVMT-R z-score=2.
Values presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).
p-values: a=ANOVA, b= Pearson's chi-square test.

Table 2. BICAMS Impairment Distribution (Impairment defined as 1.5 SD below the mean of country specific normative data)

Number of Tests Impaired	Frequency	Percent
None	38	13.92
One		
SDMT only	109	39.9
CVLT-II only	9	3.3
BVMT-R only	3	1.1
Two		
SDMT + CVLT-II	44	16.1
SDMT + BVMT-R	28	10.3
CVLT-II + BVMT-R	1	0.4
All Three	41	15.02

*2 participants are not included as they were missing at least one test

Figure 1. Scatter Plot depicting correlation between the SDMT and CVLT-II Total z Score (r=0.21, p=0.0003). Linear regression analysis was also statistically significant (R^2=0.046)

Figure 2. Scatter Plot depicting correlation between the SDMT and BVMT-R Total z Score (r=0.516, p<0.0001). Linear regression analysis was significant (R^2=0.27)