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Perceived cognitive dysfunction and observed neuropsychological performance: Longitudinal relation in persons with multiple sclerosis

CHRISTOPHER CHRISTODOULOU, PATRICIA MELVILLE, WILLIAM F. SCHERL, TINA MORGAN, WILLIAM S. MACALLISTER, DAWN M. CANFORA, STEPHEN A. BERRY, AND LAUREN B. KRUPP

Department of Neurology, State University of New York at Stony Brook, Stony Brook, New York

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Abstract

The relation between self-reported cognitive dysfunction and neuropsychological performance over 24 weeks was assessed in a sample of 53 multiple sclerosis patients. Subjects were assessed at Weeks Zero and 24 as part of a clinical trial to enhance cognition. At baseline, subjects had at least mild cognitive impairment on the Rey Auditory Verbal Learning Test and an absence of depression. Neuropsychological performance was assessed with a modification of the well standardized Brief Repeatable Battery. The 5-item Perceived Deficits Questionnaire and a 2-item memory and attention/concentration questionnaire assessed self-perceived cognitive impairment. Self-assessed cognition did not correlate with neuropsychological performance at either baseline or 24 weeks. However, changes in the self-assessment measures did correlate with changes in neuropsychological performance. Patients accurately perceived some changes in their level of cognitive dysfunction, though they were insensitive to the degree of their current dysfunction. Possible explanations of this pattern of results are discussed. (*JINS*, 2005, *11*, 614–619.)

Keywords: Multiple sclerosis, Cognition, Neuropsychological tests, Memory deficit, Self assessment (psychology), Meta-cognition, Longitudinal study

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disease affecting the central nervous system. MS typically affects young adults with a mean onset prior to 30 years of age (Kurtzke et al., 1992). It is one of the most frequent causes of disability in early to middle adulthood, affecting approximately 100–130 per 100,000 people in the United States (Kurtzke & Wallin, 2000). Cognitive dysfunction affects approximately half of individuals with MS and is a leading cause of disability in the disorder (Peyser et al., 1980; Rao et al., 1991a). Cognitively impaired persons are less likely to be employed and engage in fewer social activities than those without impairment, despite similar levels of physical disability (Rao et al., 1991b). Because persons with MS generally live with the disorder for decades, it is important to monitor their symptoms over time, including cognitive dysfunction. Deficits in learning and recalling new information are the most common area of dysfunction (Deluca et al., 1998; Rao et al., 1991a; Thornton et al., 2002; Thornton & Raz, 1997). Also frequent are impairments in attention and information processing speed/efficiency, and verbal fluency (Rao et al., 1991a; Wishart & Sharpe, 1997; Zakzanis, 2000). General intelligence and remote memory are less often affected (Rao et al., 1991a; Wishart & Sharpe, 1997; Zakzanis, 2000).

The cognitive deficits of MS patients can be subtle and easily overlooked in busy clinic settings. Constraints of time and resources often limit the opportunity for careful neuropsychological evaluation of MS patients. Patients' cognitive complaints are sometimes viewed skeptically by clinicians. There is at least some empirical justification for clinician skepticism. While most MS studies have found that self-reported cognitive complaints relate to objective

Reprint requests to: Christopher Christodoulou, Ph.D., Department of Neurology, State University of New York at Stony Brook, HSC T12-020, Stony Brook, NY 11794-8121. E-mail: christopher.christodoulou@stonybrook.edu

testing (Beatty & Monson, 1991; Benedict et al., 2004; Chiaravalloti & Deluca, 2003; Hoogervorst et al., 2001; Kujala et al., 1996; Maor et al., 2001; Matotek et al., 2001; Randolph et al., 2001, 2004; Taylor, 1990), others have not (Benedict et al., 2003; Gold et al., 2001, 2003). Even among studies with significant findings, the largest reported correlations are often modest ($r < .29$; Hoogervorst et al., 2001; Maor et al., 2001; Taylor, 1990). Some report a maximum correlation coefficient in the range of $r = .30$ to .39 (Matotek et al., 2001; Randolph et al., 2001; Randolph et al., 2004), but few above $r = .40$ (Benedict et al., 2004; Chiaravalloti & Deluca, 2003).

Many studies have found that self-reported cognitive impairment correlates with depressive symptoms (Benedict et al., 2003, 2004; Bruce & Arnett, 2004; Gold et al., 2003; Maor et al., 2001; Randolph et al., 2004; Schwartz et al., 1996). In fact, cognitive complaints often correlate more highly with depressive symptoms than with cognitive performance (Benedict et al., 2003, 2004; Bruce & Arnett, 2004; Gold et al., 2003; Maor et al., 2001; Randolph et al., 2004), though not in one study without clinically depressed subjects (Matotek et al., 2001). Some investigations suggest that relations between subjective and objective cognitive measures are complex and possibly nonlinear (Marrie et al., 2005; Randolph et al., 2001, 2004; Schwartz et al., 1996). For various reasons, some persons with MS underestimate their abilities while others overestimate them (Beatty & Monson, 1991; Benedict et al., 2003, 2004; Bruce & Arnett, 2004; Gold et al., 2003; Maor et al., 2001; Marrie et al., 2005; Randolph et al., 2004; Schwartz et al., 1996). However, if people are relatively consistent in the standards they use to judge their cognitive functioning, it may be possible to obtain relatively accurate assessments of cognitive change.

We are unaware of longitudinal MS studies that have examined how changes in self-report may relate to changes in neuropsychological performance. This issue is important in a chronic and often progressive disorder such as MS, where the evaluation of cognitive change is of particular concern. It is also important in testing interventions to improve cognition in MS. The current study explored this issue of change.

METHODS

Research Participants

The university's institutional review board approved this study. All subjects provided written informed consent. Subjects with a definite MS diagnosis (Poser et al., 1983) were largely recruited from a university-based MS clinic. They were drawn from a clinical trial to enhance cognition with donepezil (Krupp et al., 2004). Results are presented for 53 subjects with data on measures of interest at baseline and 24 weeks. Data from the active medication ($n = 31$) and placebo ($n = 22$) groups were combined for the principal analyses since separate analyses of the groups led to similar results. However, individual group data are also presented.

Eligibility Criteria and Sample Characteristics

Subjects had to exhibit stable neurological functioning for at least 30 days before baseline and agree to try to continue current medications during the study. They also had to display at least mild verbal memory impairment, defined as scoring at least 0.5 standard deviations below norms on the Rey Auditory Verbal Learning Test, though mean impairment for the sample was greater, at 1.5 ± 0.8 standard deviations below norms (Spreen & Strauss, 1998). Subjects could not display severe cognitive impairment on the Mini Mental Status Examination (MMSE ≥ 26; $M = 28.6$, $SD = 1.3$; Folstein et al., 1975). Subjects could not display more than mild depressive symptoms on the Montgomery-Asberg Depression Scale (MADRS; Montgomery & Asberg, 1979). They were required to score less than 15 on the MADRS, which is roughly equivalent to the same score on the Beck Depression Inventory. Few screened subjects (16/260) were excluded on the basis of high MADRS scores (Kearns et al., 1982). Concurrent antidepressants, antispasticity agents, and disease-modifying therapies (interferon beta or glatiramer acetate) were permitted, as long as dose was constant for one month prior to baseline. Persons on benzodiazepines were excluded, as these medications may affect cognition. Other exclusion criteria included current alcohol or substance abuse, history of head injury, or other medical condition known to affect cognition. Subjects were 20 to 55 years of age ($M = 44.2$, $SD = 7.7$), with 10 to 20 years of education ($M = 14.8$, $SD = 2.2$). Most were women (67.9%). MS subtypes were relapsing remitting (58.5%), secondary progressive (37.7%) and primary progressive (3.8%). All were ambulatory, with Expanded Disability Status Scale (Kurtzke, 1983) scores below 7.0 ($M = 3.5$, $SD = 1.8$).

Neuropsychological Tests

A modified version of the Brief Repeatable Battery (BRB; Rao & Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) formed the core of the testing protocol (Christodoulou et al., 2003). The BRB tasks are quite sensitive to cognitive impairment (Rao et al., 1991a) and longitudinal changes in cognition in MS (Hohol et al., 1997). The study measures were (1) Selective Reminding Test (SRT, 6 Trial Version) total recall; (2) 10/36 Spatial Recall Test (10/36) total recall; (3) Symbol-Digit Modalities Test (SDMT, oral version) total correct; (4) Paced Auditory Serial Addition Test (PASAT) total correct for the 2- and 3-s forms combined; (5) Controlled Oral Word Association (COWA), Category Fluency; (6) mean total correct across two alternate forms of the Tower of Hanoi (TOH; Krupp & Elkins, 2000). The TOH was added to the BRB to further assess executive functions. The unweighted

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z score mean of the six measures represented overall neuropsychological performance.

Measures of Self-Reported Cognitive Impairment

Three self-report instruments measured perceived cognitive dysfunction. The first was the five-item version of the Perceived Deficits Questionnaire (PDQ; Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, 1997). The PDQ has good reliability and validity in persons with MS (Cronbach's alpha for five-item PDQ reported between .77–.97) (Fischer et al., 1999; Marrie et al., 2003). The PDQ items assess difficulties with organization, concentration, and memory over the past month. PDQ item scores range from zero to 4, with a maximum total score of 20 representing the most perceived deficits. Also administered were two single-item scales focusing on difficulties over the past week, one asking about memory and the other about attention/concentration, each scored on a 5-point scale (1 = *very well*, *could hardly be better*; 2 = *pretty good*; 3 = *good and bad parts about equal*; 4 = *pretty bad*; 5 = *very bad*, *could hardly be worse*). Scores for these two items were totaled to form a Memory and Attention/Concentration Deficit (MCD) score.

Data Analysis

Pearson correlations and partial correlations assessed the relation of neuropsychological and self-report measures. Scores at baseline and Week 24 were compared with *t* tests. Data were analyzed with SPSS 13.0 using two-tailed tests, with $p \leq .01$ considered significant and $\leq .05$ a trend.

RESULTS

Neuropsychological Performance

Table 1 presents baseline and Week 24 scores separately for each treatment group in the larger clinical trial (Krupp et al., 2004). Overall mean performance was approximately 1.5 standard deviations below norms on the SRT and between 0.5 and 1.0 standard deviations below norms on most other tasks administered. Scores increased modestly but significantly over 24 weeks on the SRT, 10/36, and overall neuropsychological performance. Overall neuropsychological performances at the two testing sessions were highly correlated ($r = .893$, $p < .001$).

Self-Report Measures of Cognitive Impairment

Baseline scores indicate moderate levels of cognitive complaints at baseline, and a modest but significant reduction on each over the course of the study (Table 1). Self-reported cognitive dysfunction at baseline and follow-up were correlated on both the PDQ ($r = .564$, $p < .001$) and MCD ($r = .443$, $p = .001$). The relation between change in overall neuropsychological performance and change in the PDQ for the two groups is shown in Figure 1.

Table 1. Neuropsychological performance and self-reported cognitive impairment at Week Zero and at Week 24 ($N = 53$)

	Week Zero		Week 24	
	Placebo ($n = 22$)	Active ($n = 31$)	Placebo ($n = 22$)	Active ($n = 31$)
SRT^{G,A}	41.0 (9.5)	43.0 (8.9)	42.6 (9.3)	47.7 (9.2)
10/36^{g,a}	18.6 (4.9)	20.6 (5.2)	20.0 (5.2)	22.4 (4.5)
SDMT^{b}	40.4 (17.0)	48.8 (11.1)	43.1 (15.6)	49.6 (13.6)
PASAT^{A,D,X}	66.2 (23.6)	70.0 (19.9)	63.0 (28.7)	76.9 (16.3)
COWA	17.7 (4.8)	18.9 (3.3)	17.8 (4.8)	18.7 (4.7)
TOH^{b}	12.6 (8.7)	17.9 (7.1)	14.6 (7.3)	18.1 (7.4)
Overall NP^{G,A}	−0.3 (0.9)	0.1 (0.6)	−0.1 (0.9)	0.3 (0.8)
PDQ^{G,p,A}	10.9 (3.9)	10.5 (4.8)	9.0 (4.3)	7.5 (3.8)
MCD^{G,P,A}	6.0 (1.7)	5.6 (1.4)	4.7 (1.7)	4.4 (1.1)

Note. b = Baseline (Week zero) difference between groups, $p \leq .05$; B = Baseline (Week Zero) difference between groups, $p \leq .01$; f = follow-up (Week 24) difference between groups, $p \leq .05$; F = Follow-up (Week 24) difference between groups, $p \leq .01$; g = global change in overall sample, $p \leq .05$; G = global change in overall sample, $p \leq .01$; p = placebo group change, $p \leq .05$; P = placebo group change, $p \leq .01$; a = active medication group change, $p \leq .05$; A = active medication group change, $p \leq .01$; d = difference in change between groups, $p \leq .05$; D = difference in change between groups $p \leq .01$; X = based on $n = 42$; SRT = Selective Reminding Test total; 10/36 = 10/36 Spatial Recall Test total; SDMT = Symbol Digit Modalities Test total; PASAT = Paced Auditory Serial Addition Test 2 and 3 second total; COWA = Controlled Oral Word Association semantic fluency mean; TOH = Tower of Hanoi mean; Overall NP = unweighted *Z*-score mean performance across tasks; PDQ = Perceived Deficits Questionnaire total; MCD = Memory and Attention/Concentration Deficit total.

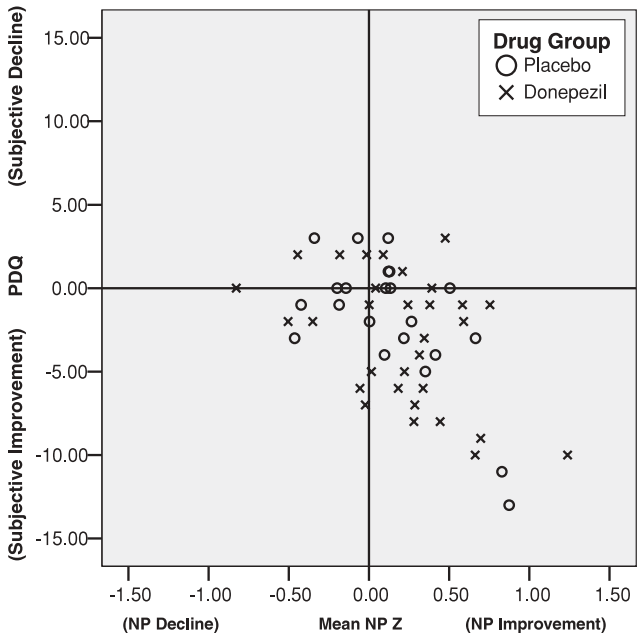

Fig. 1. The relation between change in overall neuropsychological performance (Mean NP *z* score, Week 24 minus Week Zero) and change in the perceived deficits questionnaire (PDQ, Week 24 minus Week Zero) in the active and placebo medication groups.

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Association Between Self-Report and Neuropsychological Measures

No linear correlation between self-report and neuropsychological measures reached significance at either baseline or 24 weeks (Table 2), nor was there any indication of a nonlinear relation, based on an examination of raw data scatterplots. However, a number of significant correlations were found between changes in self-report and neuropsychological performance over the study. Change in overall neuropsychological performance was correlated with change on both the PDQ and MCD self-report measures. The correlation between PDQ change and overall neuropsychological performance became a trend after controlling for drug treatment group, baseline PDQ, and baseline neuropsychological performance ($pr = -.315$, $p = .026$). An analogous partial correlation between MCD change and overall neuropsychological performance did not reach significance ($pr = -.209$, $p = .146$).

Depression

MADRS scores displayed trend correlations with both self-report measures, PDQ ($r = .319$, $p = .021$) and MCD ($r = .280$, $p = .044$), but no correlation with any neuropsychological measure (for overall neuropsychological performance, $r = -.233$; individual task correlations ranged from $-.085$ to $-.242$).

DISCUSSION

Self-reported cognitive dysfunction and neuropsychological performance did not correlate at either baseline or follow-up. Interestingly, however, change scores on the two types of measures did correlate over the 24-week study. Subjects were most attuned to overall changes in their cognitive performance. The correlation ($r = .527$) between overall neuropsychological performance change and PDQ score change was larger than that for any individual neuropsychological

Table 2. Association between self-reported cognitive impairment and neuropsychological performance over the course of the study

	Week Zero		Week 24		Change (Week 24 minus Week Zero)	
	PDQ	MCD	PDQ	MCD	PDQ	MCD
Both groups combined						
SRT	.011	−.047	−.094	−.262	−.209	−.145
10/36	−.142	−.201	−.181	−.155	−.383**	−.344*
SDMT	−.051	−.110	−.045	−.064	−.357**	−.200
PASAT[A]	−.117	−.116	−.113	−.085	−.243	−.014
COWA	.156	−.054	.164	.074	−.266	−.233
TOH	.041	−.056	−.090	−.094	−.145	−.191
Overall NP	−.013	−.128	−.049	−.110	−.527**	−.396**
Placebo group						
SRT	−.065	−.210	−.310	−.251	−.289	.131
10/36	−.253	−.332	−.418	−.091	−.549**	−.506*
SDMT	−.052	−.156	.029	.047	−.269	−.168
PASAT[B]	−.350	−.177	−.191	−.125	.019	.142
COWA	.134	−.132	.023	.053	−.357	−.075
TOH	−.163	−.115	−.002	−.113	−.569**	−.443*
Overall NP	−.139	−.243	−.158	−.077	−.662**	−.319
Active medication group						
SRT	.065	.132	.166	−.248	−.141	−.296
10/36	−.075	−.056	.111	−.190	−.273	−.253
SDMT	−.033	.044	−.032	−.151	−.462**	−.212
PASAT[C]	.028	−.071	.198	.067	−.270	−.010
COWA	.201	.092	.319	.125	−.210	−.345
TOH	.215	.106	−.083	−.031	.016	−.079
Overall NP	.109	.092	.138	−.097	−.435*	−.454**

Note. SRT = Selective Reminding Test total; 10/36 = 10/36 Spatial Recall Test total; SDMT = Symbol Digit Modalities Test total; PASAT = Paced Auditory Serial Addition Test 2 and 3 second total; COWA = Controlled Oral Word Association semantic fluency mean; TOH = Tower of Hanoi mean; Overall NP = unweighted *z*-score mean performance across tasks; PDQ = Perceived Deficits Questionnaire total; MCD = Memory and Attention/Concentration Deficit total; A = based on $n = 42$; B = based on $n = 18$; C = based on $n = 24$.
*$p \leq .05$; **$p \leq .01$.

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task. The lack of a significant correlation between self-reported cognitive complaints and objective performance at baseline and at follow-up is consistent with only a few studies in the literature (Benedict et al., 2003; Gold et al., 2001, 2003). However, given the size of the maximum resulting correlation coefficient at any given point in time (r = .262) the present study is relatively consistent with the modest correlations reported in most other studies (Hoogervorst et al., 2001; Maor et al., 2001; Matotek et al., 2001; Randolph et al., 2001, 2004; Taylor, 1990), with few studies finding a correlation coefficient of r = .40 or above (Benedict et al., 2004; Chiaravalloti & Deluca, 2003). As in most studies, baseline cognitive complaints correlated more strongly with depressive symptoms than with objective cognitive performance (Benedict et al., 2003, 2004; Bruce & Arnett, 2004; Gold et al., 2003; Maor et al., 2001; Randolph et al., 2004), though the depression finding only reached trend status ($p < .05$) in the present study, possibly due in part to restriction of range, since subjects with high depression scores were excluded.

It is unclear why subjects were sensitive to their cognitive changes (at least partially) but insensitive to their current level of cognitive dysfunction. We speculate that this may have arisen from relatively stable differences in the standards that subjects use to judge their cognitive abilities. An individual's judgment of what is considered adequate cognitive functioning is likely to have developed under the influence of many factors, including the person's individual personality characteristics, as well as the particular cognitive demands engendered by their specific social and occupational niche. For example, a person living in a small, stable social community with a longstanding occupation that makes few demands for new learning may feel that their memory was intact, even when neuropsychological testing suggested otherwise. Other persons may compensate for their cognitive deficits within their particular niche without being aware that they are doing so, only to be stymied in efforts to do so on formal neuropsychological tests. The modest correlations between self-report and cognitive performance commonly found in the MS literature leave little doubt that individuals differ in how they judge their cognitive abilities, and researchers have noted a number of factors that might lead particular persons to underestimate or overestimate their abilities (Beatty & Monson, 1991; Benedict et al., 2003, 2004; Bruce & Arnett, 2004; Gold et al., 2003; Maor et al., 2001; Marrie et al., 2005; Randolph et al., 2004; Schwartz et al., 1996). Perhaps it should not be surprising that a given level of cognitive functioning would satisfy some people but not others, and that a modest cross-sectional correlation would commonly be found between self-report and objective performance. If, however, people's standards tend to remain stable over time (at least over 24 weeks), then they may be able to judge whether their abilities have changed, even if they do not agree on what constitutes satisfactory functioning at any given time. Further research is required to test these speculative interpretations and to determine the replicability of these initial findings. Various characteristics of the study design and the subject sample potentially limit generalizability. For example, the study subjects were not depressed, so that the potential impact of mood was likely reduced. Second, these subjects were monitoring their cognition in an ongoing treatment study and they may have been sensitized to changes in cognition. Third, the intervening period was only 24 weeks and results might not generalize to longer time intervals. Fourth, average performance improved modestly and it may prove more difficult for persons to judge the degree to which their abilities have declined as opposed to improved.

If confirmed, there could be important clinical implications to the finding that MS patients are sensitive to changes in their cognitive abilities, particularly as further progress is made in the treatment of cognitive dysfunction in this chronic disorder. However, such a conclusion would only be justified by replication and extension of this line of research. In an effort to improve our understanding of these intriguing initial findings, we are currently studying a broader sample of patients over a longer time interval with a more refined set of self-assessment measures.

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