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Information processing speed impairment and cerebellar dysfunction in relapsing–remitting multiple sclerosis

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ABSTRACT

Objective: The aim of this work is to study the relationship between information processing speed (IPS) impairment and motor testing that reflects cerebellar function in persons with multiple sclerosis (PwMS).
Methods: 60 persons with relapsing–remitting multiple sclerosis with a mean disease duration of 4.2 ± 4 years were studied cross-sectionally. Motor cerebellar functioning was studied using the Nine-Hole Peg Test (NHPT) and the Kurtzke Functional Status Scales, and several cognitive domains were evaluated (IPS, working memory, episodic memory, attention, executive function). Correlations between the global NHPT score and neuropsychological test scores or impairment in each cognitive domain were studied using univariate and multivariate analyses.
Results: The NHPT and a test of IPS significantly differentiated PwMS with and without cerebellar impairment. The NHPT total score was correlated with measures of IPS. Multivariate analyses showed a correlation between the NHPT and measures of IPS, but not between the NHPT and other neuropsychological tests that did not have a speed component.
Conclusion: In this sample of PwMS, motor cerebellar impairment assessed by the NHPT was correlated with IPS impairment.

1. Introduction

Cognitive deficits are frequently present in multiple sclerosis (MS) and could affect patients at all stages of the disease, including the very early stages [1,2], and all clinical phenotypes [3]. However, the pathogenesis of this impairment is still not completely understood. The most frequent feature of cognitive impairment in MS is slowness of information processing speed (IPS) [1–4]. The nature of IPS impairment suggests that it depends primarily upon the integrity of large-scale cortical integrative processes involving long-distance white matter projections that could be damaged by the disease process; however, the damage that occurs in deep and cortical grey matter and alterations to key network nodes are likely to also be involved [2].

The cerebellum represents a major part of the central nervous system and its role in motor control and balance is well known. More recently, a role in cognition has been suspected based on anatomical, clinical and imaging studies [5–7]. It has been suggested there is cerebellar involvement in age-related IPS impairment associated with small vessel disease [8]. The cerebellum is one of the sites that have a predilection for lesion development in MS, and extensive demyelination in the cerebellar cortex has been described [9]. However, a role for the cerebellum in the cognitive impairments observed in MS has only recently become a subject of interest. There is very little clinical data available showing a relationship between cerebellar dysfunction and cognition in MS, although an association between severe cognitive impairment (CI) and cerebellar signs has been noted by clinicians in some persons with MS (PwMS), and case reports illustrate this observation [10,11]. Decreased cognitive performance on measures of IPS and verbal fluency in persons with MS (PwMS) who have predominantly cerebellar symptoms compared to PwMS who do not have any cerebellar dysfunction has been reported [12] 2009).

We hypothesized that a negative relationship between cerebellar function assessed by a motor task, the Nine-Hole Peg Test (NHPT), and IPS impairment exists in PwMS.

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2. Patients and methods

2.1. Patients

To study the correlation between IPS and motor testing, data from 60 persons with relapsing–remitting MS (RRMS) participating in a cross-sectional study about IPS in MS were investigated [3]. This study was approved by the ethics committee, including the institutional review board for human subject research of Bordeaux. All subjects gave written informed consent to participate in the study before their inclusion.

2.1.1. Eligibility criteria were as follows

2.1.1.1. Inclusion criteria. RRMS diagnosis according to the Poser criteria, 18 years of age or older, French speaker, an elapsed time since the first MS symptoms of fewer than 10 years.

2.1.1.2. Exclusion criteria. Persons with progressive MS, presence of any disease other than MS that could explain the symptoms, a history of psychiatric illness with the exception of stable depressive symptoms, starting or stopping antidepressants in the previous 2 months, alcohol, drug, or substance abuse in the previous 2 years, steroid treatment within the last 30 days, recent cognitive assessment (within less than 1 year).

2.2. Healthy controls

Normative data were obtained for the neuropsychological tests used in the MS group from a sample of 415 healthy controls (HC) divided into 20 groups according to age, sex, and education level, as previously described [4].

2.3. Measures

All PwMS and HC were evaluated by qualified senior neuropsychologists. Six cognitive domains were evaluated: IPS, attention, working memory, verbal and visual episodic memory, and executive function (Table 1).

2.4. Neuropsychological evaluation

The neuropsychological (NP) assessment was previously described in detail [3].

It included IPS evaluation using the Computerized-Speed-Cognitive-test (CSCT) [4], a newly validated digit/symbol substitution test of IPS and reaction times values of four tasks from the Test of Attentional Performance (TAP, version 2.1) [13]: alertness, visual scanning (with and without the target), divided attention and flexibility. Psychometric properties and validity data about the CSCT have been published previously [4]. Other cognitive domains were assessed using the Paced-Auditory Serial Addition Test—3 s (PASAT 3 s), the Selective Reminding Test (the SRT and its 3 sub-scores: SRT-LTS = long-term storage, SRT-CLTR = consistent long-term retrieval, and SRT-DR = delayed recall), the 10/36 Spatial Recall Test (SPART), the delayed recall test (SPART-DR), and the Word List Generation test. Accurate answers on the computerized subtests from the TAP (alertness, visual scanning, flexibility, and visual and auditory divided attention) were measured, and the Stroop 45 second test and the numerical span test (forward and backward) were also performed.

2.5. Motor tests

Motor functioning was studied using the NHPT [14] and the timed 25 foot walk (T25FW) [15]. For both tests, two trials were performed at each session and the mean of the two trials was used. For the NHPT, a global NHPT score was defined as the mean time, in seconds, to complete the test using the dominant and non-dominant hand. Disability was measured using a French-adapted version of the Expanded Disability Status Scale (EDSS) [16]. PwMS were classified as having cerebellar impairment if their cerebellar Kurtzke Functional Status Scale (CKFSS) was ≥ 2, a score associated with a significant ataxia demonstrating clinical evidence of cerebellar impairment (score 1 is characterized by signs without disability) and having pyramidal impairment if their pyramidal Kurtzke Functional Status Scale (PKFSS) was ≥ 3, a score associated with an objective weakness of at least one limb, a score of 2 being not associated with an actual deficit demonstrating clinical evidence of pyramidal involvement. Subjective fatigue was measured, as previously described, by the UK Neurological Disability Scale fatigue score [1,3,4].

Each subject answered questionnaires concerning depressive symptoms (Beck Depression Inventory II, BDI II). Subjects were considered to be free of depressive symptoms if their BDI II scores were below 13, to have mild depressive symptoms if their BDI II scores were between 14 and 19, to have moderate depressive symptoms if their scores were between 20 and 28, and to have severe depressive symptoms if their scores were greater than 29.

2.6. Statistical analysis

Statistical analyses were performed using StatView version 5.0 software for Windows. For age and disease duration, the results are shown as the means ± SDs. For the EDSS, the results are shown as the medians (ranges). For all analyses, differences were considered significant when p values were less than 5%.

In the MS group, the z scores were calculated for each NP score using the following formula: (patient's score − mean value of HC group matched for age, sex, and education level) / SD of the matched HC. Z scores were calculated for each cognitive domain using the following formula: sum of the patient's NP z scores for each domain / the number of z scores in each domain. For a given NP test, patients were considered impaired if their z scores were below the fifth percentile for their matched

Table 1
Cognitive domains and neuropsychological tests.

Domains	IPS	Attention	Working memory	Executive function	Episodic verbal memory	Episodic visual memory
Tests	CSCT Alertness (RT) Visual scanning (RT): - with a target - without target Ratio divided attention (RT): - auditory - visual Flexibility (RT)	Ratio divided attention (AA): - auditory - visual Visual scanning (AA): - with a target - without target	PASAT 3 Numerical span test: - forward - backward	Flexibility (AA) Stroop 45 WLG 90	SRT: - SRT-LTS - SRT-CLTR - SRT-DR	10/36 SPART: - Immediate recall - Delay recall

IPS: Information Processing Speed, CSCT: Computerised Speed Cognitive Test[4], RT: reaction time, in milliseconds, AA: Accurate Answers, PASAT 3 or 2: Paced Auditory Serial Addition Test 3.0 s or 2.0 s, WLG 90: Word List Generation test, SRT: Selective Reminding Test, LTS: Long-Term Storage, CLTR: Consistent Long-Term Retrieval, SRT-DR: Delay Recall, 10/36 SPART-IR: Spatial Recall Test for the immediate recall of short visuo-spatial memory, 10/36 SPART-DR: Spatial Recall Test for long-term visuo-spatial memory.