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ORIGINAL COMMUNICATION

Sub-threshold cognitive impairment in multiple sclerosis: the association with cognitive reserve

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Abstract Multiple sclerosis (MS) patients with high premorbid intellect have the advantage of cognitive reserve that may mitigate the effects of cognitive decline. A fall-off in cognition may nevertheless still occur, even should it fail to meet global impairment thresholds. The present cross-sectional study explores the neurologic and behavioral characteristics of this little known group of patients. A consecutive sample of 144 MS patients underwent neuropsychological testing with the minimal assessment of cognitive function in the MS (MACFIMS) battery. Premorbid IQ was assessed with the ANART reading test. A validated algorithm based on ANART errors and verbal fluency scores was used to predict whether current cognitive function matched premorbid estimates. Three MS groups were thus defined: cognitively intact ($n = 53$), impaired ($n = 46$) and cognitively intact on the MACFIMS, but falling short of premorbid predictions ($n = 45$). Patients who were cognitively intact on the MACFIMS but fell short of verbal fluency predictions had higher premorbid IQ ($p = 0.007$) and lower EDSS ($p = 0.002$) than cognitively impaired, but not intact patients. They outperformed impaired patients on every MACFIMS variable, but were more impaired than intact patients on the Paced Auditory Serial Addition Test-3 (PASAT-3) ($p = 0.009$). They were more likely to be employed (48.9 %) than the impaired (26.1 %) group ($p = 0.025$). We defined a group of MS patients deemed cognitively intact on conventional neuropsychological testing, but who, nevertheless, had deficits relative to premorbid intellectual abilities. The high premorbid IQ in this group does not prevent, but 'softens' the impact of cognitive decline. These findings provide novel evidence supporting cognitive reserve as a protective factor in relation to cognitive dysfunction in MS.

Keywords Cognitive reserve · Neuropsychological tests · Multiple sclerosis · Cognition

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Introduction

Cognitive dysfunction affects 40–60 % of patients with multiple sclerosis [1] and exerts a deleterious effect on employment, relationships, recreation pursuits and general activities of daily living [2]. Given these wide spread negative consequences, research is currently focusing on factors that may mitigate against decline. Cognitive reserve has emerged as one such putative protective influence [3] with high premorbid intelligence, in particular, considered a key variable [4]. Superior premorbid intellect, however, is not immune from the effects of brain atrophy, demyelination and destructive plaques. In theory, cognitive decline may still occur, but given that baseline abilities are above average to begin with, fall off in performance across one of more psychometric tests may still translate into results that fall within the normal range. Patients whose results conform to this pattern would, therefore, still be deemed cognitively intact.

The current study focuses on those multiple sclerosis (MS) patients, usually of superior or above average

intellect, whose cognitive function has declined from premorbid levels, but not to a degree that meets the threshold for designated impairment. The latter marker is somewhat arbitrary, but has typically been set at 1.5 standard deviations (SDs) below age, education and gender matched data obtained from healthy control subjects [5]. Little is known of this MS group. Their descriptive characteristics in terms of neurological variables, psychopathology and employment have yet to be defined. Notwithstanding the potential benefits of increased cognitive reserve, the effects of more subtle cognitive decline are, therefore, not known. It is here that we address our inquiry.

Methods

A consecutive sample of 144 patients between the ages of 18 and 60 were enrolled from two hospital based outpatient MS clinics. All subjects met modified McDonald criteria [6] for a diagnosis of MS. Demographics and disease variables (e.g., education, employment, type and course of MS, physical disability according to the EDSS [7]) were collected.

Exclusion criteria included the presence of developmental delay, concurrent neurological disease, serious illness (e.g., cancer), enrolment in another study, major psychiatric disorder (e.g., psychosis, dementia), substance abuse, a history of a traumatic brain injury, and visual acuity below 20/100 in both eyes.

Cognitive testing was completed at Sunnybrook Health Sciences Centre.

Cognitive assessment

The MS subjects were administered the minimal assessment of cognitive function in MS (MACFIMS), [8] a battery of cognitive tests that has been developed for patients with MS. Each MACFIMS test has published normative data (according to age, gender and education, where applicable) that were used for scoring. This battery includes seven tests and encompasses the following five cognitive domains:

1. Information processing speed is measured by the Paced Auditory Serial Addition Test (three and two second trials) (PASAT) [2, 9] and the Symbol Digit Modalities Test (SDMT) [2, 10].
2. Verbal and visual memory is determined using the California Verbal Learning Test-II (CVLT-II) [11] and the Brief Visuospatial Memory Test-Revised (BVMT-R) [12, 13].
3. Executive function is assessed with the D-KEFS Sorting Test [14].
4. Spatial processing is measured using the Judgement of Line Orientation (JLO) [15].
5. Verbal fluency is quantified using the Controlled Oral Word Association Test (COWAT) [16].

Failure on each test was defined as a score 1.5 SDs below the mean of normative scores. Global impairment on the MACFIMS was defined, by convention, as impairment on two or more cognitive measures [17]. The COWAT scores were not included in determining global impairment given that this test was used to define a group of subjects whose cognition was deemed to have declined from premorbid levels. Global cognitive impairment was defined by failure on two of the remaining six MACFIMS indices (i.e., PASAT-3 s, SDMT, CVLT-II Total Recall, BVMT-R Total Recall, D-KEFS Sorting Score, JLO). In addition, all subjects completed the American National Adult Reading Test (ANART) [18], which was used to assess premorbid IQ. This test is a valid measure of premorbid IQ, even in patients with cognitive disorders [19].

A separate index was created to denote decline from premorbid intellect that did not meet the threshold for MACFIMS designated impairment. This was based on a projection of verbal fluency scores (i.e., the COWAT) according to ANART derived errors. Crawford et al. [20] have derived an algorithm that accurately predicts this association in healthy controls and have also demonstrated how this relationship is affected by the presence of neurological diseases, including multiple sclerosis. The authors provide a table linking each ANART error score to a summed total of words generated over the 3 min verbal fluency test period. For the purpose of the present study, patients whose verbal fluency scores fell 1.5 SDs below their projected scores were deemed to have declined from their premorbid level of functioning on this cognitive index.

Of the 144 patients, 46 (31.9 %) were rated cognitively impaired on the MACFIMS. Focusing on the 98 intact patients, 45 (31.3 %) failed to meet their threshold on the projected COWAT score, leaving 53 cognitively intact subjects, five of whom (3.5 %) performed 1.5 SDs above estimated premorbid levels. The remaining 47 subjects (33.3 %) had COWAT scores consistent with premorbid abilities. Behavioral comparisons were then undertaken between these three groups, designated, respectively, as cognitively impaired; cognitively intact; and intact on the MACFIMS, but functioning below premorbid expectations.

Statistical analysis

The distribution of all continuous data was checked using the Kolmogorov–Smirnov test. Thereafter, between-group comparisons were undertaken with Oneway ANOVA, or Kruskal–Wallis Oneway ANOVA, according to Gaussian distribution. Ordinal comparisons were completed with Chi

square analyses while correlations (Pearson or Spearman rank) were based on data distribution. Predictors of global cognitive dysfunction on the MACFIMS were sought with a logistic regression analysis. Statistical significance was set at $p < 0.05$.

Standard protocol approvals, registrations, and patient consents

The study received approval from the Ethics committees of both Sunnybrook Health Sciences Centre and St. Michael's Hospital and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was also obtained from all subjects. No participants were cognitively impaired to the extent that they could not give consent.

Results

Group descriptive data

The descriptive data for the entire sample revealed 88 (61.1 %) were female while the mean age was 46.8 (SD = 10.32) years. The mean duration of illness was 11.45 (SD = 8.62) years and disease course comprised 79 (54.9 %) subjects with relapsing-remitting MS and 45 (31.3 %) and 20 (13.9 %) with secondary and primary progressive disease, respectively.

The mean ANART score for the entire sample was 112.2 (SD = 8.4). The mean COWAT score was 34.8 (SD = 11.4) and the mean predicted COWAT score 43.9 (SD = 6.9). The difference between the actual and predicted COWAT scores was significant ($t = -10.73$; $p = 0.0001$).

Demographic comparison

The demographic and neurologic comparisons between the three groups are shown in Table 1. The most notable findings were that cognitively impaired patients had higher EDSS scores than patients who were cognitively intact ($p = 0.001$) or who fell short of premorbid estimates ($p = 0.002$). The MS patients who failed to meet premorbid cognitive expectations were more likely to have a PPMS disease course than patients who were cognitively intact ($p = 0.008$).

A comparison of employment data revealed that 48.9 % of the group performing below premorbid expectations was still working as opposed to 40.4 % of the cognitively intact group and 26.1 % of the impaired group. A three-way Chi square analysis did not reveal a significant difference. However, when between group differences were explored, cognitively impaired patients were shown to be less frequently employed than those who had not reached predicted premorbid ability ($p = 0.025$).

Cognitive comparisons

Cognitive comparisons across 11 indices derived from the MACFIMS and the additional ANART variable appear in Table 2. Of note is that the cognitively intact patients and those who had not reached premorbid potential did not differ from one another in terms of premorbid verbal IQ based on the ANART, but the latter group had significantly higher scores than those obtained from the cognitively impaired patients ($p = 0.007$). As expected cognitively intact patients performed significantly better than impaired patients on every test. Similarly, subjects who had not reached premorbid potential also performed significantly better than the impaired patients on all tests, apart from the obvious exception of the COWAT. However, this group had more deficits than the cognitively intact group on the 3 s PASAT ($p = 0.009$).

There were no between group differences on indices of depression or anxiety according to HADS scores (see Table 2).

Predictors of cognitive impairment

A logistic regression analysis was undertaken with cognitive impairment as the dependent variable. Those neurological variables that differed amongst the three groups, i.e., EDSS and disease course were entered as potential predictors together with ANART, age, disease duration, and depression and anxiety scores. The sample size of 144 had robust statistical power in relation to nine predictor variables. The results appear in Table 3 and show that two variables were found to be highly significant independent predictors of impairment, i.e., ANART scores as a marker of premorbid verbal IQ ($p = 0.001$) and EDSS ($p < 0.001$).

Discussion

The gist of the present paper demonstrates the importance once more of cognitive reserve as a protective, mediating factor in the development of cognitive dysfunction in MS patients. It also extends our understanding of how effective this mediation can be by looking at a hitherto unexplored aspect of MS patients' cognition, i.e., that subgroup of individuals who are deemed cognitively intact on a well-validated, conventional battery of neuropsychological tests and yet whose intellectual performance falls short of predicted premorbid abilities.

Table 1 Demographic and neurologic comparisons between cognitively impaired, cognitively intact, and cognitively below predicted MS patients

	Cognitively impaired ($n = 46$)	Cognitively intact ($n = 53$)	Cognitively below predicted ($n = 45$)	ANOVA/x^2 square analyses	Sig.	Impaired vs. intact	Impaired vs. below predicted	Intact vs. below predicted
Age	47.0 (10.0)	48.0 (8.6)	45.1 (12.3)	$F = 0.995$	$p = 0.372$	$p = 0.871$	$p = 0.658$	$p = 0.343$
Gender (female)	29 (63.0 %)	33 (62.3 %)	26 (57.8 %)	$x^2 = 0.312$	$p = 0.855$	$p = 0.936$	$p = 0.608$	$p = 0.651$
Duration of MS	11.7 (8.9)	12.6 (8.7)	9.9 (8.2)	$F = 1.189$	$p = 0.308$	$p = 0.867$	$p = 0.591$	$p = 0.282$
EDSS	5.1 (2.3)	3.2 (2.5)	3.3 (2.4)	$F = 9.124$	$p < 0.001$	$p < 0.001$	$p = 0.002$	$p = 0.978$
Disease course				$x^2 = 10.58$	$p = 0.032$	*	**	***
RRMS	20 (43.5 %)	34 (64.2 %)	25 (55.6 %)					
SPMS	18 (39.1 %)	17 (32.1 %)	10 (22.2 %)					
PPMS	8 (17.4 %)	2 (3.8 %)	10 (22.2 %)					
Working (no)	34 (73.9 %)	31 (59.6 %)	23 (51.1 %)	$x^2 = 5.13$	$p = 0.077$	$p = 0.135$	$p = 0.025$	$p = 0.400$
Education	14.6 (2.5)	14.2 (2.4)	14.8 (2.5)	$F = 0.811$	$p = 0.446$	0.693	0.909	0.429

* Group A vs. B: RR vs. PP; $p = 0.012$

** NS

*** Group B vs. C: RR vs. PP; $p = 0.010$. SP vs. PP; $p = 0.008$

Table 2 Cognitive comparisons between cognitively impaired, cognitively intact and cognitively below predicted MS patients

Tests	Cognitively impaired ($n = 46$)	Cognitively intact ($n = 53$)	Cognitively below predicted ($n = 45$)	F/x^2	p	Impaired vs. intact	Impaired vs. below predicted	Intact vs. below predicted
ANART	109.20	112.92	114.49	$F = 5.05$	0.008	0.067	0.007	0.612
COWAT	28.85	43.38	29.84	$x^2 = 57.90$	<0.001	<0.001	0.236	<0.001
BVMT-TR	16.67	26.11	24.64	$F = 33.36$	<0.001	<0.001	<0.001	0.454
PASAT-3	28.64	49.11	43.29	$F = 56.22$	<0.001	<0.001	<0.001	0.009
JLO	22.72	27.42	26.78	$x^2 = 30.19$	<0.001	<0.001	<0.001	0.148
SDMT	34.04	53.36	48.91	$F = 50.85$	<0.001	<0.001	<0.001	0.069
CVLT-TR	40.74	53.25	51.62	$x^2 = 27.48$	<0.001	<0.001	<0.001	0.308
DKEFS SORT	7.85	10.42	10.18	$F = 14.94$	<0.001	<0.001	<0.001	0.888
HAD-depression	7.65	6.58	6.73	$F = 0.908$	0.406	0.417	0.548	0.983
HAD-anxiety	8.48	6.94	7.53	$F = 1.329$	0.268	0.239	0.603	0.809

Before discussing the results of our study in further detail, a brief general comment on the overall composition and behavioral characteristics of our sample is in order. The breakdown in gender distribution and disease course is typical for a representative sample of MS clinic patients [21]. In addition, the 31.9 % prevalence of cognitive dysfunction based on the complete MACFIMS battery overlaps with previous findings [22]. What is new, however, is the finding that 31.3 % of the entire sample, or 45.9 % of the cognitively intact individuals, were not performing at their premorbid level. In arriving at this figure we relied on a reading test to obtain a marker of cognitive functioning that predated the onset of MS. This method has also been used by previous researchers exploring cognitive reserve [3]. A limitation of the study, however, is that we took into consideration only one component of what may constitute cognitive reserve, other factors being intellectual enrichment as captured by an index of vocabulary [23] and premorbid leisure activities [24].

With the focus on those patients whose cognition falls short of predicted estimates, some interesting new findings become apparent. Notwithstanding the fact that this group was defined by deficiencies in their verbal fluency according to the COWAT, additional cognitive abnormalities emerged when their performance was compared to that of patients deemed intact across both measures. Increased difficulty with information processing speed, considered the hallmark cognitive abnormality in MS [8] was elicited. Despite these relative deficits, this group of patients still outperformed the cognitively impaired group on every other measure of the MACFIMS. The biggest factors to account for this were not disease course, a

Table 3 Predictors of cognitive impairment: results of logistic regression

	B	SE	Wald	*p*	Exp (*B*)
ANART	−0.092	0.029	10.284	0.001	0.912
Disease course	−0.046	0.253	0.033	0.855	0.955
Age	−0.005	0.025	0.037	0.847	0.995
Gender	−0.421	0.456	0.849	0.357	0.657
Education	0.172	0.099	3.036	0.081	1.188
Years since diagnosis	−0.040	0.030	1.737	0.188	0.961
HAD depression	−0.052	0.065	0.641	0.423	0.949
HAD anxiety	0.102	0.059	2.942	0.086	1.107
EDSS score	0.475	0.123	14.873	<0.001	1.608

variable on which the three patient groups differed, but rather EDSS and, in particular, the ANART. The robustness of premorbid intelligence in this regard highlights the utility of this variable in future research exploring predictors of cognitive dysfunction. This is further underscored by the fact that there were no ANART differences between the intact and premorbid deficient groups, with the latter having significantly higher scores than the 31.9 % of subjects considered cognitively impaired. What, therefore, sets this finding apart from earlier cognitive reserve studies is that our data highlight the relatively protective influence of high premorbid intellect not only in patients considered intact, as previously reported [3, 25], but also now in those subjects with more subtle evidence of cognitive dysfunction. Adding to the ecological validity of this result is the observation that these patients, even with their processing speed and memory challenges, are more likely to be employed than cognitively impaired patients.

The protective nature of high cognitive reserve has been reported in many neurological disorders including traumatic brain injury [26, 27], stroke [28], Alzheimer's disease [29], HIV [30] and age linked cerebral white matter changes [31]. Within the MS literature, it has emerged as an important moderator of other factors known to impair cognition, such as brain atrophy [32], and inefficient cerebral activation [33]. Of particular interest is the finding that MS patients with higher intellectual enrichment required less cerebral resources, i.e., less cerebral activation to perform a test of working memory. They were also better able to maintain resting state activity during cognitive processing. Our findings, therefore, complement what has already been shown by others, namely that the deleterious effect of multiple sclerosis on cognition is not eliminated, but can to varying degrees be attenuated by higher premorbid intelligence.

While the evidence supporting the protective nature of cognitive reserve is compelling, and our data add to this literature, our findings also reveal that this composite entity does not confer immunity to decline. Indeed, 45.9 % of our cognitively intact subjects based on MACFIMS criteria, still had objective evidence, albeit more subtle, of some cognitive slippage when assessed with a different criterion. Cognitive reserve may, therefore, best be seen as a buffer that either prevents or slows decline and by extension prolongs the ability of patients to retain employment and remain more socially active [24].

Our study was not without a potentially important limitation. Failure to attain predicted cognitive abilities was based on the performance of a single psychometric test, namely verbal fluency as captured by the COWAT. While this index is part of the consensus established MACFIMS battery, verbal fluency is not the most sensitive aspect of cognition affected by MS [8]. We are, therefore, likely to have underestimated the number of subjects who, while classified intact on the MACFIMS, were also showing other subtle signs of impaired cognitive performance. An algorithm like the one we applied to the ANART-COWAT prediction has not, however, been defined for other MACFIMS tests. With our choice limited by this constraint, the validity of our approach was subsequently bolstered by the finding that the group so defined had more extensive deficits on the PASAT. Another limitation of the study was that cognitive reserve was based solely on premorbid IQ (i.e., ANART) and other variables such as work, social activities, and premorbid leisure activities were not taken into account. Additionally, MRI data were not collected so the relationship between brain indices and cognitive reserve could not be assessed. Furthermore, because the study was cross sectional by design, we were not able to measure this relationship with respect to time.

In summary, our study brings a new insight into how one aspect of cognitive reserve, namely premorbid verbal intelligence, can partly offset the deleterious effects of multiple sclerosis on cognition. The findings speak to a continuum in cognitive functioning, with cognitive reserve mediating many shades of grey that can be found occupying that intermediate zone between psychometric scores considered intact and impaired.

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Conflicts of interest Dr. Feinstein has served on scientific advisory boards for Merck Serono and Avanir Pharmaceuticals; has received speaker honoraria from Merck Serono, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Biogen Idec; serves on the editorial boards of *Multiple Sclerosis* and the *African Journal of Psychiatry*; receives publishing royalties for *The Clinical Neuropsychiatry of Multiple Sclerosis* (Cambridge University Press, 2007); chairs the Medical Advisory Committee for the Multiple Sclerosis

Society of Canada; conducts neuropsychiatric evaluation, cognitive testing, brain imaging in neuropsychiatry in his clinical practice; and receives research support from the Canadian Institute of Health Research, the Multiple Sclerosis Society of Canada and Teva Pharmaceutical Industries Ltd.

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Dr. O'Connor serves on scientific advisory boards for Novartis, Sanofi-Aventis, Bayer Schering Pharma, Genentech, Inc., and Roche; has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Novartis, and Sanofi-Aventis; has served as a consultant for Biogen Idec, Actelion Pharmaceuticals Ltd., Bayer Schering Pharma, EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., Genentech Inc., and Warburg Pincus; has received research support from Abbott, Bayer Schering Pharma, Novartis, BioMS Medical, Sanofi-Aventis, CIS Pharma, Genmab A/S, Cognosci, Inc., Wyeth, Daiichi Sankyo, and Roche; and serves as the National Scientific and Clinical Advisor to the MS Society of Canada.

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