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# Cognitive impairment in different MS subtypes and clinically isolated syndromes

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**Abstract**

*Objective:* To investigate the pattern of cognitive impairment in patients with relapsing–remitting (RR), secondary progressive (SP), primary progressive (PP) multiple sclerosis, and patients with clinically isolated syndrome (CIS) suggestive of MS, relative to control participants in the Greek population.
*Methods:* RR patients ($N=75$), SP patients ($N=29$), PP patients ($N=23$), CIS patients ($N=33$), and healthy control participants ($N=43$) were assessed by the Brief Repeatable Battery of Neuropsychological Tests (BRBN).
*Results:* The overall prevalence of cognitive dysfunction in our patients was 52.8% with CIS patients excluded and 47.5% with CIS patients included. All MS patients differed significantly from controls in all BRBN measures. Similar was the pattern of cognitive dysfunction in patients with CIS suggestive of MS, although verbal learning/memory capacity (as measured by the Selective Reminding Test) remained relatively spared. The comparisons between patient groups revealed some differences in the performance mainly in favor of CIS and RRMS patients. These differences largely disappeared after controlling for physical disability (EDSS).
*Conclusion:* All MS subtypes patients exhibit a pattern of cognitive impairment running across the studied cognitive domains. The pattern of cognitive dysfunction in patients with CIS is similar with relative sparing of verbal learning.


*Keywords:* Brief Repeatable Battery; Cognitive impairment; Speed processing deficit; Multiple sclerosis subtypes; Clinically isolated syndromes suggestive of multiple sclerosis

## 1. Introduction

Cognitive impairment is present in 40–65% of patients with multiple sclerosis (MS), encompassing all disease stages and types of clinical course. [1–3] These figures usually do not include patients with clinically isolated syndrome (CIS), though cognitive dysfunction has also been demonstrated in patients with CIS [4]. MS-related cognitive dysfunction is characterized by prominent involvement of recent memory, sustained attention, information processing speed, and executive functions [5].

The evidence at present suggests that relapsing–remitting (RR) patients perform better than primary progressive (PP) or secondary progressive (SP) patients on the Brief Repeatable Neuropsychological Battery (BRBN) [2,6] and on several other cognitive tasks. [7] Comparative data on the performance of PP and SP patients have demonstrated more severe cognitive deficits in SP patients [8,9]. Other studies have shown significant differences in particular cognitive domains between all three subtypes (RR, PP, SP) [2,10], suggesting heterogeneity and distinct cognitive profiles depending on disease course [3]. To the best of our knowledge no single study has compared cognitive dysfunction between RR, PP, SP and CIS patients.

The present study investigated differences in cognitive profile, as assessed by BRBN [6,11], between different MS

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subtypes (RR, PP, SP), and CIS patients and further compared performance to that of controls in the Greek population. It represents the first systematic study of cognitive function in Greek MS patients, allowing an estimation of the prevalence of cognitive impairment in the different subtypes of MS.

## 2. Methods

### 2.1. Participants

One hundred sixty consecutive patients with MS under regular follow-up care at the Clinic for demyelinating diseases, Department of Neurology, University of Athens were studied. McDonald's criteria [12] were used for inclusion. Patients with acute relapse during the preceding month, severe visual or upper limb involvement interfering with neuropsychological testing, major psychiatric illness, other neurological disease, learning disability, non Greek origin or insufficient command of the Greek language were excluded from the study. Patients were classified as RRMS ($N=75$), SPMS ($N=29$), PPMS ($N=23$), or CIS suggestive of MS ($N=33$). A detailed neurological examination was obtained for all patients. Physical disability was scored using the Expanded Disability Status Scale (EDSS) [13].

In addition, 43 Greek control participants were recruited from the community, so as to obtain a sample with demographic characteristics as close as possible to our patients' sample. Their medical history was obtained by an interview preceding assessment. The volunteers were excluded in case of learning disabilities or any psychiatric or other neurological disorders, traumatic brain injury, cardiovascular illness and drug or alcohol abuse. They were all native Greek speakers and had normal visual acuity. All participants gave informed consent to participate in this study, which was approved by the Ethics Committee of the Hospital. Table 1 shows age, education, and gender distribution for patients and controls, as well as EDSS, Beck Depression Inventory [14] scores and disease duration for MS patients.

### 2.2. Neuropsychological assessment

Neuropsychological assessment was performed with the Brief Repeatable Battery of Neuropsychological Tests (BRBN) [6,11] adapted in the Greek language. The Beck Depression Inventory (BDI) [14] was also administered to all patients, in order to evaluate their mood.

The Bushke Verbal Selective Reminding Test (SRT; 6-trial version) [15] is a measure of verbal learning/memory of a 12-word list. The Long-Term Storage (SRTL) score represents the sum of words recalled on two consecutive trials without reminding. The Consistent Long-Term Retrieval (SRTC) score is the sum of words recalled on all subsequent trials without reminding. The Delayed Recall (SRTD) score is the number of words recalled after a delay of 15 min.

The 10/36 Spatial Recall Test [11] measures visuospatial learning and memory. It requires participants to recall the placement of 10 checkers that are randomly placed on a $6\times6$ checkerboard. Two scores are recorded; one is the sum of correct responses in the three immediate recall trials (SPARTi), and the second is the delayed recall after 15 min (SPARTd).

The Symbol Digit Modalities Test (SDMT: oral version) [16] examines speed of visual information processing, complex visual scanning, and sustained attention. Participants have to verbally substitute meaningless symbols by the corresponding number. The score is the number of correct substitutions in 90 s.

The Paced Auditory Serial Addition Test (PASAT) [17] requires mental calculation, working memory and interference suppression, concentration and information processing speed. Participants are instructed to add 60 pairs of digits, such that each number is added to the one immediately preceding it, and report the outcome verbally. The digits are presented by audiotape, first at a rate of 3 s per digit (PASAT3), then, in a second trial, at a rate of 2 s per digit (PASAT2). Scores are the sums of correct responses for the 3- and 2-seconds forms of the task.

The Word List Generation (WLG) [6] is a semantic verbal fluency test evaluating the spontaneous production of names of a given category (fruits and vegetables) within 90 s. The score is the number of correct words.

We classified as cognitively impaired through examination with the present screening battery (BRBN), patients who failed on at least 33% (3/9) of the included measures. [18] We considered that patients had failed a particular test if they scored below the 5th percentile for controls. The frequency

Table 1
Demographic and clinical characteristics of patients and controls

| | Controls | RRMS | SPMS | PPMS | CIS | Significant differences |
|---|---|---|---|---|---|---|
| *N* | 43 | 75 | 29 | 23 | 33 | |
| Age (years) | 36.2 (11.3) | 34.3 (8.9) | 42.0 (8.5) | 42.8 (9.9) | 34.7 (8.7) | RR<PP, SP; CIS<SP, PP |
| Education (years) | 14.1 (3.7) | 14.2 (2.9) | 14.1 (2.7) | 12.8 (3.0) | 13.5 (3.0) | ns |
| Gender, M/F, % | 41.9/ 58.1 | 32.0/68.0 | 44.8/55.2 | 43.5/56.5 | 45.5/54.5 | ns |
| EDSS | | 1.9 (1.6) | 5.6 (1.3) | 3.7 (1.6) | 1.5 (1.2) | CIS, RR<SP, PP; PP<SP |
| Duration (years) | | 6.2 (4.9) | 15.3 (7.9) | 4.7 (5.3) | 1.0 (1.5) | SP>CIS, RR, PP; RR>CIS |
| Beck | | 10.8 (8.6) | 18.9 (9.5) | 13.3 (9.0) | 8.2 (9.1) | SP>CIS, RR |

Values are mean (SD); one-way ANOVA for age, disease duration, age of onset, education ($p<0,05$), Mann–Whitney *U* test for EDSS, Pearson $\chi^2$ for gender; RRMS = relapsing–remitting; PPMS = primary progressive; SPMS = secondary progressive; CIS = clinically isolated syndrome.