Identifying perceptual, motor, and cognitive components contributing to slowness of information processing in Multiple Sclerosis with and without depressive symptoms.

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Introduction: Increasing findings suggest that different components of the stimulus-response pathway (perceptual, motor or cognitive) may account for slowed performance in Multiple Sclerosis (MS). It has also been reported that depressive symptoms (DS) exacerbate slowness in MS. However, no prior studies have explored the independent and joint impact of MS and DS on each of these components in a comprehensive manner. The objective of this work was to identify perceptual, motor, and cognitive components contributing to slowness in MS patients with and without DS. Method: The study includes 33 Relapsing-Remitting MS patients with DS, 33 without DS, and 26 healthy controls. Six information processing components were isolated by means of ANCOVA analyses applied to five Reaction Time tasks. Results: Perceptual, motor, and visual search components were slowed down in MS, as revealed by ANCOVA comparisons between patients without DS, and controls. Moreover, the compounding effect of MS and DS exacerbated deficits in the motor component, and slowed down response selection, as revealed by ANCOVA comparisons between patients with and without DS. Conclusion: DS seem to exacerbate slowness caused by MS in specific processing components. Identifying the effects of having MS and of having both MS and DS may have relevant implications when targeting cognitive and mood interventions.

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Introduction

Cognitive impairment in patients with Multiple Sclerosis (MS) has been reported across a range of cognitive domains (Rao, Leo, Bernardin, & Unverzagt, 1991). A host of studies have suggested that slowed information processing speed (IPS), i.e. an impaired ability to process information as quickly as healthy individuals, represents the key deficit underlying cognitive dysfunction in MS patients (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004).

Contrary to the idea that impaired IPS is a general or global deficit, evidences from different clinical populations have suggested that IPS may be a non-unitary construct (Chiaravalloti et al., 2003; DeLuca & Kalmar, 2007; Hsieh, Chen, Wang, & Lai, 2008; Shum, McFarland, & Bain, 1994). In a recent review about IPS in MS, it has been suggested that several steps compose information processing, starting with the input of information into the sensorial system and extending to the output (action or behavior). In this vein, Costa, Genova, DeLuca, & Chiaravalloti (2016) suggest that at least three major steps or processing components should be considered in order to disentangle the nature of IPS deficits in MS: (1) the transmission of sensorial information, (2) the completion of cognitive tasks, and/or (3) creating motor output. However, existing data are fragmented, including a limited number of components, which makes it difficult to achieve an integrative view on the nature of slowed information processing in MS. On the one hand, most investigations that compare performance of MS patients and healthy controls in simple visual detection Reaction Time (RT) tasks, have suggested slowness affecting the perceptual-motor component (De Sonneville et al., 2002; Reicker, Tombaugh, Walker, & Freedman, 2007). On the other hand, different authors found an inordinate increase of RT when increasing task complexity. This has been generally

interpreted as an evidence of cognitive slowing independent of simpler perceptual and motor factors (Kujala, Portin, Revonsuo, & Ruutiainen, 1994). In order to study specific cognitive mechanisms contributing to the so called cognitive component (e.g., attentional, memory, response selection, decision making, among others), different methods have been used such as subtraction (Parmenter, Shucard, & Shucard, 2007), percent change (Reicker et al., 2007; Tombaugh, Berrigan, Walker, & Freedman, 2010), and covariance analyses (Laatu, Revonsuo, Hämäläinen, Ojanen, & Ruutiainen, 2001). Results from these studies have led to describe a specific pattern of cognitive deficits in MS patients. For instance, focused attention (De Sonneville et al., 2002), sustained attention (De Sonneville et al., 2002; Stoquart-Elsankari, Bottin, Roussel-Pieronne, & Godefroy, 2010), and working memory (Parmenter et al., 2007) seem to be slowed down in MS patients, while response selection (Archibald & Fisk, 2000), interference control (Macniven et al., 2008), and divided attention (Stoquart-Elsankari et al., 2010) appear to remain relatively unaffected. Unfortunately, other well-known processing components such as visual search (Neisser, 1964) or decision-making (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Whyte, Grieb-Neff, Gantz, & Polansky, 2006) which may primarily modulate performance in many of the formerly mentioned cognitive tasks, have been scarcely explored in this population (Utz et al., 2013). Moreover, no previous work has aimed to control for the influence of several different components in the same study by means of a comprehensive well-structured set of RT tasks, in an homogenous sample of MS patients.

Another important aspect regarding current investigations in MS concerns the role of clinical variables such as depression as a contributing factor to slowness of information processing. Clarifying this is of particular relevance given that depression is one of the

most frequent psychiatric diagnoses in MS patients, affecting between 27% and 54% of all patients (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014), and is known to impact IPS in non-MS depressed patients (Hammar, 2003). Different studies comparing performance of MS patients with and without depression have suggested that depression may exacerbate the slowness caused by MS (Arnett et al., 1999; Lubrini, Periañez, Rios-Lago, & Frank, 2012; Lubrini et al., 2016). For instance, in an experimental design including four groups of MS patients with and without depressive symptoms (DS), depressed patients without MS, and healthy controls, Lubrini et al. (2016) described a compounding effect where having MS and DS did worsen performance in the more demanding tasks, as compared to both having MS or depression alone. However, investigations trying to determine which processing components are slowed down in MS, have not considered the contributing role of depression to MS patients' slowness. In this regard, it could be that depression may exacerbate the impairment of the components affected by MS or generate impairment in new ones. At this point, most prior studies have attempted to control for the effect of depression either by using samples with low or no depression, or by controlling its effect statistically, without disentangling the relative effect of MS and depression (Archibald & Fisk, 2000; Parmenter et al., 2007; Reicker et al., 2007; Tombaugh et al., 2010).

Given the already demonstrated effect of MS in a set of RTs tasks (Lubrini et al., 2016), the first aim of this study was to identify which information processing components may underlie RT slowness in MS patients. Second, and given that DS seems to exacerbate cognitive slowness (Lubrini et al., 2016), we aimed to identify the components responsible for the additional RTs slowness associated with DS. In consonance with preceding literature, we first hypothesized that if RT slowness is not a

generalized phenomenon, then differences between healthy controls and MS without DS will selectively affect some components with others being preserved. Second, we hypothesized that, if the compounding effect (i.e., the increasing RTs associated to depression in MS) is due to the worsening of those processing components already affected by MS, then differences between MS with and without DS will appear in the same components affected by MS. Alternatively, if the compounding effect is due to the impairment of new components, then differences between MS with and without DS will appear in those not affected by MS.

Method

Participants

Sixty-six right-handed MS patients were divided in two groups according to the presence of DS defined by a cut-off score ≥ 13 in the Spanish version of the Beck Depression Inventory (BDI; Sanz & Vázquez, 1998; Stoquart-Elsankari et al., 2010). As a result, 33 MS patients were included in the group without DS and 33 patients in the group with DS. Given the questioned utility of the BDI in MS patients due to the high load of vegetative symptoms, this classification was tested with the method described by Strober and Arnett (2010) was applied. Applying this methodology did not change the original classification. Also, 26 right-handed healthy controls (BDI score < 13) matched in age and education with the two groups of patients were included. Eligibility criteria for all participants were absence of severe motor or visual impairment that might interfere with testing; no premorbid history of learning disabilities; and no history of alcohol or drug abuse or nervous system disorder. Eligibility criteria for patients were: diagnosis of MS according to McDonald's criteria (Polman et al., 2005); diagnosis of a Relapsing Remitting course of MS; score on the Expanded Disability Status Scale (EDSS) < 6 (Kurtzke, 1983); and not having experienced a relapse or been

treated with corticoids in the one-month time window before the experimental session. Demographic and clinical features of all participants are shown in Table 1. The Ethics Committee of the institution approved the study. Subjects were informed about the purpose of the investigation before the experimental session and signed a consent form according to the Declaration of Helsinki. The sample presented here partially overlaps the group studied in Lubrini et al. (2016).

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Experimental tasks and procedures

Participants were examined with five RT tasks (Fig. 1) within the context of a larger neuropsychological assessment. Evaluation was completed in a single session lasting between 70 and 90 min. All testing was performed using a PC with a 17-inches monitor that was controlled by Presentation® software (http://www.neurobs.com). The order of task presentation was counterbalanced across participants. Both speed (RTs from correct trials) and accuracy (percent of correct responses) were measured in all tasks.

Finger Tapping task (FT): FT was used as a measure of motor function (Reitan & Wolfson, 1996). It has shown sensitivity to generalized slowing of responses (Strauss, Sherman, & Spreen, 2006), involving motor performance with only minimal amounts of central resources required in more complex measures of speeded perceptual processing (Kennedy, Clement, & Curtiss, 2003). Reliability coefficient ranges from .58 to .93 in

both healthy and clinical samples (Strauss et al., 2006)**.** In MS studies, it has been explicitly used as a measure of motor speed (Stoquart-Elsankari et al., 2010).
In the present experiment, following application norms described by Strauss et al. (2006), participants were instructed to press repeatedly, and as fast as possible, the spacebar of a computer keyboard**.** The task consisted of five trials of 10 sec. duration each to be performed with the index finger of the dominant hand. The average time between two consecutive taps in the five trials was the dependent variable.

Simple Reaction Time (SRT): SRT task was used as a measure of simple perceptual, motor, and sustained alertness processes (Jensen, 2006). According to this author, a larger fraction of the subjects' SRT consists of the time needed for the sensory transduction and neural transmission of the stimulus to the brain and thence for the neural transmission to the muscles. In the MS literature, the SRT task has been used as one of the simplest and purest ways to assess IPS. Consequently, many studies use it as a baseline or control measure of more complex processing speed tasks (Reicker et al., 2007; Stoquart-Elsankari et al., 2010; Tombaugh et al., 2010). SRT reliability tends to be high given that it shows virtually no practice effect after the first 10 trials (Teichner & Krebs, 1974). In the present experiment, following application norms described by Reicker et al., (2007), participants were instructed to press the left button of the mouse with the index finger of their dominant hand as quickly as possible when the stimulus "+" appeared in the center of the computer screen. The task consisted of 50 trials with a total task duration of 2-3 min.

Simple Reaction Time-Sustained Attention to Response Task (SRT-SART): SRT –SART task was used as a measure of response strategy-inhibition (Carter, Russell, & Helton,

2013). Significant Pearson's product-movement correlations have been found between SART RT to correct trials, and No Go errors (r=-.82; p<.001; Seli, 2016), suggesting that both scores provide useful measures of response strategy-inhibition. In the present experiment, following application norms described by Robertson et al. (1997), participants were instructed to press the left button of the mouse with the right index finger whenever a stimulus (a digit between 1 and 9) appeared in the center of the screen, but not to press if the digit shown was number 3. The task consisted of 189 trials (21 of them were No Go trials) with a total task duration of approximately 4 min.

Choice Reaction Time (CRT): CRT task was used as a measure of visual perceptual decision time. It has been related to the same processes involved in the SRT plus the processing of uncertainty as to which one of the stimulus would appear next, that is, decisional processing (Jensen, 2006; Pipingas et al., 2010). Test-retest reliability coefficient scored .81 (Pipingas et al., 2010). The CRT task has been used in previous research on IPS in MS (Reicker et al., 2007; Stoquart-Elsankari et al., 2010; Tombaugh et al., 2010). In this task, derived from Visual Choice Reaction Time task (Chiaravalloti et al., 2003), participants were instructed to press the left or the right button of the mouse every time a square or a circle, respectively, appeared in the middle of the screen. The task consisted of 80 trials. Total task duration was approximately 3 min.

Choice Reaction Time-Search (CRT-Search): CRT-Search task was used as a measure of visual search (Neisser, 1964). In this task, derived from Neisser's paradigms (1964), participants were told to press the left or right button of the mouse depending respectively on the presence or absence of the letter "Z" in a string of six letters. The task consisted of 128 trials. Total task duration varied between 5 and 8 min. Stimuli

were classified according to two different dimensions: presence/absence of the letter "Z" (Type of Stimulus: Target vs. Non Target), and the visual features of the letters in the string (rounded or angular; Level of Interference: Low vs. High, respectively). Thus, the combination of Type of Stimulus and Level of Interference resulted in four different trial types: Target-Low Interference (e.g., GODZCQ); Target-High Interference (e.g., VWMZEX); Non Target-Low Interference (e.g., CQUGRD); Non Target-High Interference (e.g., VXWEIM). A visual search component can be measured by comparing RTs in the "Non Target-Low Interference" condition of the CRT-Search task with RTs in the "Target-Low Interference" condition. At this regard, "Target-Low Interference" and "Non-Target-Low Interference" conditions differ in the difficulty of the search, as described in preceding experimental research (Neisser, 1964; Treisman, 1988). Accordingly, the "Target-Low Interference" condition would involve a fast, parallel, and unlimited capacity pre-attentive processing since the presence of the target flanked by dissimilar distracters will allow a "pop-out" detection of its basic features. On the contrary, the lack of targets in the "Non-Target-Low Interference" condition would impel a subsequent slower, serial spatially-limited attention-demanding processing, thus increasing RT (Treisman, 1988).

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Analysis

Group differences in demographic and clinical variables (sex, age, education, estimated premorbid IQ (Bilbao-Bilbao & Seisdedos, 2004), disease duration, EDSS, and BDI score) were determined by means of t-tests or Chi square statistical tests where

appropriate. The total number of medications with a psychomotor effect was also compared between the two groups of patients. Drug categories considered for this analysis included antispasmodics and muscle relaxants, tricyclic antidepressants, anticholinergics, and benzodiazepines (Arnett et al., 1999). Pearson's product-moment correlations analyses between mean RT and percentage of correct responses per task for each group were performed as a precaution against speed-accuracy trade off phenomenon accounting for RT modulations (De Sonneville et al., 2002).

In order to explore the first hypothesis regarding the processing components accounting for RT slowness in MS, comparisons were performed between healthy controls and MS patients without DS. In order to explore the second hypothesis regarding the processing components being affected by the compounding effect, comparisons were performed between MS patients with and without DS. Between group comparisons in the different components were performed by means of a series of independent sample t-tests and ANCOVAs according to the following rationale: (1) The presence of information processing slowness associated to a "motor" component was analyzed by means of independent sample t-tests comparing the FT task between groups; (2) The presence of information processing slowness associated to a perceptual, motor, and sustained alertness components, henceforth referred to as "perceptual-motor-alertness", were analyzed by means of independent sample t-tests comparing RT to the SRT task between groups; (3) The presence of information processing slowness associated to a "response strategy-inhibition" component was analyzed by means of an ANCOVA with RT in the SRT-SART task as the dependent variable and RT in the SRT task as the covariate. Using SRT as a covariate allowed controlling for perceptual, motor, and sustained alertness components shared with the SRT-SART task; (4) The presence of

information processing slowness associated to a visual perceptual decision time component henceforth referred to as "decisional", was analyzed by means of an ANCOVA with RTs in the CRT task as the dependent variable and RT in the SRT task as the covariate. At this regard, CRT has been related to the same processes involved in the SRT plus the decisional processing (Jensen, 2006; Pipingas et al., 2010); (5) The presence of information processing slowness associated to a "visual search" component was analyzed by means of an ANCOVA with RTs in the "Non Target-Low Interference" condition of the CRT-Search task as the dependent variable and RTs in the "Target-Low Interference" condition as the covariate. Using the "Target-Low Interference" condition as the covariate allowed controlling for common perceptual, motor, and cognitive processes except for serial visual search as measured in the "Non Target-Low Interference" condition.

A significance level of $p<.05$ was adopted for all analyses. All analyses were performed using SPSS v22.0.

Results

Sample characteristics and preliminary analyses

Table 1 describes participants' demographic and clinical characteristics. No differences were found between MS patients without DS and healthy controls in sex ($\chi2(1) = .001$, $p = .969$), age ($t(57) = 0.4$, $p = .666$), education ($t(57) = -1.8$, $p = .07$), estimated premorbid IQ ($t(57) = -.9$, $p = .368$) or BDI score ($t(57) = 1.3$, $p = .212$). The two groups of MS patients did not differ significantly in any demographic or clinical variable ($p > .157$ in all cases), except for BDI score ($p < .001$). Accuracy was high across tasks and groups ranging between 88% and 99.3% of correct responses (Table 2).

Results of correlation analyses between accuracy and RTs revealed a lack of significant correlations in the MS patients without DS ($p > .095$ in all cases), MS patients with DS ($p > .406$ in all cases), and healthy controls ($p > .054$) with the only exception of the SRT task in the later group ($r=.539$; $p = .005$).

Reaction Times (RTs)

Comparisons between MS patients without DS and healthy controls revealed that, in the FT task, MS patients exhibited increased response times as compared to healthy controls ($t(57) = 2.9$, $p = .006$, $d=.77$, confidence interval (CI) [5.08, 28.6]). Between group comparison in the SRT task revealed that MS patients without DS had increased RT with respect to healthy controls ($t(57) = 2.1$, $p = .036$, $d=.57$, confidence interval (CI) [2.1, 60.27]). The ANCOVA designed to measure the visual search component (as measured in Non Target-Low Interference condition of the CRT-Search task using Target-Low Interference condition as the covariate) revealed that MS patients had slower responses as compared to healthy controls ($F(1, 56) = 4.5$, $p = .039$, $d=.28$, CI [3.33, 128.14]). On the other hand, there were no differences between these groups in the response strategy-inhibition component as measured by the SRT-SART task using the SRT task as covariate ($F(1, 56) = 0.9$, $p = .342$. $d=.13$, CI [-11.41, 32.3], nor in the decisional component as measured by the CRT task using the SRT task as covariate ($F(1, 56) = 0.4$, $p = .508$, $d=.09$, CI [-17.37, 34.67]), see Table 2, and Figure 2).

Comparisons between MS patients with and without DS revealed that, in the FT task, MS patients with DS exhibited increased response times as compared to MS patients without DS ($t(52) = -3.1$, $p = .003$, $d=.77$, confidence interval (CI) [-43.6, -9.6]). Between group comparison in the SRT task revealed that there were no differences

between the groups (t(64) = -.6, p = .53, d=.16, CI [-49.51, 25.71]). The ANCOVA designed to measure the decisional component (as measured in the CRT task using SRT as the covariate) revealed that MS patients with DS had slower responses as compared to MS patients without DS (F(1, 63) = 5.1, p = .027, d=.28, CI [-93.73, -5.86]). No differences were found between groups in the response strategy-inhibition (F(1, 66) = 0.04, p = .849, d=.03, CI [-24.98, 20.61]), nor in the visual search components (F(1, 63) = 1.8, p = .184, d=.17, CI [-122.97, 24.14]; see Table 2, and Figure 3).

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Discussion

Slowness of information processing has been well established as a primary deficit in MS (DeLuca et al., 2004; Lubrini et al., 2016). The aim of this study was to identify which information components of the stimulus-response processing pathway may underlie RT slowness in MS patients with and without DS. Following preceding three-factorial proposals (Costa et al., 2016), motor, perceptual, and cognitive components were studied as potential sources of slowness. Innovatively, this was done by means of a comprehensive set of independent sample t-tests, and analyses of covariance using five RT paradigms. One of the advantages of using ANCOVA as an analytical strategy is that it does not assume any specific functional architecture about the cognitive system

i.e., either serial or parallel. Beside alternative methods being used to control the influence between cognitive components (for example, subtraction or percent change methods), the ANCOVA estimates and controls for the amount of shared variance observed between the dependent variable and the covariate.

Three of the five explored components were found to be slowed down in MS patients as compared to controls. On the one hand, both motor and perceptual-motor-alertness components, as measured in a FT and a SRT tasks, respectively, exhibited a specific impairment in the MS group. These results are consistent with those suggesting that perceptual-motor factors may account for slowness in SRT tasks (Reicker et al., 2007). On the other hand, the visual search cognitive component also revealed differences between MS patients and controls. Thus, MS seems to affect the ability to orient attention for establishing and retaining an efficient search strategy. At this regard, visual search paradigms have not been frequently used in MS. However, the present results agree with those from RT studies demonstrating impairment on the visual search component in MS using a featured-based visual search paradigm (Utz et al., 2013), and are in consonance with prior neuropsychological evidence derived from attention tests involving visual search demands, such as the Trail Making Test (Leavitt et al., 2014), and the Symbol Digit Modalities Test (Arnett et al., 1999). Response strategy-inhibition, and decisional components resulted to be relatively preserved in MS patients, in line with earlier reports (Macniven et al., 2008; Reicker et al., 2007). Taken together, the results showed that different processing components were selectively affected by MS, thus confirming the first hypothesis about the non-generalized nature of slowness of information processing.

In order to clarify whether the compounding effect is due to the worsening of processing components already affected by MS or to the impairment of new components, as established by the second hypothesis, patients with and without DS were compared by means of the same set of t-tests, and ANCOVAs described previously. Two of the five explored components revealed to be impaired in MS patients with DS. While DS did not generate differences in the perceptual-motor-alertness component, differences were found when the motor component was analyzed alone. This result is in consonance with data from non-MS depressed populations showing that depression deteriorates motor speed (Caligiuri & Ellwanger, 2000). Second, while the response strategy-inhibition component was preserved, a marked decline in performance was found in the decisional component. This result indicates that patients with DS were able to mobilize resources to complete controlled tasks so long as a decision between different responses was not required. However, when task demands involved to select between alternative responses (i.e., CRT task), a marked decline in performance was observed (Thomas, Goudemand, & Rousseaux, 1999). None of the remaining components resulted to be affected in the MS with DS group as compared to MS without DS group. Lastly, correlation analyses between mean RTs and the percentage of correct responses in each task for each group revealed, in general, an absence of significant positive correlations that allowed to reject the possibility of an "speed accuracy trade off" effect accounting for the described RT effects (De Sonneville et al., 2002). Taken together, the results showed that the compounding effect is in part due to the worsening of the motor component already affected by MS, and in part due to impairment of the decisional component, which was not primarily affected by MS.

In summary, and contrary to the idea that slowed IPS is a general/global deficit in MS, the present findings suggest that dissociable components of the stimulus-response pathway differentially contributed to patients' slowed performance. While perceptual-motor-sustained alertness (as measures by the FT and STR tasks), and visual search components (as measured by CRT-Search) seemed to be slowed down by MS, the compounding effect of MS and DS exacerbated deficits in the motor component, and slowed down the decisional component. These results have relevant implications for both theoretical models and clinical practice. First, they could help in designing assessment and treatments oriented to specific processing stages according to patients' cognitive profiles. Second, the results suggest that, at least in early stages of MS, targeting mood might represent a potential way to address IPS deficits. This is quite promising given that there is evidence suggesting the effectiveness of both psychological and pharmacological approaches for depression in MS (Feinstein et al., 2014). Moreover, understanding the nature of cognitive dysfunction in MS would be incomplete if the interplay between IPS and DS is not considered. Lastly, taking into account the different subcomponents of the information processing pathway, it seems crucial to describe the causal mechanisms of slowed IPS in MS. As limitations, even when the present report included a wide range of processing components and tasks, further cognitive components using a wider range of tasks as well as the possible interactions between them should be studied in the future. Another limitation, and considering the small sample size, non-significant differences founded should be addressed in the future with larger samples in order to increase the power of analyses. Lastly, and given the potential influence of anxiety on certain IPS measures as evidences by recent researches (Goretti et al., 2014; Morrow, Rosehart, & Pantazopoulos, 2016), this variable should be addressed in forthcoming studies on MS.

Disclosure of interest

None of the authors have any conflicts of interest or financial ties to disclose.

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TABLES

Table 1

Differences in demographic and clinical variables between participants.

	Healthy Controls	MS without DS	MS with DS	*p*
N (male)	26 (8)	33 (10)	33 (11)	.969 [a] .792 [b]
Mean age in years (SD)	39.1 (10.4)	40.1 (8.1)	42.5 (8)	.666 [a] .234 [b]
Mean education in years (SD)	15.3 (4.1)	13.5 (3.4)	13.5 (3.6)	.07 [a] .972 [b]
Mean estimated premorbid IQ (SD)	132.6 (13.2)	129.5 (13.3)	128.7 (12.4)	.368 [a] .804 [b]
Mean BDI score (SD)	5 (3.2)	6 (2.5)	22.7 (6.6)	.212 [a] .001 [b]
Mean EDSS (SD)	-	2 (1.6)	2.6 (1.7)	.157 [b]
Mean MS disease duration in months (SD)	-	116.4 (65.6)	132.6 (99.8)	.437 [b]
Mean number of medication (SD)	-	.2 (.6)	.3 (.6)	.695[b]

Note: BDI: Beck Depression Inventory; EDSS: Expanded Disability Status Scale; DS: depressive symptoms. *p* : *p* value; [a] Comparison between MS without DS and healthy controls ; [b] Comparison between MS with DS and MS without DS ; SD: standard deviation.

Table 2

Means (Standard Deviation) of Reaction Times (RT) in milliseconds and percent of correct responses (% correct) for the RT tasks in the three groups: MS patients with depressive symptoms, MS patients without depressive symptoms, and healthy controls.

		MS with DS	MS without DS	Healthy Controls
FT	RT ms	218.7 (41.8)	192.1 (24.8)	175.2 (18.9)
SRT	RT ms	326.2 (90.8)	314.3 (58.7)	283.2 (50.9)
	% correct	98.3 (3.2)	97.5 (4)	97.8 (2.8)
SRT-SART	RT ms	392.6 (73.5)	382.9 (58.6)	349.2 (55.8)
	% correct	95.5 (2.4)	95.7 (2.8)	96.6 (4)
CRT	RT ms	529.2 (154.4)	466.2 (79)	425.5 (67.1)
	% correct	90.1 (7.8)	88 (16.7)	93 (9.1)
CRT-Search	RT ms	927.2 (251.5)	792.1 (172.8)	655.2 (118)
	% correct	94.9 (3.6)	95.6 (3.3)	96.1 (4)
*Target Low Int.**	RT ms	801.2 (205.6)	693.4 (133.5)	625.3 (109)
	% correct	93.6 (6)	94.6 (5.2)	95.8 (6.2)
*No Target Low Int.**	RT ms	981.7 (316.1)	793.8 (198)	648.4 (163.1)
	% correct	97.6 (2.8)	99.3 (1.7)	98.8 (2.5)

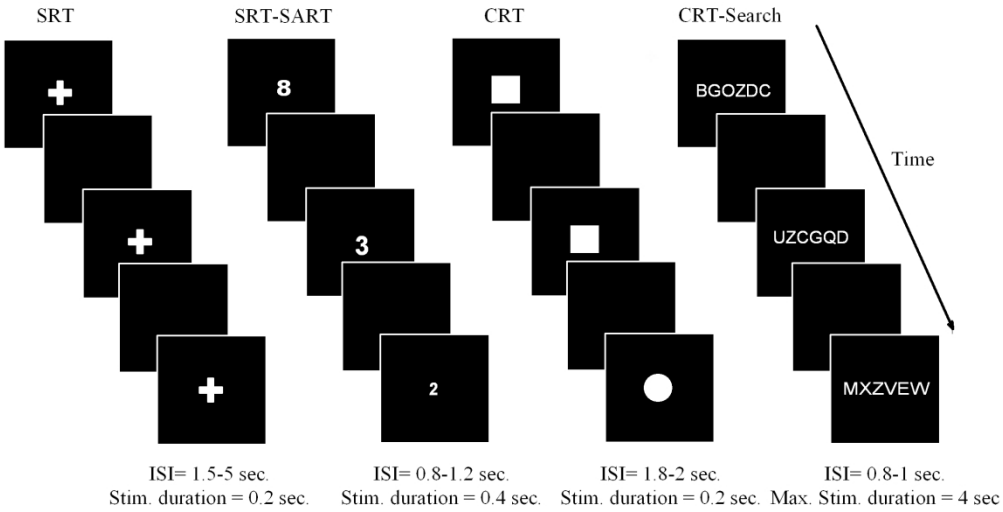
Note: DS: depressive symptoms; FT: Finger Tapping; SRT: Simple Reaction Time task; SRT-SART: Simple Reaction Time-SART task; CRT: Choice Reaction Time task; CRT-Search: Choice Reaction Time-Search task; Int: Interference; *: Conditions of the CRT-Search task.

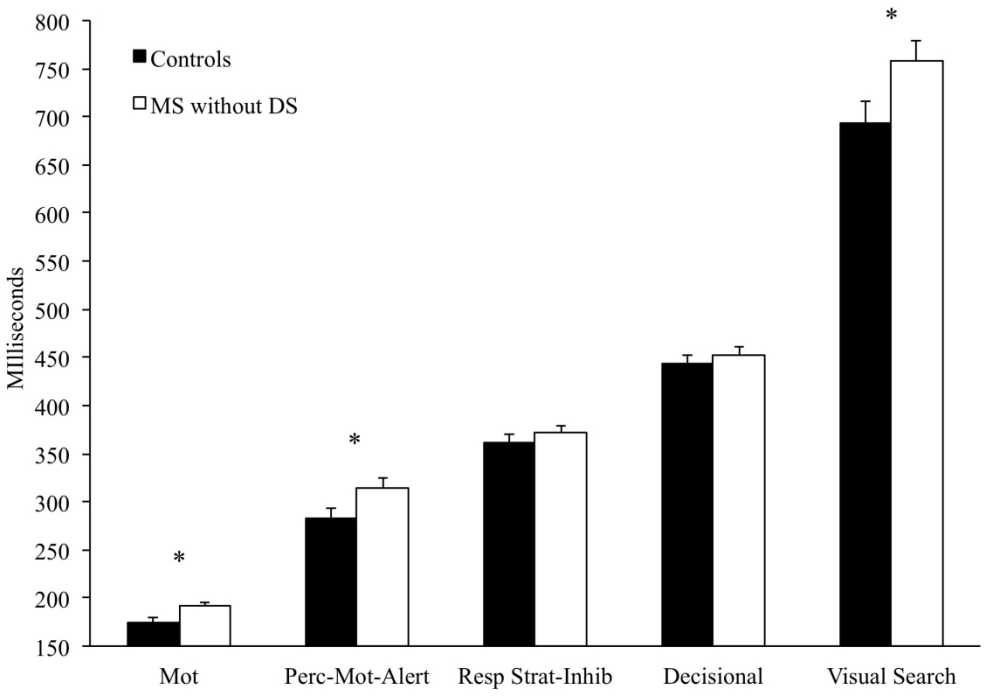
Figure legends

Figure 1. The figure illustrates from left to right a schematic example of stimuli sequence in the Simple Reaction Time (SRT), Simple Reaction Time-Sustained Attention to Response Task (SRT-SART), Choice Reaction Time (CRT), and Choice Reaction Time-Search (CRT-Search) tasks. Inter-Stimulus Interval (ISI) and stimulus duration (Stim. duration) in each task are specified.

Figure 2. Comparisons between Multiple Sclerosis patients without depressive symptoms (MS without DS), and healthy controls in different components of the stimulus-response pathway (motor, perceptual-motor-alertness, response strategy-inhibition, decisional, and visual search). Asterisks indicate statistically significant differences between groups. Mot = motor; Perc-Mot-Alert = perceptual-motor-alertness; Resp Strat-Inhib = response strategy-inhibition.

Figure 3. Comparisons between Multiple Sclerosis patients with and without depressive symptoms (MS with, and without DS) in different components of the stimulus-response pathway (motor, perceptual-motor-alertness, response strategy-inhibition, decisional, and visual search). Asterisks indicate statistically significant differences between groups. Mot = motor; Perc-Mot-Alert = perceptual-motor-alertness; Resp Strat-Inhib = response strategy-inhibition.


SRT
SRT-SART
CRT
CRT-Search
8
3
2
BGOZDC
UZCGQD
MXZVEW
Time
ISI= 1.5-5 sec.
Stim. duration = 0.2 sec.
ISI= 0.8-1.2 sec.
Stim. duration = 0.4 sec.
ISI= 1.8-2 sec.
Stim. duration = 0.2 sec.
ISI= 0.8-1 sec.
Max. Stim. duration = 4 sec



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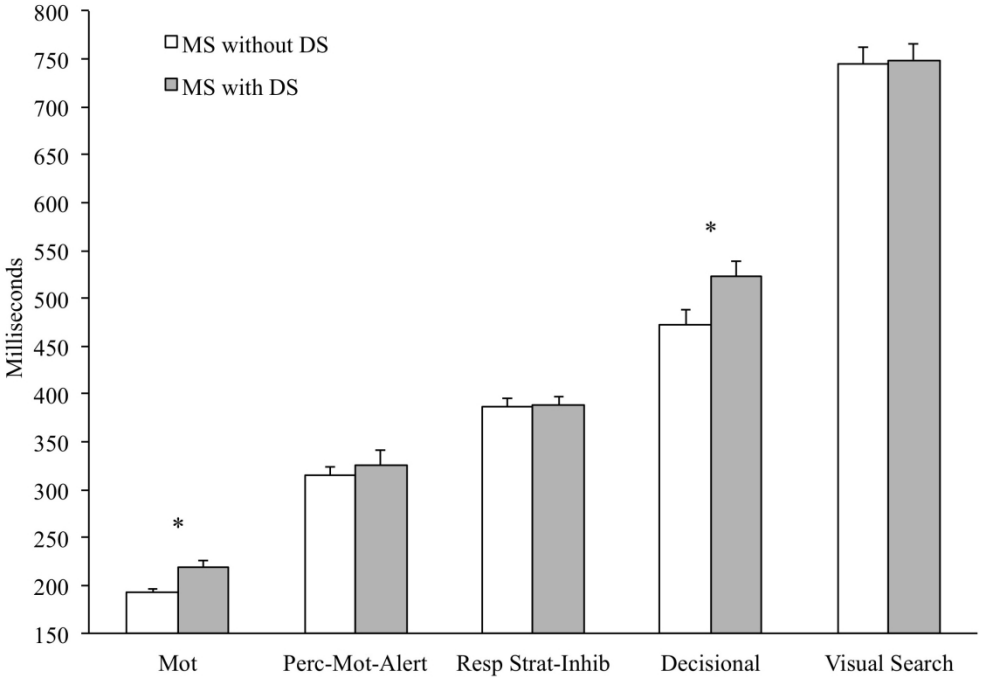

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