

INFORMATION PROCESSING SPEED AND ATTENTION IN MULTIPLE SCLEROSIS

BY

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Abstract

Information processing speed is frequently recognized as the primary cognitive impairment in multiple sclerosis (MS). Recent studies have also reported attention deficits in MS patients compared to healthy controls based on the Attention Network Test (ANT). Performance on the ANT, however, is confounded by group differences in baseline processing speed. This study investigated performance on measures of information processing speed and the ANT in a group of relapsing remitting and secondary progressive MS patients ($n = 40$) and a group of healthy controls ($n=40$). Significant group differences were found across all measures of information processing speed, including a simple reaction time task, a choice reaction time task, and the Stroop task. Performance on the Alerting, Orienting, and Executive Control attention networks of the ANT was assessed using both simple difference scores and residualized scores. The residualized scores controlled for group differences in baseline processing speed. MS patients had a significantly weaker Executive Control function than healthy participants when calculated using difference scores. This difference was no longer significant when calculated using residualized scores. A significant group difference was found for the Alerting network when using residualized scores, such that MS patients performed more poorly than controls. The complexity of the task on the Executive Control network may exacerbate group differences in processing speed. When differences in Executive Control were controlled for, no significant differences were found for any attention network using difference or residualized scores. These results are consistent with the hypothesis that group differences in processing speed are the driving factor in apparent differences in attention. The effects of fatigue on information processing speed and attention as well as differences in performance across MS subtypes were also examined.

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system involving an abnormal immune response resulting in the demyelination and loss of axons. It is characterized by a variety of physical, motor, and sensory impairments. In 43-65 percent of patients, MS is accompanied by cognitive impairment (Benedict et al., 2006; Peyser, Rao, LaRocca, & Kaplan, 1990; Rao, Leo, Bernardin, & Unverzagt, 1991). Specific domains of cognitive functioning affected include executive function, long-term memory, learning, attention, information processing efficiency, and information processing speed; verbal functions and general intelligence appear to be intact (Chiavaralloti & DeLuca, 2008; Prakash, Snook, Lewis, Motl, & Kramer, 2008; Rao, Leo, Bernardin, et al., 1991). Patients with cognitive impairments are more likely to have participated in fewer social activities, be unemployed, have difficulties performing household tasks, and be diagnosed with a psychiatric illness than individuals with physical disability alone (Rao, Leo, Ellington, et al., 1991).

Many investigators view slowed information processing speed as the primary deficit in multiple sclerosis (Archibald & Fisk, 2000; Chiavaralloti & DeLuca, 2008; DeLuca, Chelune, Tulskey, Lengenfelder, & Chiaravalloti, 2004; Denney, Lynch, Parmenter, & Horne, 2004; Macniven, Davis, Bradshaw, Szabadi, & Constantinescu, 2008). Information processing speed has been conceptualized as the speed at which information can be maintained and manipulated in the brain and is operationally measured as the time needed to execute a cognitive task or the amount of tasks that can be completed within a finite period of time (Chiaravalloti & DeLuca, 2008; Goverover, Genova, Hillary, & DeLuca, 2006). Significant differences between individuals with MS and healthy controls have been found consistently across a variety of measures related to processing speed (e.g., Denney, Gallagher, & Lynch, 2011). These differences have been found in tasks of reaction time (RT), such as simple and choice RT tests,

as well as tasks of rapid serial processing, which are characterized by the serial presentation of stimuli requiring a similar rapid response repeatedly, with little variation in the cognitive operation to be executed (e.g., Paced Auditory Serial Addition Task, Symbol Digit Modalities Test, and the Stroop Test; Hughes, Denney, & Lynch, 2011). The ability of individuals with MS to accurately complete tasks does not appear to be impaired; it simply takes them longer to do so (Denney et al., 2011; Hughes et al., 2011; Reicker, Tombaugh, Walker, & Freedman, 2007; Tombaugh, Berrigan, Walker, & Freedman, 2010).

An additional cognitive function frequently studied in the MS population is attention (Crivelli et al., 2011; Kujala, Portin, Revonsuo, Ruutiainen, 1995; McCarthy, Beaumont, Thompson, & Peacock, 2005; Paul, Beatyy, Schneider, Blanco, & Hames, 1998; Penner, Rausch, Kappos, Opwis, & Radu, 2003; Santa Maria et al., 2004; Urbanek et al., 2010). Both sustained and divided attention can be impaired in individuals with MS (McCarthy et al., 2005). Elucidating the specific relationship between MS and attention, however, has been difficult due to variability in how attention has been defined and measured (Chiaravalloti & DeLuca, 2008; Paul et al., 1998; Prakash et al., 2008). Definitions have ranged from broad (e.g., the cognitive processes related to the processing of information) to narrow (e.g., auditory or visual attention or focused, divided, or sustained attention; De Sonneville et al., 2002; McCarthy et al., 2005; Paul et al., 1998).

Further complicating the understanding of attention in MS is the frequent overlap between attention and information processing speed in the literature. The theoretical definitions of these constructs are often redundant, and same or similar measures are frequently used to assess both (De Sonneville et al., 2002; Kujala et al., 1995; Macniven et al., 2008). Additionally, performance on tasks of attention is frequently associated with performance on measures of

processing speed (Chiaravalloti & DeLuca, 2008). It is essential to distinguish between these two concepts, however, in order to develop an accurate profile of cognitive dysfunction in multiple sclerosis.

One's view of the primary cognitive domain affected by MS influences both the course of research as well as treatment considerations for patients. Attention is viewed as a localized function, associated with specific anatomical locations and neurotransmitter systems in the brain (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner & Peterson, 1990). On the other hand, processing speed is a pervasive quality that reflects the general health of the brain's white matter (i.e., myelin sheaths of neural axons) and the speed and efficiency with which nerve signals are transmitted throughout the nervous system (Kail, 1998). This latter cognitive domain seems more closely aligned with the diffuse pathology observed via magnetic resonance imaging in multiple sclerosis. Empirical studies have also identified correlations between the quantity of white matter lesions and the degree of impairment in processing speed (Dineen et al., 2009; Lazeron, De Sonneville, Scheltens, Polman, & Barkhof, 2006; Sperling et al., 2001).

In terms of neuroimaging, a belief in attention as the primary deficit in MS would lead to localized imaging of specific brain regions associated with attention, such as the thalamus, prefrontal cortex, or anterior cingulate gyrus. If, instead, research was focused on processing speed, tools such as diffusion tensor imaging and magnetic resonance (MR) spectroscopy may be more appropriate in order to concentrate on measuring white matter tracts, atrophy, and brain metabolites. Distinguishing between attention and processing speed as the primary cognitive deficit is also relevant to treatment efforts for individual patients. Deficits in attention networks, each associated with a neurotransmitter system, have already elicited discussion of possible pharmacological interventions to correct for neurochemical imbalances (Urbanek et al., 2010).

Alternatively, if the deficit is better characterized by impaired processing speed, individuals may be better served by a treatment plan involving compensatory strategies and cognitive rehabilitation programs.

The necessity of differentiating information processing speed and attention has become more salient in light of recent developments in the study of attention in MS, particularly in the application and interpretation of the Attention Network Test (ANT). The ANT was developed based on a theory postulating the existence of three interrelated neural networks serving attention (Posner & Petersen, 1990; Fan, McCandliss, Sommer, Raz, & Posner, 2002). The three networks have been defined both functionally and anatomically as alerting, orienting, and executive control. Functionally, alerting has been defined as achieving and maintaining an alert state; orienting involves selecting information from sensory input; and executive control includes resolving conflict among competing responses. The alerting network is associated with thalamic, frontal, and parietal areas anatomically and with the norepinephrine system neurochemically. The orienting system is identified with the inferior and superior parietal lobule, frontal eye fields, superior colliculus, and regions in the thalamus; this network appears to be modulated by acetylcholine. Finally, the executive control system is affiliated with the anterior cingulate and lateral prefrontal cortices and is associated with dopamine (Fan et al., 2009).

The Attention Network Test was specifically designed to assess the efficiency of the three alerting, orienting, and executive control networks. It is a computer-based test that has been demonstrated to measure the three attention networks independently and with acceptable reliabilities (Fan et al., 2002). Participants respond to a target stimulus arrow by indicating through a mouse click whether the arrow points to the left or to the right. The target arrow can be presented either above or below a fixation point. It may be presented either independently

(Neutral condition) or surrounded on each side by two flanker arrows. The arrows may point either in the same direction as the target (Congruent condition) or in the opposite direction (Incongruent condition). The target stimuli may also be preceded by a warning cue, intended to provide the participant with temporal information (Center and Double Cue conditions) or temporal and spatial information (Spatial Cue condition) regarding the target presentation, or the warning cue may be absent (No Cue condition).

Scores for each attention network are calculated based on differences in RT associated with the various cue and flanker conditions. The alerting network (No Cue – Double Cue) is intended to index participants' ability to utilize a temporal warning cue to improve response time as compared to their response with no warning. The orienting network (Center cue – Spatial cue) measures participants' ability to capitalize on spatial warning information in addition to temporal cues. Finally, the executive control network (Incongruent – Congruent) assesses participants' ability to resolve conflict.

Recently, the ANT has been applied in the multiple sclerosis population (Crivelli et al., 2011; Urbanek et al., 2010; Wojtowicz et al., 2013). Both Urbanek et al. and Crivelli et al. have found deficits in MS patients' alerting network. These results have been interpreted as suggesting that individuals with MS are not as capable as healthy individuals at utilizing temporal information to achieve a state of alertness to effectively respond to a target. However, an important aspect not being taken into account in these studies is the contribution of information processing speed to the ANT results. All network effects in the ANT are calculated based on reaction time scores. It is clear, then, that while the ANT assesses attention, it also measures information processing speed, an observation noted by other researchers as well (Wojtowicz et al., 2013). While this might not be problematic in healthy populations, which are relatively

homogenous in processing speeds, it is well documented that MS patients differ substantially in processing speed compared to controls.

Of further concern is research demonstrating differential effects of task difficulty on processing speed in MS patients and healthy controls. Increased demands on cognitive processing result in slower reaction times when compared to less demanding tasks (Hughes et al., 2011; Reicker et al., 2007; Tombaugh et al., 2010). The slowing in reaction time applies to all participants; however, it appears that this “complexity effect” is more potent in MS patients than in healthy controls. As task difficulty increases, the disparities in reaction time between patients and controls progressively increase (Hughes et al., 2011; Reicker et al., 2007). Therefore, tasks with greater complexity—or greater amounts of cognitive load—lead to enhanced differences in processing speed between MS patients and controls than simpler tasks. Previous research has demonstrated that choice RT tests, such as those used throughout the ANT, constitute a sufficient demand on cognition to elicit amplified processing speed deficits between groups (Hughes et al., 2011; Tombaugh et al., 2010). This further suggests that the ANT may be sensitive to information processing speed, and, therefore, differences in processing speed between groups become an even more pressing issue to resolve.

Thus, information processing speed presents a confounding variable in drawing conclusions about attention processing in the MS population based on ANT data. Previous work has shown that when differences in processing speed between groups are not properly controlled in measures that require participants to respond rapidly, test results can generate misleading interpretations (Denney & Lynch, 2009). For example, the Stroop test, similarly to the ANT, assesses multiple constructs—executive control and information processing speed—and its primary score of interest (the interference score) is calculated based on a difference score

comparing performance on two different trials (Macniven et al., 2008). When the Stroop is administered to populations of individuals with MS and healthy individuals, simple difference score calculations suggest that significant group differences exist (Denney & Lynch, 2009). The interference value, as calculated by a difference score, can be equally affected by both constructs measured in the Stroop task—executive control or information processing speed. When assessing a healthy population only, the effect of processing speed on individual differences is negligible because of the relative homogeneity within the population. However, the effect of processing speed becomes a concern when comparing groups that differ in their rates of information processing. Therefore, in order to have meaningful scores to interpret on the Stroop (or any other measure confounded by information processing speed) within the MS population, it is necessary to adjust for the influence of processing speed. When Denney and Lynch did so, differences between patients and healthy individuals on executive control and interference scores were no longer significant.

The same challenge presented by difference scores on the Stroop task exists in the interpretation of the ANT. The Attention Network Test uses a choice reaction time format, which measures processing speed in addition to the intended construct of attention. Reaction times from various cue conditions are subtracted from one another (i.e., No Cue RT – Double Cue RT) to generate network effect difference scores. If either or both cue conditions used in the difference score is influenced differentially by processing speed, the score may be distorted in a misleading manner. In order to make conclusions strictly about participants' attention networks, differences in processing speed must be controlled. One way to do this is to avoid using simple difference scores all together. Instead, we propose using residualized scores to determine the status of the three attention networks. The effectiveness of this scoring method has been demonstrated in the

similar situation discussed above involving the Stroop (Denney & Lynch, 2009). We believe a residualized score (calculated by regressing Double Cue RT on No Cue RT and then analyzing the residuals) may lead to different conclusions concerning attention deficits in MS patients. One possibility is that these deficits do not exist and that the results stemming from the Attention Network Test can be fully attributed to slowing in MS patients' overall information processing speed.

Thus, the purpose of the present study was to examine potential attention deficits in the multiple sclerosis population using the Attention Network Test, while controlling for group differences in baseline processing speed. We anticipated significant differences in reaction times between MS patients and healthy controls across cue conditions. We expected simple difference scores to reveal a significant effect of group on network scores, based on the current literature. However, we predicted that this effect would disappear when more appropriate residualized scores were used to analyze the data. Therefore, when information processing speed is properly controlled for, no differences would exist between MS patients and healthy controls in the efficacy of their attention networks.

This investigation expanded upon previously published research by broadening the MS population studied. All three previous studies utilizing the ANT were confined to patients with relapsing-remitting MS; this study investigated both relapsing-remitting and secondary-progressive MS patients. To support the contention that the ANT is influenced by processing speed, we administered three measures of information processing speed, a simple reaction time task, a choice reaction time task, and a computerized Stroop test. We expected to observe slower RTs in individuals with MS than healthy controls. We also examined the effect of fatigue on the results of the ANT to verify that the scores are not being further confounded by fatigue, a highly

prevalent symptom of MS (Bakshi et al., 2000; Freal, Kraft, & Coryell, 1984). Previous studies have reported a significant fatigue effect on the executive control network of the ANT (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2011) as well as on the alertness subtest of the Test of Attentional Performance, a measure similar to the ANT (Weinges-Evers et al., 2010).

Method

Participants

Forty patients between the ages of 20 and 60 who met the revised McDonald criteria for multiple sclerosis were recruited from the University of Kansas Medical Center in Kansas City, KS (Polman, et al., 2005). All patients were under the care of the same neurologist (S. G. L.) and had a diagnosis of either relapsing-remitting or secondary-progressive MS of at least one year duration. Patients were excluded from participation based on the existence of any of the following: a neurological disorder other than MS, a history of drug or alcohol abuse, a premorbid psychiatric disorder, a severe visual impairment (including visual acuity greater than 20/50 or impaired color vision), or a severe cognitive impairment that would interfere with the ability to comprehend testing instructions or questionnaire items.

Forty healthy control participants were also recruited from the surrounding community. Healthy participants were between the ages of 20 and 60 with no history of neurological illness, head trauma, or other chronic medical conditions. They were excluded from the study based on the same criteria identified for MS patients. This study was approved by the local ethics board, and all participants were provided written informed consent forms.

Measures

Information regarding fatigue levels was collected from participants with written self-report questionnaires. All cognitive testing was conducted using an IBM-compatible, 14.4 in. screen, Dell laptop computer running Microsoft Windows XP.

Expanded Disability Status Scale (EDSS). The degree of patients' neurological impairment was assessed by their neurologist (S. G. L.) using the EDSS scale. The scale specifies physical disability and ranges from 0 (no neurological abnormality) to 10 (death from MS) (Kurtzke, 1983).

Fatigue Severity Scale (FSS). Participants completed a brief, self-report measure related to their experience of fatigue over the last week. Responses are given using a 7-point Likert scale, ranging from *strongly disagree* to *strongly agree*. This measure consists of nine questions. It was designed for and has been validated for use in the multiple sclerosis population (Krupp, LaRocca, Muir-Nash, & Steinbert, 1989). High scores indicate a greater degree of fatigue.

Fatigue analogue scale. Participants completed a visual analogue scale assessing fatigue and alertness (Bodling, Denney, & Lynch, 2012). Participants were instructed to place a mark on a 100 mm line indicating their current state of fatigue, alertness, anxiety, happiness, and sadness. The scale ranged from 0 (i.e., not fatigued at all) to 100 (i.e., very fatigued).

Epworth Sleepiness Scale (ESS). Participants completed a brief, self-report measure of their general daytime sleepiness over the last week (Johns, 1991). Participants rated the likelihood of dozing or falling asleep while completing eight different daily tasks on a 4-point Likert scale, ranging from *no chance* to *high chance* of dozing. High scores indicate a greater degree of daytime sleepiness.

Simple Reaction Time Task. Participants completed a 20-item computerized measure of the speed of reaction to a change in the on-screen stimuli (Bodling, Denney, & Lynch, 2012; Hughes, Denney, & Lynch, 2011). A fixation point in the shape of a plus sign (+) was presented for a variable duration (1500-4000 ms). When the fixation changed to the target stimuli (000), the participant clicked a button on the built-in laptop mouse as quickly as possible. Latency to depressing the mouse button was automatically measured and recorded by the computer program for each trial. The overall mean reaction time and standard deviation was also calculated.

Choice Reaction Time Task. Participants also completed a 20-item computerized measure of reaction time when determining whether a target stimulus appeared on the left or right half of the computer screen. A fixation point (+) was located on both the left and right sides of the computer screen for a variable duration (1500-4000 ms). On each trial, one of the fixation points changed to the target stimuli (0). Using the built-in laptop mouse, participants pressed the left or the right mouse button, corresponding to the location of the presentation of the target stimuli. Accuracy and reaction time for each trial were recorded, as well as overall mean reaction time and standard deviation.

Stroop Test. A computerized Stroop task involving three 60-s trials was administered. The first trial (word reading) involved reading color words (RED, BLUE, YELLOW, and GREEN). The second trial (color naming) involved naming the color of ink of a row of four Xs. The third trial (color-word naming) required naming the color of the ink in which color words were printed; all stimuli in the third trial were incongruent (e.g., the word “RED” was printed in blue letters). In all three trials, the participants were instructed to respond to each stimulus out loud and then press the space bar on the keyboard to advance the presentation of the next

stimulus. The total number of items completed was recorded for each trial as a measure of information processing speed.

Attention Network Test (ANT). The ANT is a computerized task measuring the speed of participants' response under different cue conditions in determining whether a target stimuli (an arrow) points to the left or to the right. The ANT was administered as described by the authors of the test (see Figure 1; Fan et al., 2002). Each trial within the ANT consisted of five elements. First, a fixation point (+) was presented in the center of the screen for a variable duration (400-1600 ms). Second, a warning cue was presented for 100 ms. The warning cue provided temporal information (Center Cue, Double Cue), temporal and spatial information (Spatial Cue) or no information (No Cue). All spatial information was valid. The warning cue was followed by a short fixation period of 400 ms before the target stimulus was presented. The target appeared either above or below the fixation point and was accompanied either with or without flankers. The flanker conditions included arrows adjacent to the target stimuli pointing in the same direction (Congruent) or opposite direction (Incongruent) of the target arrow. The target stimulus and flankers remained on the screen until the participant responded or 1700 ms had elapsed. A brief post-target fixation occurred before the next trial began. Following an initial practice block consisting of 24 trials, the different cues and targets were presented in a randomized order with 96 trials per block. There were three blocks, resulting in a total of 288 trials.

Network effects for alerting (No Cue – Double Cue), orienting (Center Cue – Spatial Cue), and executive control (Incongruent – Congruent) were calculated based on difference scores in correct median reaction times (RT) less than a 1700 ms ceiling associated with the various cue and flanker conditions. Network effects were also calculated using residualized

scores. The alerting network was found by regressing Double Cue on No Cue; the orienting by regressing Spatial Cue on Center Cue, and the executive network by regressing Incongruent on Congruent trials. Larger scores on the alerting and orienting networks indicate faster cue-related performance. On the executive network, however, larger scores are indicative of poorer performance (i.e., longer RTs required to resolve conflict).

Procedures

Multiple sclerosis patients were introduced to the study during the course of a regular appointment at the MS Clinic. If an individual expressed an initial willingness to participate, his or her disability was assessed using the Expanded Disability Status Scale. A research assistant then met with the patient to obtain written consent and proceed with the cognitive testing session or schedule an appointment for later testing in the individual's home.

Each testing session began with the administration of the Epworth Sleepiness Scale and the Fatigue Severity Scale to measure levels of daytime sleepiness and fatigue over the past week. Cognitive testing began with the administration of three computerized measures of information processing speed: a simple reaction time task, a choice reaction time task, and the Stroop test. Each of these tasks began with a brief practice period before testing began. The fatigue analogue scale was administered immediately before and after the Attention Network Test to assess state-level fatigue. The ANT began with a practice session with performance feedback and was followed by three testing blocks without feedback. Each block took approximately 6 minutes to complete. Between each block, a brief break was provided. The ANT was typically completed within 25 minutes. For all cognitive testing, participants were instructed to respond as quickly and accurately as possible.

Cognitive testing was followed by a short debriefing to respond to any questions participants had. Testing sessions, from consent to debriefing, were typically completed within 60 minutes.

Statistical Analyses

Results are expressed as arithmetic mean \pm SD, and the median and range for EDSS. Individual outliers for measures of information processing speed and ANT cue conditions were identified as any value beyond three standard deviations from the group mean. Outliers were replaced with the next highest score plus one (Field, 2009). Group differences in demographic variables, performance on information processing speed tasks, and performance on ANT cue conditions and network effects were assessed using independent samples *t*-tests. The occurrence of fatigue over the course of the testing session was measured using a 2 (group) X 2 (time) repeated measures ANOVA of the fatigue analogue scale. Fatigue during the course of the ANT was also assessed using a 2 (group) X 3 (block) repeated measures ANOVA with accuracy and mean RT as dependent variables. Significant subtype differences in relapsing-remitting and secondary progressive MS patients were also assessed using independent samples *t*-tests. All analyses were completed using SPSS version 20.

Results

Outliers were identified and replaced across measures of information processing speed (HC 2.5%, MS (0.0%), ANT cue conditions (HC 0.2%, MS 1.7%), and ANT summary scores for accuracy (HC 2.5%, MS 3.75%) and reaction time across testing block (HC 0.0%, MS 2.5%). When cue conditions were altered, network effects were adjusted accordingly (HC 0.0%, MS: 0.8%).

Participants

Forty healthy controls and 40 individuals with multiple sclerosis participated in the study. Half of the MS patients were of the relapsing-remitting subtype, and half were secondary progressive patients. The clinical and demographic characteristics of the participants are summarized in Table 1.

Information Processing Speed

Performance on a simple reaction time task, a choice reaction time task, and the three trials of the Stroop task are summarized in Table 2.

Reaction time tasks. Significant group differences were observed on both the simple reaction time task ($t(78) = 4.22, p < .001, d = 0.94$) and the choice reaction time task ($t(78) = 4.52, p < .001, d = 1.01$). MS patients were significantly slower than controls on both measures.

Stroop task. Significant group differences were observed across the first ($t(78) = -3.07, p = .003, d = -0.69$), second ($t(78) = -3.98, p < .001, d = -0.89$), and third ($t(78) = -3.88, p < .001, d = -0.87$) trials of the Stroop tests. MS patients consistently made fewer responses than healthy controls across all trials.

Attention Network Test

Network effects, mean RT for each cue condition, overall RT, and accuracy for the two groups are reported in Table 3. MS patients had a significantly slower RT overall ($t(78) = 5.16, p < .001, d = 1.15$) as well as on each cue condition (See Table 3) compared to healthy controls. Effect sizes were very large for each of these measures (i.e., 1.08 to 1.20; Cohen, 1988). When network effects were calculated based on subtraction scores, only the executive control network was significantly different between the groups ($t(78) = 2.41, p = .019; d = 0.54$), with MS

patients having a poorer performance (See Figure 2). When network effects were recalculated using residualized scores, the difference in the executive control network was no longer significant ($t(78) = 0.93, p = .356; d = 0.21$). However, when using residualized scores, the difference in the alerting network became significant ($t(78) = -2.14, p = .035; d = -0.48$), indicating poorer performance in MS patients. (See Figure 3).

Fatigue analyses

An independent samples t test indicated that MS patients experienced significantly more trait-level fatigue as measured by the Fatigue Severity Scale ($t(78) = 5.93, p < .001$) and more daytime sleepiness as measured by the Epworth Sleepiness Scale ($t(78) = 2.27, p = .026$) compared to healthy controls. Pearson correlations between FSS, as well as between ESS, and measures of information processing speed and performance on the ANT were calculated by averaging the correlation for the patient group with that of the control group using Fisher's z transformation. FSS was significantly correlated with performance on the first ($r = -.28, p = .011$), second ($r = -.25, p = .026$), and third ($r = -.24, p = .033$) trials of the Stroop. ESS was significantly correlated with performance on the first ($r = -.24, p = .034$) and second ($r = -.26, p = .018$) trials of the Stroop.

State-level fatigue was also measured before and after the ANT using the fatigue analogue scale to assess for changes in self-reported fatigue. A 2 (group: MS, HC) X 2 (time: pre, post) repeated measures ANOVA was performed. There were significant main effects for group ($F(1,78) = 5.47, p = .022, \eta^2 = .670$) and for time ($F(1, 78) = 23.86, p < .001, \eta^2 = .234$) on reported levels of fatigue. MS patients reported significantly more fatigue at both pre- and post-test. There was no significant interaction ($F(1,78) = 0.76, p = .387$).

In addition to self-report, fatigue was also assessed based on two performance measures compiled on each of the three testing blocks of the ANT. A mean RT and an accuracy rate were calculated for each testing blocks. A 2 (group: MS, HC) X 3 (blocks: 1, 2, 3) repeated measures ANOVA was conducted for each of these performance measures. Significant main effects for group were found for both accuracy ($F(1,78) = 7.33, p = .008, \eta^2 = .086$) and mean RT ($F(1,78) = 15.29, p < .001, \eta^2 = .164$). There was no significant effect of fatigue across the three testing blocks on either measure, nor were either of the Group X Time interactions significant.

Subtype differences

In addition to differences between MS patients and healthy controls, we also were interested in investigating differences between MS subtypes. As would be expected, there were significant differences in age ($t(38) = -2.96, p < .001$), duration of disease ($t(38) = -3.35, p = .002$), and level of disability ($t(38) = -7.30, p < .001$), with secondary progressive MS patients being older, having had MS longer, and being more disabled, on average, than relapsing-remitting patients. There were no significant group differences on measures of information processing speed. There were significant group differences across measures of the ANT. Secondary progressive patients had a significantly slower mean RT overall ($t(38) = -2.51, p = .016, d = -0.79$) as well as on each of the cue conditions, except for the No Cue condition (See Table 4). There was also a significant difference between relapsing-remitting and secondary progressive patients in the alerting network, when calculated both with subtraction scores ($t(38) = 2.02, p = .05, d = 0.64$) and with residualized scores ($t(38) = 2.09, p = .043, d = 0.66$). The alerting effect was weaker for secondary progressive patients.

Discussion

Overall, we replicated the consistent finding in the literature that individuals with multiple sclerosis have a slowed rate of processing speed compared to healthy controls (Archibald & Fisk, 2000; Denney, Gallagher, & Lynch, 2011; Kail, 1998). This was evidenced by robust differences between patients and controls on each direct measure of information processing speed (simple RT, choice RT, Stroop trials) as well as on the reactions times for each of the cue conditions on the Attention Network Test.

We were also interested in examining whether the substantial differences between the groups in reaction times affected the results concerning attention networks on the ANT. The Attention Network Test is based on differential reaction times to various cue conditions. Accordingly, the test measures both attentional processes and information processing speed. In order to draw conclusions about attentional functioning on the ANT, group differences in processing speed must be statistically controlled. The way to accomplish this as advocated by Fan et al. (2002) is to treat each network cue condition pair as consisting of a baseline measure representative of information processing speed and a more complex measure representative of the combined functions of processing speed and attention. For example, the alerting network is calculated by the No Cue – Double Cue difference score. The No Cue condition represents the speed at which participants are able to respond to an on-screen stimulus when provided with no temporal or spatial warnings. The Double Cue condition represents the speed at which participants are able to respond to a stimulus when provided with a temporal warning. We would expect to see a quicker response time for the Double Cue condition compared to the No Cue condition. This faster response is a product of the alerting function of attention. The pattern of a baseline condition being paired with a more complex, cued conditioned is repeated across the

orienting and executive control networks as well. The network effects are intended to measure how much performance changes when additional attentional cues are provided relative to the baseline condition within each pair.

We first calculated network effects using the simple difference scores recommended by Fan et al (2002) and adopted by other investigators (Crivelli et al., 2011; Urbanek et al., 2010; Wojtowicz et al., 2013). Two previous studies have found significant group differences in the alerting effect, which were interpreted to indicate that MS patients were impaired in their ability to use temporal cues to achieve a state of alertness (Crivelli et al., 2011, Urbanek et al., 2010). In the present study, group differences in alerting failed to reach significance ($p = .053$, $d = -0.44$). We did, however, find a significant group difference on the executive control network, which assesses individuals' ability to resolve conflict between two competing stimuli. This finding replicates the result reported by Wojtowicz, Omisade, & Fisk (2013).

Owing to the substantial differences in information processing speed between patients and controls, a better way to obtain scores corresponding to the three attentional networks is to use residualized scores rather than difference scores. Here again, the paired cue conditions associated with each network can be conceptualized as a baseline measure representing an information processing speed component and a more complex measure representing both information processing speed and an attentional (alerting, orienting, executive control) component. Performance on the baseline measure can be used to predict performance on the more complex measure (e.g., performance on the No Cue condition can predict performance on the Double Cue condition). Thus, we can regress Double Cue performance on No Cue performance and can then analyze the residuals to see if the actual performance of individuals or groups differs significantly from their predicted performance. This method of analyzing change

across the cue conditions allows us to statistically control for performance on the baseline measure of processing speed in a way that is unaffected by the between group differences on this baseline measure and thereby obtain a more refined estimate of attentional processes.

When we reanalyzed our data using the residualized scores instead of difference scores, group differences on the executive control network were no longer significant ($t(38) = 0.93, p = .356, d = 0.21$), and the effect size became substantially smaller. The group difference in the alerting effect that just failed to attain significance when based on difference scores was now found to be significant when using residualized scores ($t(38) = -2.14, p = .035$); however, the effect size ($d = -0.48$) remained small relative to the differences in processing speed.

In addition to processing speed directly affecting the baseline conditions of each network difference score, we also believed that processing speed might explain the significant group differences in the executive control network. When we controlled for processing speed by using residualized network scores, the group differences on the executive network disappeared. However, we were concerned that the group differences in performance on the executive control network might also be affecting performance on the other attention networks. Evidence suggests that group differences in processing speed can be magnified by the complexity of a task (Hughes et al., 2011; Reicker et al., 2007, Tombaugh et al., 2010). The executive network involves adding flankers (congruent, incongruent) to the already existing (neutral) cue conditions. This increases the complexity of the task and magnifies group differences in processing speed. In a secondary analysis, a 2 (group: MS, HC) X 2 (flanker: congruent, incongruent) repeated measures ANOVA indicated a significant interaction, such that incongruent flanker conditions affected MS participants to a greater degree than healthy controls ($F(1, 78) = 5.81, p = .018, \eta^2 = .069$).

Due to the design of the ANT, the alerting and orienting networks are both confounded by performance on the executive control network. Each of the paired cue conditions making up the alerting and orienting networks are defined as the average reaction time collapsed across three flanker conditions—congruent, incongruent, and neutral. We were concerned that collapsing across flanker conditions to determine the mean No Cue, Double Cue, Center Cue, and Spatial Cue values could magnify existing group differences in processing speed. Thus, to truly identify a pure alerting or orienting effect, both processing speed and performance on the executive network must be controlled for. Therefore, we also ran post hoc analyses of the alerting and orienting network effects using RTs from only neutral trials. Following these procedures, no significant group differences across networks were found using either difference or residualized scores. These results provided additional evidence that group differences in processing speed are the driving factor in the apparent differences in attention.

In addition to group differences across MS patients and healthy controls, we were also interested in characterizing differences within the MS population. Patients with a relapsing remitting subtype are typically earlier in their disease course than other subtypes; they experience alternating periods of symptom exacerbation and remittance. The term “secondary progressive” describes individuals who have converted from the relapsing remitting profile of symptom presentation to a persistent, progressive worsening of symptoms. Secondary progressive patients are typically older and more disabled than relapsing remitting individuals. A population of secondary progressive patients has not yet been studied using the ANT. Unexpectedly, we did not observe any group differences across the direct measures of processing speed (i.e., SRT, CRT, Stroop task). However, we did find significant group differences in the information processing speed measures obtained on the ANT, including overall RT, RTs on the

Double, Center, and Spatial Cue conditions, and RTs on the congruent and incongruent flanker conditions. These results are consistent with the literature demonstrating differences in processing speed between MS subtypes (Denney, Gallagher, & Lynch, 2001; De Sonneville et al., 2002). We also found a significant MS subtype effect on the alerting network, using both subtraction scores and residualized scores. These results also remained significant when calculated using only neutral cue conditions (Subtraction - $F(1,77) = 3.88, p = .025, q = 2.40, p = .049$; Residualized - $F(1, 77) = 4.69, p = .012, q = 2.57, p = .032$). This suggests that as the disease course progresses, attentional deficits, as measured by the ANT, may emerge. These deficits currently appear to be confined to the alerting network, although patients with more advanced disease progression might be discovered to have difficulties in orienting and executive control networks as well. Several investigators (De Sonneville et al., 2002; Huijbregts et al., 2004; Potagas et al., 2008; Ruet, Deloire, Charré-Morin, Hamel, & Brochet, 2013) have commented on the changes that seem to occur in the profile of cognitive deficits over the course of MS. For patients with relapsing-remitting disease, deficits are confined largely, perhaps exclusively, to information processing speed. However, with more advanced, progressive forms of MS, the problems with information processing speed not only become greater (De Sonneville et al., 2002) but are also accompanied by deficits in other cognitive domains (Huijbregts et al., 2004; Potagas et al., 2008; Ruet, Deloire, Charré-Morin, Hamel, & Brochet, 2013). The findings of the present study are generally consistent with this characterization.

In addition to analyzing subtype differences within MS, we also performed secondary analyses to replicate the previous three studies that used the ANT to compare healthy controls to only relapsing remitting patients. There were no significant group differences between relapsing remitting MS and healthy controls in age or education level. The median EDSS score for patients

was 3.0, with a range of 1.0 to 6.0. There were significant group differences in performance across the SRT ($t(58) = -2.60, p = .017, d = 0.80$), CRT ($t(58) = -3.11, p = .003, d = 0.73$) and Stroop trial 2 ($t(58) = 2.36, p = .026, d = -0.69$). However, the group differences on Trial 1 and Trial 3 of the Stroop were no longer significant. On the ANT, group differences across overall RT and each cue condition remained significant. No significant group differences were found for networks, using either subtraction scores (Alerting – ($t(58) = 0.43, p = .668, d = -0.21$), Orienting – ($t(58) = 1.53, p = .132, d = -0.44$), Executive – ($t(58) = -1.61, p = .121, d = 0.48$) or residualized scores (Alerting – ($t(58) = 0.55, p = .588, d = -0.15$), Orienting – ($t(58) = 1.94, p = .057, d = -0.51$), Executive ($t(58) = -0.98, p = .335, d = 0.13$). This suggests that the inconsistencies between our study and the previous studies pertaining to attention networks were not due to sampling differences across the studies.

Finally, we also investigated the relationship between fatigue and the ANT. We were concerned that the length and repetitive nature of the ANT might be particularly challenging for MS patients, who already report higher levels of fatigue than healthy individuals. We assessed fatigue related to the ANT using both a self-report measure and performance measures. On the self-report measure, there was a significant effect of time, such that fatigue had increased from before administration of the ANT to after it. There was also a significant effect of group, such that MS patients reported feeling more fatigued than healthy participants. However, there was no significant interaction, which suggests that MS patients were not differentially fatigued by the task demands. Additionally, analysis of performance across the three testing blocks of the ANT revealed no significant changes in accuracy or mean RT in either group. These results suggest that while fatigue does not differentially affect performance on the ANT, it may make the ANT a more subjectively aversive task for individuals with MS. Previous research has reported a

significant effect of fatigue on attention-based performance. Weinges-Evers et al. (2010) reported that scores on the Fatigue Severity Scale independently predicted performance on the alertness subtest of the Test of Attentional Performance. No significant correlation was found in the present study between FSS scores and performance on the Alerting network ($r = 0.029, p = .800$).

Overall, this study provided an alternative explanation for previously reported deficits in multiple sclerosis patients' alerting network. We demonstrated that when group differences in information processing speed are adequately controlled, apparent deficits in attention are no longer evident. This is the first study to examine the Attention Network Test within a population of secondary progressive MS patients. A limitation of this study was small sample sizes for these subtype groups. Future studies should expand their samples to include additional MS subtypes. Additionally, future research should consider the use of the Attention Network Test – Interactions (ANT-I), which corrects for some of the limitations of the ANT by removing confounds affecting interpretation of network interactions (Callejas, Lupiàñez, Funes, & Tudela, 2005; Ishigami & Klein, 2010).

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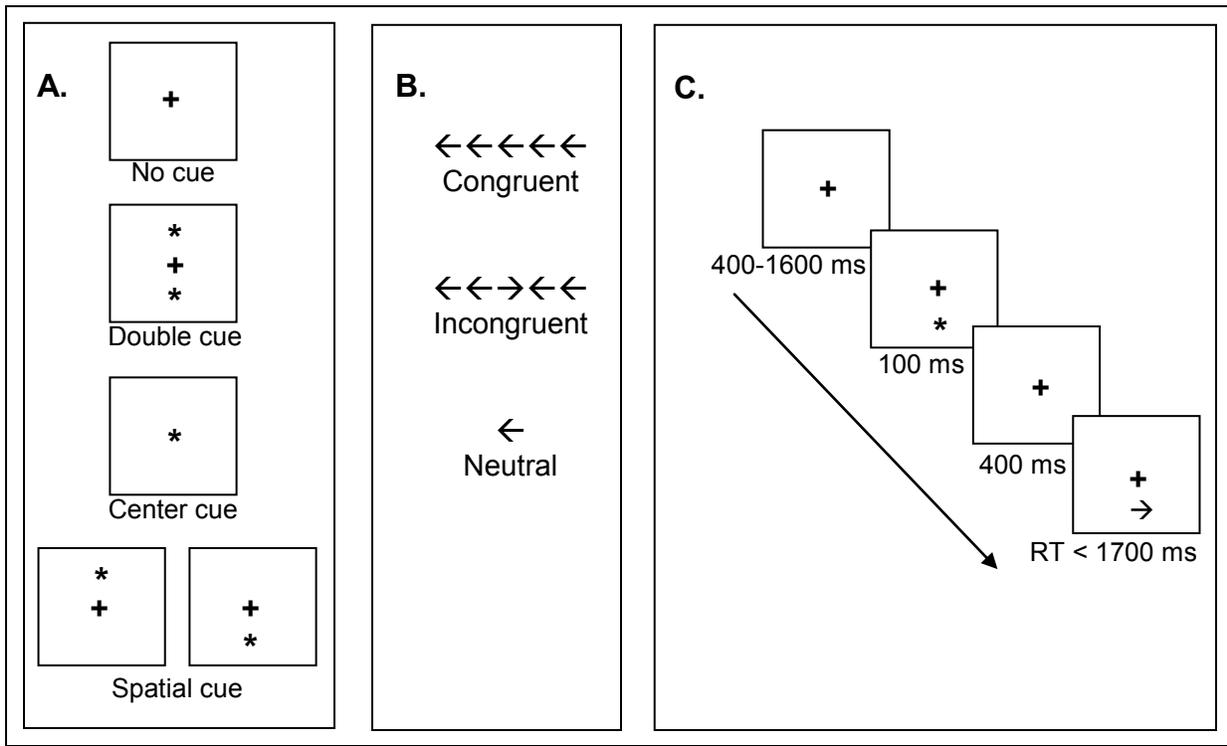
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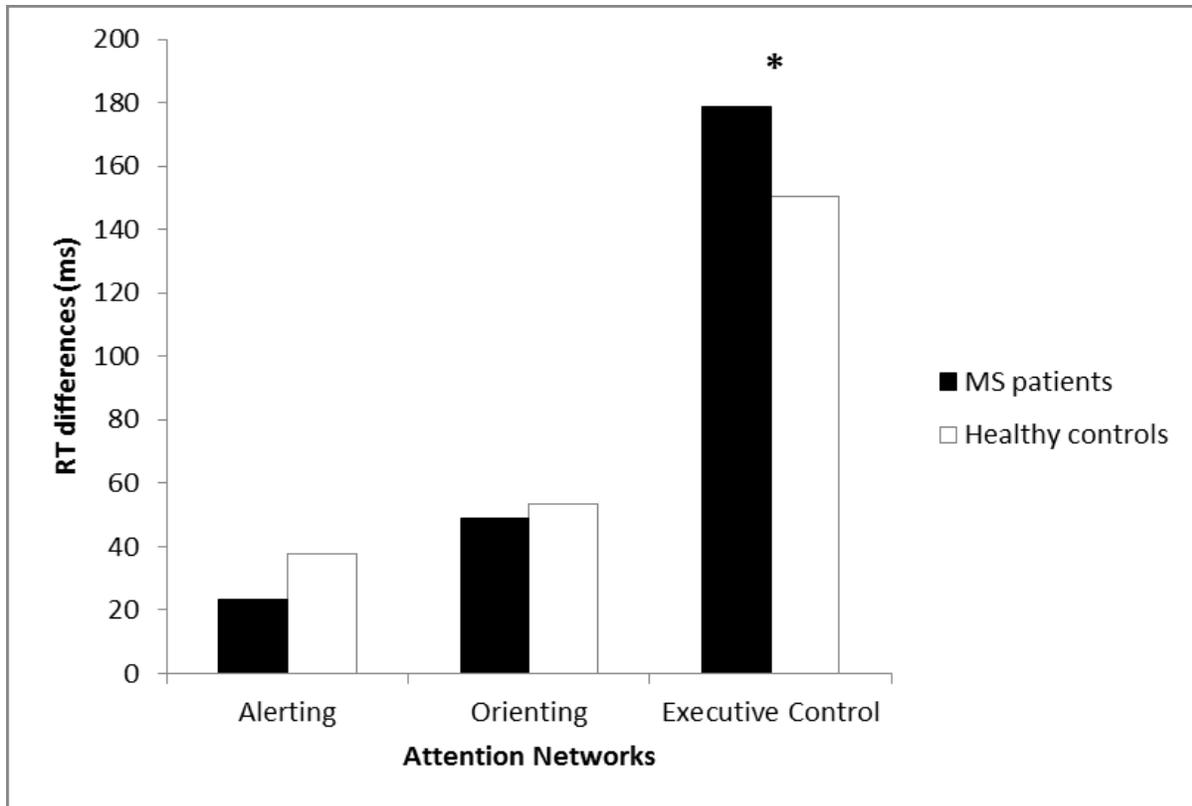
Figure 1.
Design of the Attention Network Test.



Note. (a) The four warning cues that precede the presentation of the target stimuli. (b) The three flanker conditions. (c) An example of the ANT procedure.

Figure 2.

Group differences in performance on attention networks (alerting, orienting, executive) based on subtraction differences scores.

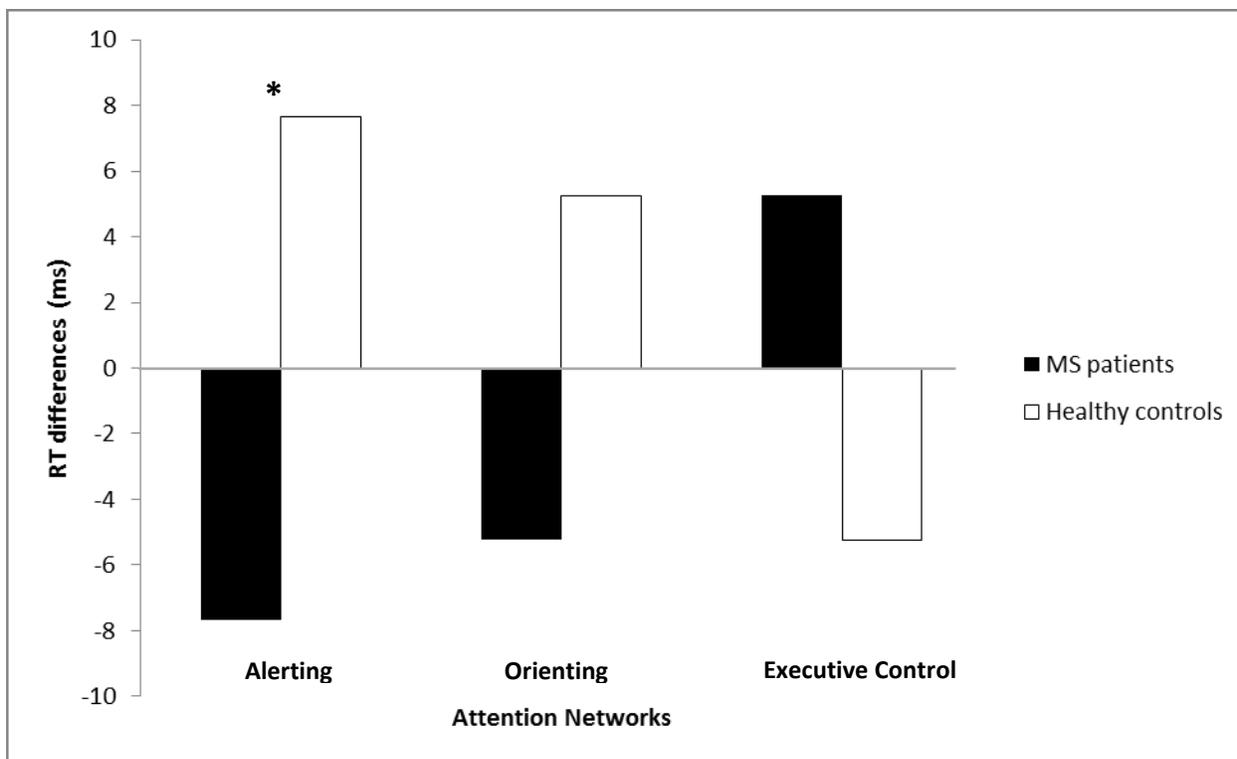


Note. Larger scores on the alerting and orienting network effects indicate faster cue-related performance. Larger scores on the executive control network are indicative of slower, conflict-related poorer performance.

* $p < .05$

Figure 3.

Group differences in performance on attention networks (alerting, orienting, executive) based on residualized difference scores.



Note. Larger scores on the alerting and orienting network effects indicate faster cue-related performance. Larger scores on the executive control network are indicative of slower, conflict-related poorer performance.

* $p < .05$

Table 1.
Demographic and clinical data of participants.

	MS patients (n = 40)	Healthy controls (n = 40)	Significance tests df = 78
Sex (M:F)	7:33	9:31	$\chi^2 (1) = .313,$ $p = .576$
Age (years, mean \pm SD)	47.08 (8.38)	46.23 (8.70)	$t = 0.45,$ $p = .657$
Education (years, mean \pm SD)	16.63 (4.49)	16.75 (1.60)	$t = -0.17,$ $p = .869^a$
Duration of Disease (years, mean \pm SD)	14.68 (8.00)	N/A	
EDSS (median, range)	4.0 (1.0-8.5) ^b	N/A	
FSS item average (mean \pm SD)	4.06 (1.76)	2.20 (0.91)	$t = 5.93,$ $p < .001^a$
ESS (mean \pm SD)	7.70 (4.46)	5.77 (2.98) ^b	$t = 2.27,$ $p = .026^a$

Note. EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; ESS, Epworth Sleepiness Scale

^a t corrected for unequal variances; Levene's corrected t -value reported

^b Sample size n=39

Table 2.

Performance on measures of information processing speed.

	MS patients (n=40) (mean ± SD)	Healthy controls (n=40) (mean ± SD)	<i>P</i> value (<i>t</i> -test) df = 78	Effect size (Cohen's <i>d</i>)
Simple RT task (ms)	577.41 ± 163.18	459.75 ± 66.63	<i>t</i> = 4.22, <i>p</i> < .001^a	0.94
Accuracy on CRT (%)	99.50 ± 1.89	99.75 ± 1.10	<i>t</i> = -0.72, <i>p</i> = .473	-0.16
Choice RT task, correct responses only (ms)	620.52 ± 147.50	508.50 ± 52.66	<i>t</i> = 4.52, <i>p</i> < .001^a	1.01
Stroop – Word Reading trial (# of words)	75.90 ± 16.25	87.53 ± 17.61	<i>t</i> = -3.07, <i>p</i> = .003	-0.69
Stroop – Color Naming trial (# of words)	64.10 ± 11.86	73.15 ± 8.16	<i>t</i> = -3.98, <i>p</i> < .001^a	-0.89
Stroop – Stroop Word trial (# of words)	45.53 ± 10.43	53.13 ± 6.71	<i>t</i> = -3.88, <i>p</i> < .001^a	-0.87

^a *t* corrected for unequal variances; Levene's corrected *t*-value reported

Table 3.
Performance on the Attention Network Test.

	MS patients n = 40 (mean \pm SD)	Healthy controls n = 40 (mean \pm SD)	<i>P</i> value <i>t</i> tests df = 78	Effect size (Cohen's <i>d</i>)
Overall reaction time (ms)	913.98 \pm 167.13	763.10 \pm 79.40	<i>t</i> = 5.16, <i>p</i> < .001 ^a	1.15
Overall accuracy (%)	94.65 \pm 6.37	97.53 \pm 2.44	<i>t</i> = -2.67, <i>p</i> = .010 ^a	-0.60
Median No Cue trials (ms)	937.08 \pm 159.54	799.33 \pm 84.55	<i>t</i> = 4.83, <i>p</i> < .001 ^a	1.08
Median Double Cue trials (ms)	913.50 \pm 160.48	761.58 \pm 78.84	<i>t</i> = 5.37, <i>p</i> < .001 ^a	1.20
Median Center Cue trials (ms)	924.03 \pm 173.30	773.1 \pm 79.39	<i>t</i> = 5.01, <i>p</i> < .001 ^a	1.12
Median Spatial Cue trials (ms)	877.38 \pm 169.00	720.33 \pm 81.67	<i>t</i> = 5.29, <i>p</i> < .001 ^a	1.18
Median Congruent Cue trials (ms)	890.43 \pm 168.32	739.05 \pm 79.51	<i>t</i> = 5.14, <i>p</i> < .001 ^a	1.15
Median Incongruent Cue trials (ms)	1069.35 \pm 190.88	889.95 \pm 100.02	<i>t</i> = 5.27, <i>p</i> < .001 ^a	1.18
Subtraction				
Alerting effect (ms)	23.43 \pm 34.34	37.50 \pm 29.47	<i>t</i> = -1.97, <i>p</i> = .053	-0.44
Orienting effect (ms)	48.95 \pm 31.82	53.40 \pm 32.49	<i>t</i> = -0.62, <i>p</i> = .538	-0.14
Executive control effect (ms)	178.50 \pm 62.06	150.48 \pm 39.37	<i>t</i> = 2.41, <i>p</i> = .019 ^a	0.54
Residual				
Alerting effect (ms)	-7.66 \pm 34.44	7.66 \pm 29.34	<i>t</i> = -2.14, <i>p</i> = .035	-0.48
Orienting effect (ms)	-5.23 \pm 38.55	5.23 \pm 32.32	<i>t</i> = -1.32, <i>p</i> = .192	-0.29
Executive control effect (ms)	5.26 \pm 61.18	-5.26 \pm 37.27	<i>t</i> = 0.93, <i>p</i> = .356 ^a	0.21

Note. Larger scores on the alerting and orienting network effects indicate faster cue-related performance. Larger scores on the executive control network are indicative of poorer performance.

^a *t* corrected for unequal variances; Levene's corrected *t*-value reported

Table 4.
Differences between multiple sclerosis subtypes.

	RRMS (n = 20)	SPMS (n = 20)	t-test (df=38)	Effect size (Cohen's <i>d</i>)
Sex (M:F)	3:17	4:16	$\chi^2(2) = 0.47,$ $p = .791$	
Age (years, mean \pm SD)	43.50 \pm 8.91	50.65 \pm 6.15	$t = -2.96,$ $p < .001^a$	
Education (years, mean \pm SD)	16.70 \pm 4.26	16.55 \pm 4.82	$t = 0.10,$ $p = .917$	
Duration of Disease (years, mean \pm SD)	10.90 \pm 7.79	18.45 \pm 6.39	$t = -3.35,$ $p = .002$	
EDSS (median, range)	3.0 (1.0-6.0)	6.0 (4.0-8.5)	$t = -7.30,$ $p < .001$	
FSS item average (mean + SD)	3.76 \pm 1.84	4.35 \pm 1.66	$t = -1.06,$ $p = .295$	
ESS (mean + SD)	7.00 \pm 4.16	8.40 \pm 4.74	$t = -0.99,$ $p = .327$	
Simple RT task (ms)	577.34 \pm 196.94	577.49 \pm 125.98	$t = -0.003,$ $p = .998$	0.00
Accuracy on CRT (%)	99.75 \pm 1.12	99.25 \pm 2.45	$t = 0.83,$ $p = .411$	0.26
Choice RT task, correct responses only (ms)	587.66 \pm 143.80	653.37 \pm 147.34	$t = -1.43,$ $p = .162$	-0.45
Stroop – Word Reading trial (# of words)	79.35 \pm 14.55	72.45 \pm 17.46	$t = 1.36,$ $p = .183$	0.43
Stroop – Color Naming trial (# of words)	66.05 \pm 12.17	62.15 \pm 11.52	$t = 1.04,$ $p = .304$	0.33
Stroop – Stroop Word trial (# of words)	47.75 \pm 11.33	43.30 \pm 9.19	$t = 1.36,$ $p = .181$	0.43
Overall reaction time (ms)	851.75 \pm 128.44	976.20 \pm 180.79	$t = -2.51,$ $p = .016$	-0.79
Overall accuracy (%)	95.95 \pm 3.39	93.35 \pm 8.26	$t = 1.30,$ $p = .205^a$	0.41
Median No Cue trials (ms)	888.45 \pm 135.90	985.70 \pm 169.71	$t = -2.00,$ $p = .053$	-0.63
Median Double Cue trials (ms)	854.35 \pm 124.67	972.65 \pm 173.06	$t = -2.48,$ $p = .018$	-0.78
Median Center Cue trials (ms)	850.85 \pm 119.06	997.20 \pm 190.26	$t = -2.92,$ $p = .006$	-0.92
Median Spatial Cue trials (ms)	814.80 \pm 140.82	939.95 \pm 174.80	$t = -2.49,$ $p .017$	-0.79
Median Congruent Cue trials (ms)	827.05	953.80 \pm	$t = -2.54,$	-0.80

	+133.97	178.18	<i>p</i> = .015	
Median Incongruent Cue trials (ms)	1004.70 ± 153.49	1134.00 ± 205.99	<i>t</i> = -2.25, <i>p</i> = .030	-0.71
Subtraction				
Alerting effect (ms)	34.00 ± 29.97	12.85 ± 35.89	<i>t</i> = 2.02, <i>p</i> = .050	0.64
Orienting effect (ms)	40.80 ± 24.49	57.10 ± 36.60	<i>t</i> = -1.66, <i>p</i> = .106	-0.52
Executive control effect (ms)	117.40 ± 69.61	179.60 ± 55.29	<i>t</i> = -0.11, <i>p</i> = .912	-0.03
Residual				
Alerting effect (ms)	3.27 ± 29.53	-18.58 ± 36.22	<i>t</i> = 2.09, <i>p</i> = .043	0.66
Orienting effect (ms)	-13.73 ± 41.65	3.26 ± 34.11	<i>t</i> = -1.41, <i>p</i> = .166	-0.45
Executive control effect (ms)	11.31 ± 70.65	-0.79 ± 57.12	<i>t</i> = 1.21, <i>p</i> = .234	0.19

Note. RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; ESS, Epworth Sleepiness Scale

^a *t* corrected for unequal variances; Levene's corrected *t*-value reported