Running Head: EXECUTIVE DYSFUNTION IN MULTIPLE SCLEROSIS

# Executive Dysfunction Syndrome in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system. Several authors consider that an attentional damage is the underlying cause of cognitive dysfunction in MS. However, while some studies of MS report attentional deficits, others suggest that attention remains unaffected by this disease. The presence of attentional deficits in MS thus remains a disputed matter. We suggest that these discrepancies stem from the use of a wide range of attentional tests, we need only consider that attention is not a unitary function, and that the convergent validity of the different tests has not been demonstrated. Thus our main aims are: to obtain a set of attentional tests which taps the whole range of attentional functions; to assess the clinical contribution of some reaction time tests derived from theoretical models of attention, which will be used along with classical psychometric tests; and to evaluate the convergent validity of the different tests employed. In our study MS patients exhibit diverse and specific attentional deficits. That is, they show an attentional profile consisting in a series of specific impairments in visual selective attention, (visual search and attentional capture), executive function (cognitive flexibility or capacity to overcome automatic responses) and sustained attention (fatigue problems). However, some aspects of these attentional components remain unaffected (concentration and accuracy in selective attention, alertness, interference from distractors, and capacity for maintaining information with low memory loads in executive control). We also discuss the relationship between attentional deficits and cognitive and affective disorders in MS.

KEYWORDS: MULTIPLE SCLEROSIS, ATTENTION, EXECUTIVE FUNCTIONS, PSYCHOMETRIC TESTS, AFFECTIVE DISORDERS.

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (brain and medulla). It occurs frequently in young people. The patches of hardened tissue (sclerotic plaques), typical for MS are due to inflammatory lesions as well as due to axonic death and *demyelization*. EM is a relatively unpredictable condition; its symptoms can be relatively weak, incapacitating or even devastating for the patient. While some people affected by MS can lead a relatively normal life, other may loose their ability to write, speak and/or walk. What is the origin of MS? While there are multiple possible causes (viral infections, hereditary dispositions…) which act as a trigger of MS, specific mechanisms of acquisition remain unknown. In any case, it is generally accepted that MS involves a failure of the immunologic system which erroneously attacks the nervous system (NS) causing lesions, i.e. sclerotic plaques. It seems that hereditary factor play an important role in MS.

What are the symptoms of MS? The symptoms can be weak or severe, limited to relatively short periods in time or long-lasting. Symptoms vary depending on the specific regions of the NS affected by the disease. Consequently, particular patients may experience different symptoms. The commonest symptom is the inflammation of the optic nerve (connecting the eye to the brain), a.k.a. optic neuritis, that can lead to blurred or "foggy" vision or even to complete loss of vision. The demyelization of motor nerves (transmitting “orders” from the brain to muscles) produces patients’ walking difficulties and impaired arms mobility. Tonic spasm of the affected muscles as well as balance and coordination problems are often observed. Changes in skin sensations and sensitivity are due to demyelization of sensory nerves. Urinary incontinence, sexual dysfunctions and fatigue may be present (Poser and Brinar, 2003).

The course of MS is difficult to predict. Frequently the onset of MS is accompanied by isolated occurrences of symptoms, followed by months or even years with no visible symptoms. However, in some patients the symptoms aggravate and generalize in terms of weeks of few months. In 1995, Poser proposed a series of criteria that allow for a clinical diagnosis of the MS onset. A recent revision of the diagnostic criteria can be found in McDonald et al. (2001). Koopmans et al. (1989) suggest a classification of the temporal courses of MS:

- relapsing-remitting: onset of symptoms followed by a complete recovery or minimal repercussions; patients are clinically stable in between the symptomatic periods.
- chronic-progressive: symptoms tend to worsen and they generally do not decrease in intensity; may be progressive from the onset (primary progressive MS) or following a period of relapsing-remitting MS (secondary progressive MS).
- The severity of the symptoms is usually evaluated by Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The scale allows for a assessment of the degree of impairment in eight Functional Systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other). The scale is rated from 0 to 9. The final EDSS rating results from the partial scores for each of the eight systems. A score from 0 to 2.5 indicate minimal dysfunction. The scores from 3.0 to 5.0 the indicate a range of dysfunction from moderate to relatively severe. Finally, a score of 5 or higher indicate a high degree of dysfunction with severely affected mobility.

## Cognitive damage in MS

The British Society of Rehabilitation Medicine suggests there are 15 functional areas affected by MS ("Working Party on Multiple sclerosis" report, 1993). Cognitive area is number four in the list, preceded by motility, continence and emotional area. When additional cognitive problems are present, physical disability is harder to cope with (problems to judge distance, orientating problems, poor action planning and limited awareness of one's own physical limitations…). In other words, the cognitive dysfunction can actually enhance and accelerate physical disability.

Cognitive dysfunction associated to MS shows large interindividual variability (Beatty et al., 1995, 1996; Ficher et al., 1994; Amato et al., 1995; Camp et al., 1999). Even though certain regions of the central nervous system are more prone to produce sclerotic plaques (namely, the optic nerve, the spinal cord and the white matter surrounding the ventricular system), the development and the progress of the plaques is random and completely patient-specific. Because cognitive deficits are a consequence of this pathology, they are also unpredictable and vary from patient to patient.

Finally, it should be mentioned that caution is necessary when standardized test batteries are use for assessing the degree of cognitive dysfunction in MS. The scoring of the tests normally implies a comparison to a healthy control group, matched for age. However, the results of a given test may be affected not only by specific deficits of the patient, but also by symptoms which are not cognitive in nature, i.e. sensory and motor deficits, fatigue, etc. Results of a test which involve answering question, writing, copying or drawing, can be easily distorted by the non-cognitive deficits present in the patient. Specialized literature on MS offers specific recommendations concerning test selection and evaluation (Peyser, Rao, LaRocca y Kaplan, 1990).

First reports referring to cognitive dysfunction in MS are relatively old. In 1951 Canter studied scores achieved in the Army General Classification Test by soldiers recently diagnosed with MS. He compared the results with those obtained by the same subjects four years earlier, when they did not suffer from MS. The disorder led to a significantly lower score. In 1986 Rao suggested that MS patients had a specific cognitive profile: language and social abilities were preserved, but there was a marked lack of "insight" as well as poor problem solving. Other authors emphasize that the main problem in EM is decreased processing speed (Demmarre et al., 1999; De Sonneville et al., 2002; Archibald et al., 2004; DeLuca et al., 2004).

The role of neuropsychology is to determine what cognitive functions are affected and what is their relation to the brain lesions present in MS. There have been two types of studies focused on MS. First, investigations that seek to establish a general pattern of neurocognitive deficits present in MS and, second, studies focused on specific and detailed analyses of distinct components of the cognitive dysfunction The present study is in line with the latter approach; highly specialized methods are used for studying particular processes.

## Attentional deficits in MS

Several authors (Rao, 2004) believe that attentional damage is in fact the underlying cause of cognitive dysfunction in MS. In this way poor memory and problem solving skills derive from the attentional damage. On the other hand, it has been suggested that the attentional deficit could be a secondary problem itself: either a consequence of the lower cognitive processing speed and/or of emotional, motor and other functional problems (fatigue) which accompany the MS (Sandroni et al., 1992).

In any case, proper diagnosis of preserved and damaged attentional function is fundamental for neurocognitive rehabilitation of MS patients (Plohmann et al., 1998).

It is possible that the contradictory results of studies on attentional deficit in MS are due to the fact that not all attentional tests and tasks measure the same thing. It is largely accepted that attention is not a homogeneous, unitary function. There are at least three different components of attention: alerting, orienting and executive control, which are essential for proper information selection, sustained attention and dividing attention, respectively (Fan et al., 2002).

Statistical data showing differences between patients and healthy control subjects may reflect a vast variety of attentional problems with different degrees of impact on the patients' lives. These attentional conditions can range from minor problems, such as having to write down phone numbers at the same time they are being said, to serious deficits that can make a person absolutely incapable of following the plot of a movie. We will now proceed with a detailed description of specific attentional deficits observed in MS.

De Sonneville et al. (2002) evaluated cognitive processing and attentional functions in different subtypes of MS. They found multiple attentional deficits which conditioned patients' slower controlled processing. At the same time, these deficits affected more complex cognitive abilities (planning of daily activities and working skills). The general slow-down of cognitive processes requiring executive control is more frequent in progressive MS patients (50%) than in the relapsing-remitting subtype (24%). Accuracy performance is usually less affected than speed (reaction time).

Gonzáles-Rosa et al. (2005) employed Visual Event Related Potentials (16 electrodes neuroscan) along with Posner's (1980) orienting paradigm (selective attention) with 80% cue validity. They found that MS patients were 60 to 90 ms slower than control subjects. In addition, visual P300 component appeared approximately 45 ms later in patients than in controls. Finally, a minor attentional effect was observed (valid vs. invalid trials difference). The executive control in MS has been usually studied indirectly, e.g. in working memory tasks and abstract reasoning tasks (Litvan et al., 1988; Mendozzi et al., 1993; Arnett et al., 1994). Foong et al. (1997) examined the relationship between the executive deficits and the extent of frontal lesions in MS, using magnetic resonance imaging (MR). They employed a series of tests such as Raven's progressive matrices test (1958), which examines reasoning abilities, a verbal fluency task, Cognitive Estimations task (Shallice y Evans, 1978), Stroop task, a spatial amplitude test (to remember a sequence of lit squares), a working memory test and a strategic planning test (a variation of the London Tower task). Test scores in verbal fluency, working memory and London Tower tasks correlated with the amount of frontal damage. Nonetheless, this correlation was not significant when the total amount of damage (including periventricular lesions) was taken into account. The most significant deficits were observed in the verbal fluency tasks, the Stroop task, the cognitive estimation task, the spatial amplitude task, the working memory task and the strategic planning task. However, the observed degree of dysfunction varied from one task to another. For instance, in the London Tower the differences between patients and controls were only significant in the most difficult levels of the task. In summary, the results indicate that executive control is not a unitary function but includes a series of independent dimensions some of which may be more affected than others. These deficits are independent from visuoperceptual, emotional and psychiatric problems of the patients. Arnett et al. (1994) found a significant correlation between the degree of frontal damage and patients' performance in the Wisconsin Card Sorting Test. It should be noted that quite frequently patients with different type of brain lesions show the same

cognitive deficits (Rao et al., 1986; Foong et al., 1997). Hence, we are dealing with a discriminative validity problem. In fact, similar cognitive profiles can be found when executive function deficits of different neurodegenerative disorders are compared by means of traditional test like the WCST, the Stroop test or the Hanoi Tower task (Ozone and Jensen, 1999). On the other hand, if we take into account that the so-called central executive encompasses various cognitive components (including mental set shifting, working memory control, cognitive flexibility, planning, etc.), we find that dysfunction profiles are varying across different conditions and may also show important variations in patients with the same disorder (MS) but different degrees of brain lesion.

Stablum et al. (2004) studied cognitive flexibility (another executive function) in MS by means of the task shift paradigm where participants had to alternate between two different tasks. In this context it is normal to observe a cognitive cost in normal subject in terms of a longer reaction time when switching from one task to another. However, Stablum et al. reported that this cost was bigger in MS patients (167 ms) than in controls (97 ms). Tinnefeld et al. (2005) and Nebel et al. (2007) also showed attentional deficits in attention related structures in MS patients. In summary, in MS there are cognitive and brain deficits affecting attention. They are more pronounced in situations requiring sustained attention, but they are also present in selective attention and executive functions. Forn et al. (2006) showed evidence of cortical reorganization (a compensatory mechanism to overactivate specific brain areas) in MS patients in order to perform attentional tasks as well as controls .

However, two are the main obstacles that we find when trying to explore the attentional functioning of MS patients: first, the non-unitary character of attention; and second, that attentional functioning is studied with both an empiric and a theoretical approach. In other words, we must select tasks and tests from the wide range available. These tests and tasks can be broadly classified into pencil and paper psychometric tests, and chronometric or RT tasks. To this point, no one has demonstrated that these different tests and tasks measure the same construct, that is, the pattern of correlations between the scores of the same participants in the different psychometric tests and cronometric tasks (Gonzalez et al., 2003). This pattern of correlations between classic psychometric tests, widely accepted as indexes of attentional functioning by clinical psychologists, and RT tests, mainly related to theoretical models of attention, is precisely what this study intends to evaluate.

From a theoretical perspective, it is widely admitted that the concept of attention incorporates the functions of alertness, orientation and control of information processing. Therefore, we should at least obtain a measure of each of these three components. Moreover, these attentional functions are not unitary themselves, which is especially true in the case of the control component, which, to emphasize the point, is usually referred to as “executive functions” (Miyake et al., 2000). If a single measure of executive function is obtained, results will probably suggest an impaired executive function in MS patients, but the pattern of cognitive deficits will not allow differentiating MS from other neurodegenerative diseases. Thus, it is fundamental to work with a sample of specific executive functions, which are often independent of each other (e.g., cognitive flexibility, maintenance of information, inhibitory functions…), if we are to obtain the executive profile of MS.

## Research aims

While some studies of MS report attentional deficits, others suggest that attention remains unaffected by this disease. Thus, the presence of attentional deficits in

MS remains a disputed matter (Kujalo et al., 1995; Pelosi et al., 1997; Arnett et al., 1997; Olivares-Pérez, 1996). We suggest that these discrepancies stem from the use of different attentional tests: given that attention is not a unitary function, and that the convergent validity of the different tests has not been demonstrated, it is not safe to assume that we are measuring the same function (Spikman et al., 2000, 2001). Thus our main aims are: to obtain a set of attentional tests which taps the whole range of attentional functions; to assess the clinical contribution of some reaction time tests derived from theoretical models of attention, which will be used along with classical psychometric tests; and to evaluate the convergent validity of the different tests employed.

Furthermore, the same tasks do not always produce the same results across different studies, probably due to the heterogeneity of the patients in terms of MS type, stage of evolution of the disease, different functional deficits, different brain lesions… In order to avoid this possible confound, this study focuses on the cognitive deficits associated with a specific type of MS: the Relapsing-remitting MS (RRMS).

In summary, this study intends to control for the variability in procedures and samples that has hampered the research into the cognitive deficits associated with MS. The following hypotheses are tested:

- RRMS is accompanied by a general slowing in information processing.
- RRMS is accompanied by an attentional deficit.
- The attentional deficit is not caused by any of the other symptoms (such as slow information processing, depression, anxiety or general cognitive impairment), nor by the size/localization of the brain injuries.

About the specific pattern of Attentional deficit in MS, we also hypothesize that:

- Attentional deficits in RRMS are specific, not general, which would explain the contradiction between previous results.
- Psychometric tests measure general attention, that is, they tap several components of attention, and therefore, scores on these test show moderate correlations with any other attentional task.
- Attentional RT tasks measure specific components of attention, therefore, scores on these tests should only correlate with those obtained in tests which tap the same attentional component.
- RT tasks are better suited to “capture” the specific attentional deficits associated to RRMS.

## Method

### Participants

26 RRMS patients participated in this study. They were selected from a sample of participants provided by the Neurology Department of the “Hospital Virgen de las Nieves” in Granada, Spain. Participants provided informed consent. None of the patients showed motor impairment, and all of them scored between 1 and 4 in the Expanded Disability Status Scale (EDSS). Results from these 26 patients were compared to results from a control group of 26 participants of similar age.

### Materials

Psychometric attentional tests :

- The Attentional Rating Scale (Ponsford and Kinsella, 1991).

This questionnaire evaluates the participants' perception of their own attentional problems and it possesses great between-observer reliability. It consists of 18 questions about distractions, slowness, focussing difficulties and problems with dual tasks. A scale ranging fro 0 to 4 is used, with a score greater than 2 indicating problems in processing speed, on focusing capacity or an inability to divide attention

- R. Brickenkamp's d2, Spanish adaptation by Seisdedos, TEA.

The "d2" test is designed to measure those processes usually referred to as attention, focusing, effort and attentional control. Often defined as concentration or focusing, selective attention can be thought of as the capacity of focusing in only one of two relevant stimuli, while the consciousness of distractors stimuli is deliberately suppressed (e.g., Zillmer and Spiers, 1998). On the other hand, the construct referred to as vigilance or sustained attention, which is also related to selective attention, refers to the capacity of exerting a sustained attentional activity during a relatively long period of time. The d2 test is thus a measure of selective attention and mental concentration.

- VSAT (Trennerry, Crosson, DeBoe and Leber, 1990).

Our second index of attention, the VSAT, is a visual search task. In visual search tasks participants must keep a target in the focus of attention while ignoring distractors and maintaining a prolonged state of alertness. This task is thought to possess a great ecological validity.

- "Zoo map" test, from the Behavioural Assessment of the Dysexecutive Syndrome (BADS) battery (Wilson, Alderman, Burgess, Emslie and Evans, 1996).

The Zoo map is a test of a specific executive function, planning. Participants must plan a route to visit 6 out of 12 possible locations in a zoo, with certain constraints on the strategy to follow. There are two versions of this test: in the first version participants must follow an externally imposed strategy; in the second version little external structure is provided. Participants mark their route using coloured pencils. Direct scores are obtained by subtracting the number of mistakes in the sequence (i.e. deviations, visiting the same location twice…) from the number of correct answers. The direct scores are then translated into a scale, ranging from 0 to 4, which also considers the time taken to complete the test.

RT attentional tests:

- Attentional Network Test, ANT (Fan et al., 2002).

This test measures alertness, orientation and control and is a development of Posner's "costs and benefits" task (e.g. Posner, 1980). In this task, a fixation point (a "+" sign) located on the centre of the screen is followed by a warning signal (an "*" sign), which warns the participant about the imminent onset of the target stimulus. This warning signal may appear in the centre of the screen ("non-spatial" or "central" condition), on one side of the screen ("spatial" condition), on both sides ("double signal" condition), or it may not appear at all ("no signal" condition). Thus, the

difference in RT between the "no signal" and "central" conditions reflects the effect of alertness; while the difference between the "double signal" and "spatial conditions" allows to measure the effect of orientation.
The warning signal is followed (after 400 ms.) by the target, an arrow located on the centre of the screen which may point left or right. Importantly, this target is flanked by two additional arrows, one below and one above the target. Participants are then required to indicate the direction in which the target arrow is pointing (by pressing the corresponding button in a mouse). Each stimuli subtends 2 degrees of visual angle, the target and the warning signal appear at a distance of 2 and 3 degrees from the fixation point respectively. The flanker arrows may point in the same direction as the target arrow ("congruent" condition), in the opposite direction ("incongruent" condition), or they may not point in any direction ("neutral" condition). This manipulation of congruence allows to measure interference effects, which are related to the control function of attention. Therefore, the ANT provides three attentional measures which are often orthogonal, that is, they do not correlate with each other.

- Task-switching paradigm (Tornay and Milán, 2001).

With this task we intend to measure cognitive flexibility, another executive function. Many tasks provide measures of cognitive flexibility, even if they have not been designed with this specific purpose. One of the best examples of such a task is the Wisconsin Card Sorting Test (WCST), but we can also mention the Seisdedos Switches Task (1994), the Trail Making Test (TMT, part b), the Stroop task, or the Hanoi Tower.

When switching from an activity to a new one, there is often a transient impairment in performance, which can be measured both as a decrease in accuracy and as an increase in RT, the so-called "task-switching cost". When performing a task, different processes have to be organized and linked together to produce coherent behaviour, in other words, we must adopt a certain "task-set". When a task switch is in order, this task-set has to be reconfigured to meet the new demands. Many consider the time needed to complete this task-set reconfiguration to be the main cause for the task-switching cost. To study this effect in the laboratory, the participant has to alternate between to simple cognitive tasks, task one (T1) and task two (T2). In our study, the participant has to indicate the colour of a character (a number from 1 to 9) in trial N (T1), but report if it is odd or even in trial N+1 (T2), again its colour on trial N+2, etc. When participants' performance is measured in this condition a switch cost is found with respect to the pure or baseline conditions in which the participant carries out a single task throughout the experimental session. In this case, the task sequence will be: T1, T1, T1, T2, T2, T2, that is, a predictable switch of task every 3 trials. For both tasks, participants respond by pressing the B and N keys on the keyboard, which stand for left and right respectively. The target subtends 2 degrees of visual angle and it is presented in the fixation point. An asterisk like fixation point indicates task one and the plus sign like fixation point indicates task two. The target appears one second after fixation point.

- Computerized Stroop task (Stroop, 1935).

J. R. Stroop devised an experimental paradigm which has generated a great amount of psychological research. Nowadays, computers allow to present long series of Stroop stimuli and register responses in a trial by trial basis. Thus, in a determined experimental block, participants are presented a random series of congruent (i.e. the word "green" printed in green colour), incongruent (i.e. the word "green" printed in blue colour), and neutral trials (i.e. the word "pencil" printed in any colour). When RT is the dependent variable, higher latencies are observed in incongruent than neutral trials

(interference effect), and lower latencies are observed in congruent than neutral trials (priming effect). In this study, we use a different version of this paradigm, the "spatial Stroop task", here participants must indicate the direction in which an arrow points. Importantly, the arrow may appear right or left of the fixation point, thus producing congruent (i.e. an arrow pointing left, presented on the left side) and incongruent trials (i.e. an arrow pointing right, presented on the left side).

- N-back tasks (Carlson et al., 1998).

This task measures the ability to maintain information online, introducing variations in memory load. WM is widely thought of as the interaction between short-term memory (STM) and the central executive, but it has proven difficult to dissociate the limited capacity STM component from the processing control function.

Spikman (2001) differentiates between processing speed or control capacity and WM. The former is related to situations where there is temporal pressure. The latter is related to the structure of the task. Some WM tasks however, put more emphasis on either on the control or the capacity component. The N-back task measures the ability to maintain information online, with the advantage that it allows to manipulate the relative weight of the control and capacity components. In this task, participants have to indicate whether the target in the current trial is the same as in the previous trial (N-1), or two trials before (N-2), etc. This "same or different" discrimination is made in a continuous manner, in a trial by trial basis. In the present study, participants have to indicate whether the target (the letters X or O) in trial N is the same as the one presented 1 (N-1) or 2 (N-2) trials before. Stimuli are presented on the centre of the screen and subtend 2 degrees of visual angle. The keys B and N of the keyboard are used to indicate that the target is equal or different respectively. The comparison of accuracy and RT in the N-1 and N-2 conditions allows to compute the effect of memory load on the online maintenance of information.

- Processing speed measurement.

It is also necessary to differentiate between the speed at manipulating and exploring information in STM from general processing speed. Generally, the cognitive style of an individual before and after disease can be assessed with any RT task, be it a detection task (simple RT) or a discrimination task (choice RT). There is a close relation between speed and accuracy in information processing, even if we do not consider attentional effects (i.e. when priority instructions are provided). Thus, people can be fast and inaccurate, slow and accurate, etc. By comparing participants' mean RT and percentage of errors with those of a control group or with normative scores, it is possible to assess their information processing profile (once motor or perceptive impairments have been discarded as cause of the results). Other basic measures that can be obtained with any RT tasks are practice and fatigue effects. By observing the development or RT and errors throughout block of trials, we can determine the presence of a learning curve or fatigability in performance variability.

Non-attentional tasks employed in this research:

- Folstein's Mini-Mental State Examination (MMSE). Spanish version by TEA.

It measures general cognitive deterioration. It is a short screening test, which provides a rapid assessment of the mental status of a patient. It is usually employed in brief neuropsychological batteries as well as in larger assessment protocols in MS. Our interest in this test stems from it being the most common general test used in MS, along

with the PASAT, to assess cognition. The test consists of a series of questions on a number of areas: orientation, fixation, arithmetic, language, memory and basic motor skills. Any score below 24 (for elderly people) or 28 (for young adults) out of 30 is considered as proof of cognitive impairment.

- State-trait anxiety inventory, STAI (Spielberger et al., 1970). Spanish version by TEA.
It measures trait or personality anxiety, and state or situational anxiety. It consist of 20 Likert type questions, the global score indicates the level of anxiety (low or high).

- Beck Depression Inventory, BDI (Beck, 1978). Abbreviated form.
This is a questionnaire about symptoms of depression (including cognitive symptoms). The global score provides a measure of intensity of the patients' depressive state (non-psychotic).

### Relation between research aims and selected tasks

The non-attentional tasks included in this study were selected with the aim to contrast two hypotheses about cognitive deterioration in MS: the motivational hypothesis and the general cognitive deficit hypothesis.

Psychometric attentional tasks will answer two main questions: first, is attentional function generally affected? And second, do the different tests of attentional function measure the same construct?

RT tasks can help to obtain an attentional profile of MS, according to Posner's neuropsychological theory of attention, one of the most widely accepted theories of attention. Moreover, RT tasks will provide us with a number of different measures of executive function, allowing to consider the different components of cognitive control (this further division of executive function is lacking in Posner's theory) and to study their pattern of correlations. If different attentional tests measure the same attentional component, the correlations between them should be higher than the correlation with attentional tests tapping a different attentional component.

The pattern of correlations between RT and psychometric tests will also be studied to ascertain whether they measure the same construct, and if they measure it with the same sensitivity (as the dependent variable differs in each case). At the same time, we can obtain measures of accuracy and speed of information processing in each task, along with measures of fatigue and practice effects, which at the same time will allow to test the motivational hypothesis.

### Procedure

Each participant took part in two experimental sessions, each of which lasted one hour. The order of presentation of the two sessions was counterbalanced. For half the participants, the first session included the MMSE, two RT tasks (a switching task and a Stroop task), the STAI, Ponsford and Kinsella's Attentional Rating Scale and the VSAT. In the second session, participants completed two RT tasks (ANT and N-back task), d2, the Zoo Map and the BDI. The remaining half of the participants performed these sessions in reverse order. RT tasks took about 10' each, psychometric tasks lasted an average 5' (except the Zoo map which takes about 10'). 5' rest periods were introduced between each pair of tasks within a session. RT tasks consisted of 200 to360 trials presented in blocks of 20-30 trials.

## Results

### 1. Non-attentional tasks

The three non attentional tests used were the MMSE, the STAI and the BDI. With respect to the MMSE, none of the patients exhibited general cognitive deterioration. The minimum score was 29 and the maximum was 35, the average score was 34.

In the STAI, regarding state anxiety, all of the patients obtained scores that were below the 50$^{th}$ percentile (direct score below 20), except two patients who obtained a direct score of 31, corresponding to the 75$^{th}$ percentile. With respect to trait anxiety there is a great variability though. We divided all patients in three groups: trait anxiety inferior to the 50$^{th}$ percentile (direct score of 16 or less); trait anxiety between the 50$^{th}$ and 60$^{th}$ percentile (direct score between 20 and 26); and trait anxiety above the 80$^{th}$ percentile (direct score above 32). The average score of the low trait anxiety group was 12, the medium group scored an average 25; and the high anxiety group scores averaged 38. The low anxiety group was constituted by six participants, the medium anxiety group by six participants and the high anxiety group by 14 participants. Differences in anxiety between groups were significant: low anxiety – medium anxiety, $F$ (1, 23) = 33.35, $p < .000$; low anxiety – high anxiety, $F$ (1, 23) = 138.58, $p < .000$; medium anxiety – high anxiety, $F$ (1, 23) = 25.68, $p < .000$.

Three groups were formed as well regarding the BDI scores: no depression (scores from 0 to 4, 8 participants); low depression (scores from 7 to 9, 8 participants); and moderate to severe or significant depression (scores above 12, maximum is 21, 10 participants). Average scores were 2, 7 and 16 for the three groups respectively. All the differences between groups were significant: no depression – low depression, $F$ (1, 23) = 46.69, $p < .000$; no depression – severe depression, $F$ (1, 23) = 106.23, $p < .000$; low depression – severe depression, $F$ (1, 23) = 10.90, $p < .000$.

The correlation between anxiety and depression tests was a significant .77, a great amount of patients shows high scores both in depression and trait-anxiety.

Finally, effect sizes were obtained using Cohen's *d* statistic, departing from the differences in the groups' average scores and the conjoined standard deviation (Zakzanis, 2001). Once the *d* was obtained, we calculated the overlap statistic (OL%), which represents the degree of overlap in the distribution of means between pairs of groups. For example, for a *d* of 3, the OL% value is 7.2. In other words, the effect is extra-large and the measure is sensitive to the differences between groups. Bezeau and Graves (2001) differentiate between the small effects (*d* about .3), medium effects (*d* about .6), large effects (*d* about .8) and Extra-large effects (*d* about 1.35). In our particular case, the *d* for the comparison of the low and high anxiety groups was 2.4, which translates into an OL% of 13. Therefore, the difference between the low and high anxiety groups is evident. In table 1, the *d* and OL% values for all the group comparisons are presented.

*Table 1. Effect size for the comparison of groups with different levels of depression and anxiety.*

| **Group difference** | Cohen's *d* | OL% | Effect Size |
|---|---|---|---|
| High vs. low anxiety | 2.4 | 13 | Extra-large |
| Low vs. medium | 4 | 2 | Extra-large |

| | | | |
|---|---|---|---|
| anxiety | | | |
| Medium vs. high anxiety | 2.1 | 15 | Extra-large |
| Low vs. no depression | 2.8 | 8.8 | Extra-large |
| Severe vs. no depression | 4 | 2 | Extra-large |
| Low vs. severe depression | 1.3 | 32 | Extra-large |

2. Psychometric attentional tests

This section depicts the results obtained with Ponsford and Kinsella's questionnaire, the d2 test, the VSAT and the Zoo map test (see tables 2 and 2b).

*Table 2. Statistical differences in the means and SD's (bracketed) between the experimental and control groups. Significant differences are marked with an asterisk.*

| | Experimental Group | Control Group | Statistic | |
|---|---|---|---|---|
| **Psychometric attentional tests** | **MS** | CN | *F* | *P* |
| TOT d2 | 360 (107) | 415 (76) | 5.15 | 0.02 (*) |
| CON d2 | 125 | 160 | 4.03 | 0.05 |
| VAR d2 | 14.90 | 15.15 | 0.02 | 0.80 |
| TA d2 | 175 | 180 | 0.57 | 0.63 |
| Zoo map | Perfil 2.10 (1.20) | Perfil2.5(0.9) | 1.64 | 0.20 |
| VSAT | 90 (36.3) | 170 (19.50) | 72.27 | 0.00 (*) |
| Ponsford and Kinsella | 21 (12.67) | 14 (6.12) | 4.48 | 0.03 (*) |

*Table 2.b. Effect size for the significant differences between the experimental and control groups, in the psychometric attentional tests.*

| **Group differences** | Cohen's *d* | OL% | Effect Size |
|---|---|---|---|
| D2 | 0.6 | 61.8 | Medium |
| Zoo map | 0.3 | 78.7 | Small |
| VSAT | 2.6 | 10.7 | Extra-large |
| Ponsford and Kinsella | 0.6 | 61.8 | Medium |

Results show that the only significant differences between the patients and control groups were observed in Ponsford and Kinsella's questionnaire, the visual search task and two components of the d2 test. Table 2 shows the direct scores from Ponsford and Kinsella's questionnaire, composed of 17 items. It is worth noting that item 18 is a general question about the participants' self perception of changes in attentional capacity before and after the disease, rating it from 0 to 3. Average scores were 1.8 for the patient group, and 0 for the control group, this difference was significant. Therefore, patients felt that they had attentional problems, and this was

supported by the results. However, only in one psychometric test the differences with the control group were significant. The VSAT test shows significant differences between patients and controls both in the direct score and percentile analyses, $F$ (1, 50) = 85.46, $p < .000$, and the effect size was extra-large. Only 1 in every 10 patients shows scores within the range of the control group. Direct scores were 90 ($10^{th}$ percentile) for the MS group, and 170 ($50^{th}$ percentile) for the control group. The d2 test does not seem to discriminate between both groups in the percentile analysis, but it does in the direct score analysis for some components, although effect size is medium (that is, the difference between groups is near to chance levels).

The pattern of correlations between d2 components reveals that the correlation between TOT and CON is significant (.94). In the d2 manual that correlation is also significant with a value of .89. The correlation between VAR and the remaining d2 measures was not significant in our data. The correlation between TOT and CON respect to TA were also significant (.82 and .89 respectively). Finally, the Zoo map test does not differentiate between both groups, either on direct score and percentile analyses.

In summary, some behavioural differences are observed in general attentional tests, like the d2 and the VSAT, with the latter proving more sensitive than the former. Pearson correlations between VSAT and the different d2 components are: .44 with TOT (significant); .34 with CON (significant); .13 with VAR (not significant); and .56 with TA (significant). It can be concluded that both attentional tests show a significant but moderate positive correlation, which indicates a maximum common variance of about 25% in our sample.

3. RT attentional tasks

The RT tasks in our protocol can be divided in two groups:

a) The ANT by Fan et al., which measures alert, orientation and general executive function, the three attentional networks in Posner's theory (see table 3a).

b) Tasks acting as indicators of specific executive functions (see tables 3b and 3c).

*Table 3a. Shows the mean RT in milliseconds (SD bracketed) for the experimental and control groups in: executive function (incongruent vs. congruent flanker); alertness (no signal vs. double signal); and orientation (central signal vs. spatial signal).*

| | Experimental Group | Control Group |
|---|---|---|
| **ANT** | **MS** | CN |
| Neutral flanker | 737.3 (183) | 500.9(95.6) |
| Congruent flanker | 745.2 (188.5) | 505.9 (100.9) |
| Incongruent flanker | 847.1 (204.8) | 608.8 (126.1) |
| No signal | 795.9 (193.6) | 573.1 (120) |
| Central signal | 782.4 (201.3) | 547,2(119.8) |
| Double signal | 765.8 (193.8) | 533.3(118.9) |
| Spatial Signal | 752.1 (200.4) | 496.6(102.8) |

Analyzing the data shown in table 3a, it was observed that mean RT was higher for the MS group than the control group, $F$ (1, 46) = 53.36, $p < .000$, and the size of the effect was extra-large, with a $d$ of 2.15 and an OL% of 15. The effect of congruence between the target and flanker arrows was significant, $F$ (2, 92) = 250.88, $p < .000$, the difference between both conditions was of 102 ms. The congruence effect did not differ between the MS and control groups, $F$ (1, 46) = .96, $p < .033$.

The effect of alertness, that is, the difference between the no signal and double signal conditions was significant both in the MS group, $F$ = 37.62, $p < .000$, and the control group, $F$ = 77.57, $p < .000$ (30 ms and 40 ms of difference respectively). The difference between groups with respect to alertness was marginally significant, $F$ (1, 46) = 3.57, $p < .006$.

The orientation effect, that is, the difference between the central and spatial signal conditions was of 30 ms for the MS group, $F$ (1, 46) = 25.29, $p < .000$; and of 51 ms for the control group, $F$ (1, 46) = 68.61, $p < .000$. The MS and control groups differed in the magnitude of the orientation effect, $F$ (1, 46) = 5.29, $p < .02$.

Between group differences in alertness and orientation had a medium sized effect, with $d$ values of .45 and .72 respectively, that is, an overlap of about 60%. There were no differences in the accuracy of responses, which was of 98% for controls and 96% for patients.

Summarizing, Fan and Posner's ANT did not succeed completely in discriminating between the MS and control groups. MS patients were slower, but they were equally accurate than the control group. MS patients showed as well a smaller orientation or attentional capture effect and a marginally smaller alertness.

Turning now to the tasks that acted as indicators of specific executive functions, results showed that the MS and control groups differed in the three measures obtained. See tables 3b and 3c.

*Table 3b. RT and percentage error (SD bracketed) for the experimental and control groups in the measures of specific executive functions. The statistic refers to the RT dependent variable. Significant differences are marked with an asterisk.*

| | Experimental Group | Control Group | Statistic | |
|---|---|---|---|---|
| **Executive Function Measures** | **EM** | CN | *F* | *P* |
| N-1 task | 78% - 616.3 (234.4) | 84% - 439.2 (74.2) | 3.97 | 0.051 |
| N-2 task | 65% - 998.8 (299.1) | 68% - 656.1 (220.5) | 5.39 | 0.02 (*) |
| Task-shift trials | 87% - 833.8 (198.4) | 93% - 444.5 (92.8) | 6.96 | 0.01 (*) |
| Task-repeat trials | 93% - 761.1 (193) | 97% - 395 (90.8) | 7.49 | 0.08 (*) |
| Congruent spatial Stroop | 92% - 745.6 (236.9) | 96% - 358.1 (78.2) | 6.30 | 0.01 (*) |
| Incongruent spatial Stroop | 91% - 860 (277.5) | 96% - 422.5 (94.4) | 4.28 | 0.04 (*) |

*Table 3c. Effect size for the executive function measures.*

| **Group differences** | Cohen's *d* | OL% | Effect size |
|---|---|---|---|
| Switching cost | 4 | 2.3 | Extra-large |
| Memory load | 0.8 | 52.6 | Large |
| Spatial Stroop | 1.7 | 24.6 | Extra-large |

*N-back task.* The MS and control groups were compared in two versions of a WM task, which consisted in indicating whether the target in trial N was the same or different that the target in trial N-1 (version 1), or the target in trial N-2 (version 2). Version 1 is easier than version 2, as the latter entails a higher load of WM, but both versions imply online maintaining of information. With respect to accuracy of responses, the effect of memory load (N-2 vs. N-1) was significant, $F$ (1, 50) = 94.09, $p$ < .000, although similar for the two groups (13% errors for the MS group; 16% errors for the control group). The main between-group difference was observed in RT, the increase in RT when moving from then N-1 to the N-2 condition was 400 ms. for the MS group and 200 ms. for the control group, $F$ (1, 50) = 5.40, $p$ < .002. The differences in RT between the N-1 and N-2 conditions were significant both for the MS group, $F$ (1, 50) = 57.59, $p$ < .000, and the control group, $F$ (1, 50) = 18.52, $p$ < .000. Finally, the difference in mean RT between both groups was also significant, $F$ (1, 50) = 26.48, $p$ < .000. Effect size for the latter difference was large (Cohen's $d$ = 1.3; OL% = 34.7) and, as can be seen in table 3c, the size of the memory load effect was large to differentiate between groups.

*Task-switching paradigm*. The measure of cognitive flexibility, the task-switching cost, is computed from the difference between task-shift and task-repeat trials, the tasks being to indicate the colour of the stimulus or to judge if it is odd or even. Both tasks were presented in regular sequences of three repetitions. The magnitude of the RT switching costs differed for the MS and control groups (72 vs. 49 respectively), $F$ (1, 50) = 6.90, $p$ < .001. The switching cost was significant for both groups, $F$ (1, 50) = 136.52, $p$ < .000, for the MS group, and $F$ (1, 50) = 63.23, $p$ < .000, for the control group. Accuracy switching costs were also significant, $F$ (1, 50) = 86.05, $p$ < .000, but the interaction with group was not, $F$ (1, 50) = 1.60, $p$ < .21 (5% mean percentage error for both groups). However, mean accuracy differed between groups, 95% for the control group and 90% for the MS group, $F$ (1, 50) = 4.84, $p$ < .003. Effect size for the RT difference between the two groups was extra-large (Cohen's $d$ = 2.6; OL% = 10.7%). The effect size for the difference between groups respect to the switching cost was also extra-large, that is, this measure discriminates well between patients and controls.

*Spatial Stroop*. Regarding RT, all of the effects were significant, that is: the difference in mean RT between groups, $F$ (1, 50) = 61.86, $p$ < .000; the general difference between the congruent and incongruent conditions, $F$ (1, 50) = 80.19, $p$ < .000; the congruent-incongruent difference both for the MS, $F$ (1, 50) = 65.72, $p$ < .000, and control groups, $F$ (1, 50) = 20.77, $p$ < .000; and finally, the interaction between the congruence effect and group, $F$ (1, 50) = 6.90, $p$ < .001. Regarding accuracy of responses, only the general difference between groups was significant, $F$ (1, 50) = 4.28, $p$ < .04. The effect size for the differences in RT between both groups was extra-large

(Cohen's $d$ = 2.4, OL = 13%), moreover the comparison of the congruence effect between groups yielded differing results: 64 ms. for controls, 115 ms. for patients.

In summary, patients showed again slower RT's but equal accuracy than controls. All of the executive function measures produced significant between-group differences; patients showed larger switching costs, larger congruence effects and suffered more from the increase in memory load. In order to verify the proposed independence of these three measures we calculated the correlations between them, finding that: the correlation between the switching task and n-back tasks was significant (.60); the correlation between the switching task and Stroop tasks was significant (.67), and the correlation between the n-back task and Stroop tasks was also significant (.51). These correlations would seem to indicate that the three tasks measure the same, though not completely, as the R squared values indicate that only a 25% to 36% is explained by a common factor.

Effects of practice and fatigue

Note that all the RT attentional tasks used consisted of a maximum of 360 trials divided in 12 blocks of 30 trials each, this allowed us to study the effects of practice and fatigue. We found that fatigue affects mainly in the RT, not in the accuracy. In RT, the interaction between group and block was significant, $F$ (2, 9) = 6.86, $p < .01$. Patients showed both an effect of practice and sustained attention problems. The practice effect was evidenced in that the RT descended from the first block of trials (mean RT: 915 ms. for patients; 530 for controls) until block 7 (mean RT: 725 ms. for patients; 400 ms. for controls). The sustained attention problems were revealed by the fact that, only for patients, the mean RT increase significantly from block 7 to block 12 (800 ms.), while for the control group RT kept stable (425 ms. in block 12). Effect size for the mentioned difference was: $d$ = 1.7, OL% = 24.6

4. Correlation Matrices

We turn now to the results form the correlation matrices between the attentional tasks and tests employed in this study. Rather than presenting the complete set of results in a single table, which would be difficult to interpret, we decided to present a series of smaller tables aimed to answer our research questions.

First, table 4a presents the correlation between attentional RT tasks and attentional psychometric tests. These results are the novel contribution of this study, as they tell us whether measures developed in different research fields (clinical and cognitive psychology) do actually measure the same thing. The magnitude of these correlations is then compared to the magnitude of the correlation between the attentional psychometric tests (table 4b), and to the magnitude of the correlation between the attentional RT tasks (tables 4c and 4d).

Second, correlations of the measures of Posner's attentional networks (ANT) with the attentional psychometric tests (table 4f) and the attentional RT tasks (table 4e) are also provided.

*Table 4a. Correlations between attentional RT tasks and attentional psychometric tests. Significant correlations are marked with an asterisk.*

| Correlation Matrix | Ponsford and Kinsella | VSAT | D2 | Zoo Map |
|---|---|---|---|---|
| **Task switching** | 0.41 (*) | -0.77(*) | -0.32 (*) | -0.29 (*) |
| **N-back** | 0.50 (*) | -0.63 (*) | -0.40 (*) | -0.43 (*) |
| **Spatial Stroop** | 0.42 (*) | -0.59 (*) | -0.35 (*) | -0.32 (*) |
| **Executive function average** | 0.46 (*) | -0.69 (*) | -0.35 (*) | -0.36 (*) |

*Table 4b. Correlations between the attentional psychometric tests. Significant correlations are marked with an asterisk.*

| Correlation Matrix | Ponsford and Kinsella | VSAT | D2 | Zoo Map |
|---|---|---|---|---|
| **Ponsford and Kinsella** | 1 | -0.57(*) | -0.19 | -0.31(*) |
| **VSAT** | -0.57(*) | 1 | 0.37(*) | 0.26 |
| **D2** | -0.19 | 0.37(*) | 1 | 0.32(*) |
| **Zoo Map** | -0.31(*) | 0.26 | 0.32(*) | 1 |

*Table 4c. Correlations between measures of specific executive functions. Significant correlations are marked with an asterisk.*

| Correlation Matrix | Task switching cost | N-back | Spatial Stroop |
|---|---|---|---|
| **Task switching cost** | 1 | 0.60(*) | 0.67(*) |
| **N-back** | 0.60(*) | 1 | 0.51(*) |
| **Spatial Stroop** | 0.67(*) | 0.51(*) | 1 |

*Table 4d. Correlations between the measures of Posner's attentional networks in the ANT. Significant correlations are marked with an asterisk.*

| Correlation Matrix | Control | Orientation | Alertness |
|---|---|---|---|
| **Control** | 1 | -0.08 | 0.08 |
| **Orientation** | -0.08 | 1 | 0.04 |
| **Alertness** | 0.08 | 0.04 | 1 |

*Table 4e. Correlations between measures of specific executive functions and measures of Posner's attentional networks. Significant correlations are marked with an asterisk.*

| Correlation Matrix | Control | Orientation | Alertness |
|---|---|---|---|
| **Task switching cost** | 0.16 | -0.35 (*) | -0.12 |
| **N-back** | 0.26 | -0.18 | -0.09 |

| | | | |
|---|---|---|---|
| **Spatial Stroop** | 0.15 | -0.32 (*) | -0.16 |

*Table 4f. Correlations between attentional psychometric test and measures of Posner's attentional networks. Significant correlations are marked with an asterisk.*

| **Correlation Matrix** | **Control** | **Orientation** | **Alertness** |
|---|---|---|---|
| **Ponsford and Kinsella** | 0.10 | -0.13 | - 0.13 |
| **VSAT** | -0.25 | 0.33 (*) | 0.22 |
| **D2** | -0.22 | -0.31 (*) | - 0.22 |
| **Zoo Map** | 0.08 | -0.13 | 0.09 |

The highest correlations were observed between the RT measures of specific executive functions (an average of .60). This correlation significantly differs from the rest, $p < .05$. The correlation between traditional psychometric measures of attention and RT measures of specific executive functions is negative; the largest correlation is with the VSAT (-.60), while with the other tests is an average of -.35, the difference is significant. Attentional psychometric tests correlate between them an average of .30. Ponsford and Kinsella's questionnaire correlates positively with the executive functions measures (.40), but negatively with the remaining psychometric test (-.32), the difference is significant. The measures of Posner´s attentional networks do not correlate between them, neither with the other attentional measures, except for the orientation measure in VSAT and d2 (-.32). However, the same orientation measures also correlate with the measures from the switching and Stroop tasks (-.34). Therefore, Ponsford and Kinsella's questionnaire and the RT measures of specific executive functions constitute valid measures. The VSAT is also a good measure of selective attention.

5. Effect of non attentional measures over performance in attentional tasks.

So far we have exhaustively contrasted the attentional hypothesis of MS. However, we also want to highlight the interaction between this attentional problem and certain clinical variables. It seems clear that the main cause of the cognitive deficits observed in MS is not a general cognitive deterioration, as indicated by the MMSE results. However, MS patients do exhibit specific cognitive deficits, as slowing in information processing speed or specific attentional problems.

*The role of slowness in information processing*

The general slowing in information processing could be at the base of the patients' cognitive deficits, they are as accurate as controls are, but slower. RT differences between groups are clear-cut, and exhibit extra-large effect sizes. However, if slowness was the main cause of the cognitive deficits in RRMS, then all of the attentional tasks involving priority instructions and temporal pressure should be affected to the same extent, but this is not the case. Patients' do well in many of the components of the d2 test, the ANT and the Zoo map, but have problems in the VSAT and some measurements of executive functions, despite the fact that all these tasks posit similar demands on processing speed.

As said above, the motivational hypothesis states that cognitive deficits associated to RRMS are caused by motivational or emotional problems (anxiety and depression). Indeed, many of our patients showed high scores in depression and trait

anxiety. In the following paragraphs, we evaluate how theses scores affect the performance in attentional tasks.

*The role of depression*

Participants were divided in three groups with respect to their depression scores (no, low and severe depression). The analyses of the interaction between the depression group variable with the various attentional measures yielded some significant results: N-back task (N-2), $F$ (2, 23) = 6.13, $p < .00$; Ponsford and Kinsella's questionnaire, $F$ (2, 23) = 7.52, $p < .00$; and VSAT, $F$ (2, 23) = 6.78, $p < .00$. RT´s for the N-2 condition in the N-back task were much lower for the no depression group (750 ms. mean RT), than for the low and severe depression groups (1050 ms and 1160 ms. mean RT respectively). Scores in Ponsford and Kinsella's questionnaire were 10 for the no depression group, 20 for the low depression group, and 30 for the severe depression group. Finally, in the VSAT, the no depression group detected an average 120 targets, while the average for the other two groups was of 80 targets. Thus, in the mentioned tests, participants in the no depression group are faster, more accurate and do exhibit less attentional deficits.

*The role of anxiety*

As with depression, participants were also divided in three groups regarding their levels of anxiety (low, medium and high anxiety). There were significant interactions between the anxiety group variable and two attentional measures: Ponsford and Kinsella´s questionnaire, $F$ (2, 23) = 3.73, $p < .003$; and the VSAT, $F$ (2, 23) = 3.27, $p < .005$. In Ponsford and Kinsella´s questionnaire, scores were 11 for the low anxiety group, 18 for the medium anxiety group and 26 for the high anxiety group. In the VSAT the number of targets detected was 123, 85 and 83 for the low, medium and high anxiety groups respectively. Therefore, participants with higher levels of anxiety perceive that they have more attentional problems, and they are less efficient in the visual search task. No other differences in attentional measures were found for the different anxiety groups.

Turning to the correlations between measures of depression and anxiety and performance in attentional tasks, only the N-2 condition in the N-back task and Ponsford and Kinsella's questionnaire showed significant interactions with the BDI and STAI scores. The N-2 condition showed a correlation of .59 with the BDI, and of .55 with the STAI. Ponsford and Kinsella's questionnaire correlations were .49 with the BDI, and .59 with the STAI. Correlations with the VSAT were negative and non significant (-.31 with the BDI; -.28 with the STAI). The remaining correlations were also negative and non significant, ranging from -.20 to -.28.

It can be concluded that the levels of depression and anxiety can impair performance in attentional tasks, and must therefore be taken into account, although they cannot fully explain the pattern of results. Moreover, patients with depressive symptoms are generally slower, but this does not affect their performance in many of the attentional tasks. Therefore, the latter observation provides indirect evidence that the slowness in information processing is not the cause of the attentional deficits associated to RRMS.

*The role of psychomotor problems*

Psychomotor problems could be at the base of the slow processing of information, but they cannot explain the full pattern of results Thus, the psychomotor component was present both in the VSAT and the Zoo map test, but our participants only showed problems with the former. The great majority of participants did not show any psychomotor or functional impairments. Regarding RT tasks, the psychomotor component on these is minimal, and lower than in pen and paper tasks, as they only require key presses. However, patients' mean RT in these tasks was much higher than the control groups', despite the fact that all of the RT tasks placed the same demands on the psychomotor component. Therefore, as happened with general cognitive deterioration and slowness in information processing, psychomotor problems cannot explain the present pattern of results.

*The role of the treatment and the EDSS score*

Finally, we studied the role of treatment (*interferon beta*) and functional disability on the participants´ cognitive performance. Patients were divided in two groups depending on whether they received treatment or not. No interactions with the variable treatment were significant. Patients were also divided in three groups regarding their EDSS scores: low (1 point), medium (1.5 to 2.5 points), and high (3 to 4 points), the three groups were approximately the same size. The EDDS group variable interacted with the VSAT, $F$ (2, 23) = 5.60, $p < .001$, and with the treatment variable, $F$ (2, 23) = 5.22, $p < .001$. With respect to the VSAT, there was an inverse relation between performance in this test and EDDS scores (120, 110 and 60 for the low, medium and high EDDS groups respectively). Regarding the treatment variable, the patients with higher scores on the EDDS were more likely to have received treatment. In the low EDDS group only two patients received treatments, whereas for patients in the other two groups the likelihood of having received treatment was of 80%.

## General Discussion

Listed below are the main conclusions to derive from this study:

1. Patients are slower than controls.
2. Patients are equally accurate than controls.
3. Patients perceive themselves as having attentional problems.
4. Patients exhibit depressive symptoms and high trait anxiety.
5. The motivational status (lack or excess of activation) affects the self-perception of attentional problems (Ponsford and Kinsella's questionnaire), and the performance in certain attentional tasks (VSAT, N-2 N-back).
6. Processing speed does not affect performance in every attentional task.
7. Performance in attentional tasks is not affected by the patients' having received treatment.
8. EDDS scores do not predict performance in attentional tasks (except VSAT).
9. Patients do not show a general cognitive deterioration.
10. The pattern of correlations indicates that not all attentional tasks measure the same construct.
11. The correlations between attentional tasks are higher than the correlations of attentional with non attentional tasks.
12. The correlation between tasks measuring the same attentional component (i.e. executive functions) is higher.
13. The correlation between RT tasks is higher than the correlation between psychometric tests.

14. The ANT does not discriminate between participants and controls, and the pattern of correlation between its components is of little significance (which was to be expected, as the three attentional networks are independent). However, the latter is also true for the correlations between ANT components and other attentional measures, despite the fact that, theoretically, they measure the same thing (executive function, selection and sustained attention).
15. RT tasks seem better suited to detect attentional problems in RRMS than psychometric tests, with the exceptions of the VSAT (a very sensitive psychometric task), and the ANT (an RT task with little sensitivity).
16. Patients exhibit moderate deficits in visual search, orientation, cognitive flexibility, interference control and WM.
17. Patients do not exhibit deficits in planning, alertness or concentration.
18. Patients exhibit little fatigue and mild sustained attention problems.

In light of the results depicted above, we can discard the considered hypotheses in favour of the attentional hypotheses. In what follows we intend to ground this affirmation.

MS patients exhibit diverse and specific attentional deficits. That is, the keep an attentional profile, consisting in a series of specific impairments in visual selective attention, (visual search and attentional capture), executive function (cognitive flexibility, WM capacity, capacity to overcome automatic responses), and sustained attention (fatigue problems). However, some aspects of these attentional components remain unaffected (concentration, and accuracy in selective attention; alertness; and interference from distractors, and maintaining information with low memory loads in executive control).

*Contradictions in previous results*

So far, research on cognitive deterioration in MS has offered contradictory results: sometimes patients exhibited attentional deficits and sometimes not. With respect to RRMS, and considering our data, these attentional deficits are generally moderate, as pointed by the size of the effects observed. Thus, to detect these effects is necessary to use tests with a great statistical power or a good selection of attentional tasks. We hope to have evidenced that attention is not a unitary function, and that its assessment requires sampling all of its components. This assessment is not possible in large protocols, neither in brief batteries; rather, protocols of intermediate duration focused on specific functions are needed. Results like those offered in this study can help to select the most sensitive attentional tasks, be it for large protocols or for short screening tests. Moreover, our data indicates that RT tasks are more sensitive than psychometric tasks when trying to detect cognitive deficits in RRMS, possibly due to its focus on specific attentional functions. The latter affirmation is supported by the pattern of correlations between the diverse attentional tasks: the correlation is higher between tasks measuring the same attentional component than between general tasks. It is thus essential to bring together the fields of clinical and cognitive psychology, even though results are not always positive (as it happened with the ANT). The reliability of the VSAT and Ponsford and Kinsella´s questionnaire should also be highlighted.

In summary, except for the VSAT and the switching and Stroop RT tasks (which discriminate between patients and controls in 75% of the cases), the tests and tasks employed in this study do not discriminate well between patients and controls. The

likelihood of correct classification with these tasks averages 50%, therefore, they are of little clinical utility. Another measure that discriminates well between patients and controls is the mean RT.

*Slowness in information processing as the fundamental problem*

MS patients exhibit a slower information processing and larger RT's. The causes of this are not a physical disability, rather, the cause is purely cognitive. As said above, Sandroni et al. (1992) observed that fatigue in MS patients was associated to a slowing in RT's. This does not seem to be the case with our participants, whom show a slowing in information processing, but only a moderate fatigue, which does not correlate with the mentioned slowing (that is, the are slow in all tasks, but they do not get fatigued in all tasks). Some authors identify this slowness with a general cognitive deterioration. But a key question here is whether the cognitive deterioration in RRMS is general or specific. Our data indicates that it is specific (as results in the MMSE are normal). That is, it is possible to exhibit slow information processing without suffering from general cognitive deterioration. For some authors, the slowness is the cause of the attentional and executive deficits and these, in turn, are the cause of the reasoning and memory deficits. Our data indicate that that specific cognitive deterioration in RRMS patients consists in multiple attentional deficits, but it is not fundamentally caused by the slowness in information processing. The correct working of the executive functions implies the participation of other aspects like abstract and conceptual reasoning. Another widespread idea is that the concentration problems are another defining feature of the cognitive profile of MS, which is closely related to reasoning problems (Feinstein, Yopul y Ron, 1992). De Sonneville et al. (2002) assessed information processing and attentional function (divided, focused and sustained attention, and executive function) in the different MS subtypes. Their results highlighted multiple attentional deficits as the cause of the slowness in information processing, which is in turn the cause of the deficits in complex cognitive abilities (everyday life planning and workplace activities). However, our data suggests that these complex cognitive abilities are preserved; despite the multiple attentional and executive deficits shown by patients, most of them can deal with their everyday activities.

*Selective attention*

With respect to selective attention, our results replicate those of Gonzalez-Rosa et al. (2005), whom by means of Posner's orientation paradigm (1980), with central signal (80% validity) found a slowing on patients' RT of 60-90 ms, as well as a lower attentional effect (difference between valid and invalid trials). Our results also indicate a larger RT and less capacity to orientate with the ANT. These problems were confirmed by the results of the VSAT and d2, and both tests showed a moderate but significant correlation with the ANT.

*Executive function*

Foong et al. (1997) studied exhaustively executive function in MS, as previously it had only been studied with abstract reasoning and verbal WM. The main deficits observed were those in verbal fluency, the Stroop task, cognitive assessment, spatial amplitude, WM, and planning tasks, though not all deficits showed the same severity. Thus, in planning and strategy (London Tower), the differences with controls were significant only for the most difficult levels or the task. Results from Foong et al.'s study supported the non unitary character of the executive function, suggesting that it is composed by several independent dimensions, some of which may be preserved in MS.

These deficits in executive functions are independent from any visuoperceptive problems, decline in intelligence, and psychiatric or emotional problems suffered by the patients. Our results are very similar to Foong et al.'s (1997), as they also support the division of the executive function, with some impaired components (i.e., task switching, WM and control of automatic responses), as well as some preserved components (i.e., planning, interference control). The executive dysfunctions shown by our patients are also independent from motor or emotional problems. In the same manner, the differences between patients and controls are only observed in the higher levels of task difficulty (i.e., in the N-back tasks, differences are observed only for the N-2 condition). The main difference between both studies is that in our study the planning ability is preserved, while in Foong's study is impaired.

It is worth referring as well to a study by Stablum et al. (2004), in which cognitive flexibility in EM was assessed by means of the task switching paradigm. In Stablum´s work, task switching costs were higher for MS patients, suggesting a lower cognitive flexibility. Our results replicate those of Stablum et al. (2004), although the magnitude of the effect is lower. One reason for the different magnitude of the effects is that Stablum et al. measured the endogenous switching cost observed when participants cannot anticipate the task switch. In our study, there was a regular sequence of tasks and a constant RSI of 1200 ms., thus enabling participants to anticipate the trials where the task would shift, therefore, we measured the residual task switching cost. The existence of an endogenous and an exogenous or residual component in the switching cost is widely accepted in the literature (e.g. Tornay and Milán, 2001). Therefore, both components of the switching costs seem to be affected in MS patients.

*Attention and cognitive rehabilitation: Future perspectives*

A final question is whether cognitive rehabilitation of these attentional problems could help to improve the other cognitive deficits associated to MS, as problem solving or memory problems. This is an open question, what can be said at this point is that neither functional disability nor general cognitive deterioration can explain the attentional deficits. It is also evident that the assessment of these attentional deficits is key with respect to the possibility of cognitive rehabilitation.

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