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Cognitive processing speed deficits in multiple sclerosis: Dissociating sensorial and motor processing changes from cognitive processing speed

M. Clough[a,*], J. Dobbing[b], J. Stankovich[a], A. Ternes[c], S. Kolbe[a], O.B. White[a], J. Fielding[a,c]

[a] Department of Neurosciences, Central Clinical School, Monash University, Alfred Centre, Commercial Rd, Melbourne, VIC, 3004, Australia
[b] Department of Medicine, University of Melbourne, Melbourne, VIC, 3050, Australia
[c] School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Wellington Road, Clayton, VIC, 3800, Australia

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ABSTRACT

Background: The assessment of cognitive information processing speed (IPS) is complicated in MS, with altered performance on tests such as the Symbol Digit Modalities Test (SDMT) potentially representing changes not only within cognitive networks but in the initial sensorial transmission of information to cognitive networks, and/or efferent transmission of the motor response.

Objective: We aimed to isolate and characterise cognitive IPS deficits in MS using ocular motor tasks; a pro-saccade task (used to assess and control for sensorial and motor IPS) which was then used to adjust performance on the Simon task (cognitive IPS).

Methods: All participants (22 MS patients with early disease, 22 healthy controls) completed the ocular motor tasks and the SDMT. The Simon task assessed cognitive IPS by manipulating the relationship between a stimulus location and its associated response direction. Two trial types were interleaved: (1) congruent, where stimulus location = response direction; or (2) incongruent, where stimulus location ≠ response direction. RESULTS MS patients did not perform differently to controls on the SDMT. For OM tasks, when sensorial and motor IPS was controlled, MS patients had significantly slower cognitive IPS (incongruent trials only) and poorer conflict resolution. SDMT performance did not correlate with slower cognitive IPS in MS patients, highlighting the limitation of using SDMT performance to interpret cognitive IPS changes in patients with MS.

Conclusion: Cognitive IPS deficits in MS patients are dissociable from changes in other processing stages, manifesting as impaired conflict resolution between automatic and non-automatic processes. Importantly, these results raise concerns about the SDMT as an accurate measure of cognitive IPS in MS.

Cognitive changes are a primary symptom of Multiple Sclerosis (MS), reported in up to 70% of patients across all disease stages and subtypes, (Chiaravalloti and DeLuca, 2008; Potagas et al., 2008). While a range of cognitive changes have been reported, it has been proposed that slowing of information processing speed (IPS) is a core deficit (Chiaravalloti and DeLuca, 2008; DeLuca et al., 2004; Forn et al., 2008) fundamentally impacting, or even precipitating changes in other cognitive domains (Forn et al., 2008; DeLuca et al., 2004). Consequently, IPS has become a key focus for monitoring cognitive progression in MS, proposed as an ideal target for intervention and therapy. However, the assessment of IPS in MS is complicated by the fact that neuropathology is widely disseminated throughout the CNS, potentially impacting any or all of the IPS stages; that is, the initial afferent transmission of sensory information to cognitive networks, the processing of information within cognitive networks, and/or the efferent transmission/execution of the response. This necessarily confounds the interpretation of results from most tests of IPS, specifically, the determination of whether IPS deficits are in fact due to changes within cognitive networks; an important consideration for devising and assessing the efficacy of symptomatic treatments. This is certainly the case for the Symbol Digit Modalities Test (SDMT), the current gold standard measure of IPS in MS (Lopes Costa et al., 2016). Arguably, the assessment of cognitive IPS in MS requires a more targeted approach, one that allows the dissociation of the relative effects of deficits within afferent and efferent processing from those associated with cognitive processing (see (Costa et al., 2017), for an elegant review of the issue).

Information processing represents the efficiency with which neural networks transmit and integrate information. The assessment of the proficiency of information processing requires the measurement of the speed with which this processing occurs, experimentally defined as the

* Corresponding author: Department of Neuroscience, Central Clinical School, Monash University, Alfred Centre Commercial Rd, Melbourne, Victoria, 3004, Australia.
E-mail address: meaghan.clough@monash.edu (M. Clough).

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time taken to complete a task or the amount of work completed within a set period (DeLuca and Kalmar, 2008). This 'speed' metric represents the efficiency of processing not only within cognitive networks, but also of processing in networks subserving the initial afferent transmission of task related sensory information (sensorial), and the efferent transmission of the response command (motor) (DeLuca et al., 2004). The involvement of each processing stages is modulated by the demands of a task, and can be categorised as one of two types: simple or complex. Simple IPS refers to basic processing, with demands placed primarily upon sensorial and motor processing networks, with little involvement of cognitive networks (e.g., a simple reaction time task). Cognitive IPS similarly places demands upon sensorial and motor processing, however, given the increased requirements of the task, cognitive networks are increasingly engaged; primarily the prefrontal cortex, which helps mediate the maintenance and manipulation of information (e.g., Symbol Digit Modalities Test, SDMT: Chiaravalloti et al., 2003, DeLuca and Kalmar, 2008a). Consequently, in MS, to assess IPS specific to cognitive processing it is crucial/necessary to parse out changes specific to cognitive IPS from a complex IPS task.

To achieve this, a targeted approach is required, that is the use of a simple IPS to measure simple processing deficits that can be used to adjust performance on a complex IPS task. This necessarily involves a simple IPS task that has direct correspondence with the complex IPS task, the difference being the level of cognitive processing required. For this study, we used two ocular motor (OM) tasks; OM tasks have the added advantage of having direct correspondence between the input and output modality. The first was a prosaccade task as a measure of simple processing. This task requires the generation of a reflexive eye movement to a suddenly appearing visual target. This necessarily limits the cognitive involvement, with the response being primarily generated by target specific activation of spatial maps within the superior colliculus (Hutton, 2008). The second task was an ocular motor Simon task as a measure of complex IPS.

The Simon task modulates cognitive processing requirements by introducing conflict between the location of a stimulus and the direction of the response it elicits (correspondence effect: Hommel, 2011, Simon, 2011). When the spatial location of the stimulus and the direction of the movement required do not match (incongruent), conflict is created between the automatically generated response elicited by the stimulus location and the required response. Typically, responses for incongruent trials are slower than congruent trials, where stimulus location direction matches the required movement (Hilchey et al., 2011).

Cognitive processing efficiency may be measured as the magnitude of the correspondence effect (incongruent trial latency - congruent trial latency: Simon effect), which is sequentially modulated, and prominent only when a previous trial is congruent. The magnitude of this effect is further modulated by the speed at which the response is executed (latency), with the effect normally diminishing for longer latency responses (distribution analyses); changes in this relationship provides insight into cortical control processes governing the resolution of conflict introduced by an incongruent trial (Ridderinkhof, 2002).

We anticipated that MS patients would demonstrate general IPS slowing on both simple IPS (prosaccade task) and complex IPS tasks (Simon task). However, once controlling for the impact of simple processing, we would demonstrate cognitive IPS deficits in MS, manifesting as increased susceptibility to stimulus/response conflict relative to controls. In addition, for MS patients, we anticipated that the relationship between SDMT performance and the adjusted cognitive IPS performance would be different compared to when complex IPS performance was compared. This is based on the idea that performance on the SDMT (complex IPS) by a subset of patients might be due to changes in sensorial and motor processing and not changes in cognitive processing. Consequently, the relationship between SDMT performance and cognitive IPS is likely to be modified.

1. Method

1.1. Participants

Twenty-two patients with relapsing remitting Multiple Sclerosis were recruited through private practice, Malvern Neurology. All patients had normal visual acuity 6/6 (range: 6/5–6/9). At the time of testing, no patient had experienced a clinical event, as determined by clinical assessment, within the past 60 days. All patients maintained their prescribed medication regime.

Twenty-two healthy control participants, without a history of neurological or psychiatric illness, and normal visual acuity were recruited. All participants were screened to exclude substance abuse/dependence.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethics approval was granted by the Melbourne Health Human Research Ethics Committee (2007.094).

1.2. Ocular motor apparatus and protocol

Eye movements (saccades) were recorded using an Eyelink II dark pupil, video-oculography system (SR Research Ltd, Canada). This system has high resolution (noise limited at $<0.01^{\circ}$), and an acquisition rate of 500 Hz.

Participants were seated in a darkened room, 840 mm from a 75 Hz CRT monitor (resolution: 1024 × 768), with their heads resting on a chin rest. Task stimuli were presented on a black background and comprised crosses (1.5o), and flanking boxes positioned 10o left or right of centre. Simon task stimuli included a green circle/square (1.5o), and 3 green bars (1.5o). All task stimuli were generated using Experiment Builder (version 1.10.165).

1.3. Simple IPS task

A prosaccade task was used as a measure of sensorial and motor IPS (simple IPS). Participants were instructed to fixate a central green cross, and to shift their gaze as quickly and accurately as possible as the target stepped horizontally. The target shifted pseudo-randomly every 1000–2000 ms from centre to 10° left or right and back 24 times to limit the effect and accumulation of fatigue (Finke et al., 2012).

1.4. Complex IPS task

The Simon task was used as a measure of complex IPS. At the start of every trial, participants fixated a central fixation cross for 1000 ms. A task stimulus (circle/square) then appeared in one of the two boxes for 3000 ms, with three green bars appearing concomitantly in the opposite box. If a circle appeared, participants were instructed to always perform an eye movement (saccade) to the left flanking box, irrespective of which box the circle was in. If a square appeared, participants were instructed to always perform a saccade to the right flanking box, irrespective of which box the circle appeared in. Fig. 1.

Two types of trials occurred: (Chiaravalloti and DeLuca, 2008) congruent trials, task stimulus appeared in box corresponding to the designated direction of movement; (Potagas et al., 2008) incongruent trials, task stimulus appeared in box contralateral to the designated direction of movement. In total, 4 test blocks were completed, each consisting of 16 congruent trials and 16 incongruent trials presented in a pseudo-random order (total trials 128).

Prior to commencing the test blocks, all participants were familiarised with the task by way of a guided example of each trial type, followed by a practice block consisting of 16 trials (8 congruent, 8 incongruent).

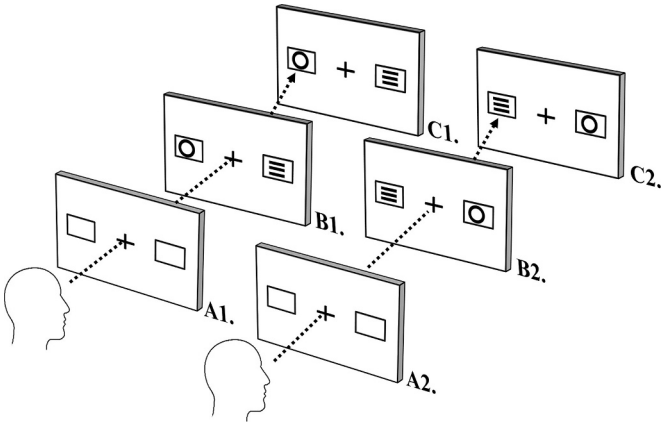

Fig. 1. Illustration of Simon task (only circle trials are depicted). (A) Participant fixates central cross; (B) a shape (circle/square) appears concomitant to the appearance of three lines in contralateral box; (C) participant determines direction of movement based on shape (e.g., circle = leftward movement) and performs an eye movement to the corresponding box. Dotted lines denotes eye position. (C1) depicts correct congruent response, and (C2) depicts correct incongruent response.

1.5. Symbol digit modalities task

The SDMT (verbal: Smith, 1973) was administered to all participants according to standardised instructions.

1.6. Data analysis

Saccade analysis was performed using a custom-built, Matlab program. Saccade latency (ms: time taken to generate a response), was calculated from a monocular eye trace, as the temporal difference between stimulus (prosaccade task: cross; Simon: circle/square) onset and saccade onset. Where internuclear ophthalmoplegia or disconjugancy between the eyes were evident, the unaffected/dominant eye was used for analysis. In all other cases the right eye was analysed. Saccade onset/offset was determined using a velocity criterion of 30°/second.

For the Simon task, latency was calculated for four trial types: (Chiaravalloti and DeLuca, 2008) Congruent previous trial-congruent current trial (congruent-congruent), (Potagas et al., 2008) Congruent previous trial-incongruent current trial (congruent-incongruent), (DeLuca et al., 2004) Incongruent previous trial-congruent current trial (incongruent-congruent), (Forn et al., 2008) Incongruent previous trial-incongruent current trial (incongruent-incongruent). Trials in which the previous trial resulted in an error were not included. Trial types were grouped and considered in two ways: (Chiaravalloti and DeLuca, 2008) previous trial type, (Potagas et al., 2008) current trial type.

For all tasks, trials were removed from the analysis of latency where; (Chiaravalloti and DeLuca, 2008) an error occurred (Simon task; a saccade performed to the incorrect spatial location. Results reported in Table 1); (Potagas et al., 2008) fixation outside of 2°; (DeLuca et al., 2004) a blink occurred around trial onset and prior to saccade onset; (Forn et al., 2008) no response was made within the trial period; (DeLuca et al., 2004) a saccade was executed < 100 ms of target presentation (predictive saccades). For controls, on average 3.94% of Simon task trials and .028% of prosaccade trials. For MS patients, 5.04% of Simon tasks trials and 0.015% of prosaccade trials were removed from the analysis of latency.

To dissociate cognitive IPS from sensorial and motor IPS, Simon task latencies were adjusted by prosaccde task latency (subject covariate), using IBM SPSS statistics version 24 mixed linear model regression analysis. Trial type was considered the repeated variable, and compound symmetry set as the repeated covariance type. Two models were determined: (Chiaravalloti and DeLuca, 2008) without prosaccade task adjustment; (Potagas et al., 2008) with prosaccade task adjustment (cognitive IPS only). For both models, the dependent variable was Simon task latency and the fixed effects were group (two levels: control, MS), previous trial type (two levels: congruent, incongruent) and current trial type (two levels: congruent, incongruent). For the adjusted model, prosaccade task latency was included as a covariate. For both models, subject was used as a random effect and restricted maximum likelihood used to estimate components of the variance. Interactions between fixed effects were examined. Where significant interaction(s) were found, post hoc comparisons were performed with Bonferroni adjustments. The Simon task residual latencies (adjusted by prosaccade task) were used to calculate Simon effect. The difference in magnitude of Simon effect was compared between groups using a *t*-test.

For distribution analysis, the calculation of latency quintiles was determined by ranking latencies (adjusted by prosaccade task) from shortest to longest, and then multiplying the number of latencies by the quintile (i.e., 0.2, 0.4, 0.6, 0.8, 1). The latency in the resultant position was then located and reported for each of the four trial types. Simon effect was determined for each quintile according to the aforementioned method. Again, results were analysed using a mixed linear model regression, with the dependent variable Simon effect, and the fixed effects group and quintile (factors). All other model parameters were consistent with those described previously.

Table 1
Demographic and clinical characteristics of patient ad control groups.

	MS (n = 22)	Control(n = 22)
Age (yrs)	47.4 (8.73)	46.55 (9.34)
Sex F(M)	18(4)	14(8)
BDI	5.05(5.33)	3.40(2.74)
NART (FSIQ)	117.14(4.89)	118.95(1.19)
SDMT	65.57(12.98)	67.65(11.18)
EDSS	0 (0–2.5)	–
Disease duration (yrs)	8 (6.04)	–
MFIS (total score)	22.67(15.93)	–
Visually guided latency (ms)	194.58(19.17)	179.41(24.86)*
Simon task (%)		
Congruent-Congruent error	4.28(6.01)	4.91(4.88)
Congruent-Incongruent trial error	7.34(7.85)	9.05(8.36)
Incongruent-Incongruent error	9.01(13.87)	8.69(12.48)
Incongruent-Congruent error	7.34(7.85)	9.05(8.36)

BDI: Beck Depression Inventory; NART (FSIQ): National Adult Reading Test (Full Scale Intelligence Quotient); SDMT: Symbol Digit Modalities Test (verbal version); EDSS: Expanded Disability Severity Scale; MFIS: Modified Fatigue Impact Scale.
Values are expressed as Mean (standard deviation), except for EDSS and visual acuity, which is Median (range).
For the NART and SDMT, higher scores indicate better performance. For BDI, MFIS and EDSS, higher scores indicate more severe symptoms.
* Significant at $p < .05$.

2. Results

Groups were not significantly different in age, depressive symptomology (BDI), intelligence (NART). All MS patients had visual acuity within a normal range and had minimal disability as measured by the EDSS, with a median score of zero. MFIS and BDI scores were not found to correlate with any ocular motor measure or SDMT performance and were not considered as a covariate in subsequent analyses.

MS patients and controls did not differ in the proportion of errors performance on any Simon task trial or in performance on the SDMT; however, three MS patients had impaired SDMT performance as determined by a z-score of less than 1.5.

MS patients demonstrated significantly slower simple IPS than controls, evident as longer latencies on the prosaccade task: $t = -2.27$, $p = .029$, 95% CI: −28.68, −1.67, point estimate = −15.17. Table 1. Conversely, there was no group difference in SDMT performance.

Table 2
Fixed effects, estimates of fixed effects and average latencies for both the adjusted and unadjusted mixed linear models.

Fixed effects	Unadjusted Df	Adjusted *F*	*p*	Df	*F*	*p*
Intercept	1,42	1290.58	3.66E-33***	1,40	4.11	.049*
Group	1,42	5.99	.019*	1,40	13.26	.001*
Previous trial	1126	.032	86	1126	.032	.86
Current trial	1126	7.92	.006	1126	7.92	.006
Group*Previous trial	1126	1.44	.23	1126	1.44	.23
Group*Current trial	1126	11.09	.001*	1126	11.09	.001*
Previous trial*Current trial	1126	36.89	1.36E-8***	1126	36.89	1.36E-8***
Group*Previous trial*Current trial	1126	1.66	.20	1126	1.66	.20
Visually guided+	–	–	–	1,40	6.29	.016*
Diagnosis*Visually guided	–	–	–	1,40	15.41	.00033**
Estimates of fixed effectsb	**Estimate**	p	**95% CI**	**Estimate**	p	**95% CI**
Intercept	563.38	1.07E-33***	515.95,610.82	−198.29	.30	−579.59,183.02
Group: control	−80.69	.019*	−147.77,−13.61	835.77	.001*	366.98,1304.55
Previous trial: congruent	76.66	.000025***	41.96,111.37	76.66	.000025***	41.96,111.37
Current trial: congruent	10.69	.54	−24.01,45.39	10.69	.54	−24.01,45.39
Group*Previous trial: control-congruent	−43.69	.081	−92.76,5.39	−43.69	.081	−92.76,5.39
Group*Current trial: control-congruent	35.78	.15	−13.29,84.86	35.78	.15	−13.29,84.86
Previous trial*Current trial: congruent-congruent	−129.13	7.58E-7***	−178.20,−80.05	−129.13	7.58E-7***	−178.20,−80.05
Group*Previous trial*Current trial: control-congruent-congruent	45.24	.20	−24.17,114.64	45.24	.20	−24.17,114.64
Visually guided	–	–	–	3.91	.00022**	1.97,5.86
Diagnosis*Visually guided: control-visually guided	–	–	–	−4.78	.00033**	−7.24,−2.31
Average latencies+	**Controls**	**MS**	**All**	**Controls**	**MS**	**All**
	M	M	M	M	M	M
Congruent-Congruent	478.25	521.61	499.93	471.71	491.92	481.81
Congruent-Incongruent	515.67	640.05	577.86	509.13	610.36	559.74
Incongruent-Congruent	529.17	574.07	551.62	522.62	544.38	533.50
Incongruent-Incongruent	482.69	563.38	523.04	476.15	533.69	504.92

+ These 'average' latencies are latencies predicted by the model for individuals with visually guided latency equal to its overall average value, namely 186.99 ms.
bAll comparisons are made relative to the reference group; the highest designated level of a factor (group: MS; previous trial: incongruent; current trial: incongruent).
* Significant at $p < .05$.
** Significant at $p < .001$.
*** Significant at $p < .0001$.

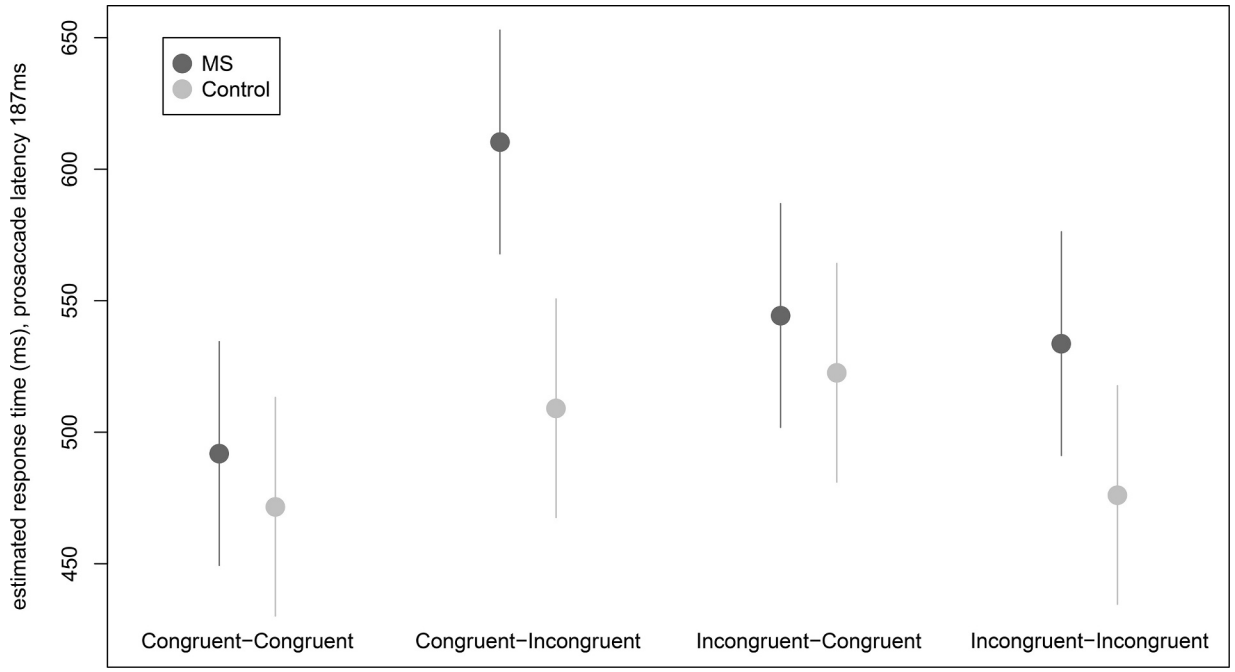

Fig. 2. Latencies (ms) on the Simon task according to trial type. Latencies shown have been adjusted by prosaccade latency.

2.1. Cognitive IPS analysis

Full description of the two models (model 1: unadjusted for simple IPS, model 2: adjusted for simple IPS) is provided in Table 2. Below is a summation of the results pertinent to the aims of this study.

The unadjusted model (Chiaravalloti and DeLuca, 2008) revealed that MS patients were significantly slower on the complex IPS task than controls, with MS latencies on the Simon task on average 73.33 ms (SE = 29.96) slower than controls: $F = 5.99$, $p = .019$, 95% CI: −133.79, −12.87. The adjusted model (Potagas et al., 2008) revealed a significant effect of simple IPS and a significant group interaction. MS were found to be slower on the complex IPS task than controls,

although this difference did not quite reach significance (MS: 50.19 ms (SE = 27.15) slower than controls: $F = 3.42$, $p = .072$, 95% CI: −105.05, 4.68).

To more fully characterise cognitive IPS changes in MS, the adjusted Simon task latencies were examined in the context of current and previous trial type. In line with previous research, a significant effect of current trial was found, with incongruent trial latencies 24.67 ms (SE = 8.77) slower than congruent trial latencies: $F = 7.92$, $p = .006$, 95% CI: −42.03, −7.32. A significant current trial by group interaction revealed significantly slower latencies for incongruent trials compared to congruent trials, for MS patients only; on average, incongruent trial latencies were 53.87 ms (SE = 12.40) slower than congruent trial latencies: $F = 18.88$, $p = 000{,}028$, 95% CI: 78.41, 29.34. For MS patients, incongruent trial latencies were significantly longer than controls, on average 124.38 ms (SE = 33.59) slower for congruent-incongruent trials ($F = 13.71$, $p = .00044$, 95% CI: 191.46, 57.30), and 80.69 ms (SE = 33.59) slower for incongruent-incongruent trials ($F = 5.77$, $p = .019$, 95% CI: 147.77, 13.61). By comparison, no overall effect of previous trial was found, a finding that was consistent for both MS and controls. Collectively these results demonstrate that cognitive IPS is significantly slower for MS patients than controls when a trial is incongruent, irrespective of the type of trial that preceded it. Fig. 2.

To investigate the Simon effect (incongruent > congruent), interactions were examined between current and previous trial types to determine whether latency of the current trial is differentially modulated depending on both the type of current trial as well as previous trial. In line with previous research, a significant interaction was found between current trial type and previous trial type, with current trial latencies modulated by the type of previous trial; this effect was consistent for controls and MS patients. Again consistent with previous research, post hoc analyses revealed that incongruent trials latencies were significantly longer only where the previous trial was congruent (77.93 ms, SE = 12.40) (i.e., Simon effect): $F = 39.50$, $p = 4.9 \times 10–9$, 95% CI: −102.47, −53.39. Importantly, the magnitude of this Simon effect was significantly larger for MS patients than controls (81.03 ms, SE = 16.91), demonstrating that MS patients have an increased susceptibility to incongruent trials compared to controls: $t = -2.54$, $p = .015$, 95% CI: 145.33, 16.72. Table 2.

2.2. Distribution analysis

A significant effect of group was found, with MS patients demonstrating a Simon effect that was on average 87.33 ms larger than controls: $F = 9.21$, $p = .004$, 95% CI: −145.39, −29.27. Overall, the Simon effect was not modulated as a function of increasing latency (no effect of quintile), however, a significant quintile by group interaction was evident suggesting that distinct profiles were evident for controls and MS patients. Specifically, controls demonstrated the expected reduction in Simon effect with increasing quintile; although this did not reach significance. In contrast, MS patients demonstrated the opposite profile, with an increased Simon effect with increasing latencies: $F = 7.11$, $p = .0000027$, 95% CI: 60.53, 254.38, central difference (i.e., difference between highest and lowest quintile) = 53.87 ms. Table 3.

2.3. Correlation analysis

When incongruent trial latencies were not adjusted for simple IPS, poor performance on the SDMT was significantly related to slower latencies for incongruent trials: congruent-incongruent: $r = -0.45$, $p = .036$, r2 = 20.25%; incongruent-incongruent: $r = -0.55$, $p = .008$, r2 = 30.25%. This is unsurprising given that both are complex IPS measures, each reflecting a combined measure of sensorial, cognitive and motor IPS. However, after adjusting for simple IPS, and with incongruent latencies now reflecting cognitive IPS only, no relationship was evident with SDMT performance.

3. Discussion

Assessment of cognitive IPS is complicated in MS, with performance on tests such as the SDMT (complex measure of IPS) potentially representing change in the initial sensorial transmission of information to cognitive networks, processing within cognitive networks, and/or efferent transmission of the motor response (DeLuca et al., 2004). This necessarily confounds the interpretation of results from these tests. Consequently, we aimed to dissociate cognitive IPS from changes in sensorial and motor IPS, collectively termed simple IPS. To do this we used performance on a simple IPS task (prosaccade task) as a measure of sensorial and motor IPS to adjust performance on a complex IPS task (Simon task), the outcome of which is an explicit measure of cognitive IPS.

MS patients were significantly slower on both the simple IPS (prosaccade task) and complex IPS tasks (Simon task). This was not similarly found for the SDMT, with no significant group difference evident; suggesting the SDMT may be relatively insensitive to changes when subtle. As expected, simple IPS was found to significantly affect complex IPS task performance in MS patients, demonstrating its necessity as a covariate. Although no overall group difference in cognitive IPS was found after controlling for simple IPS, we did find trial type specific changes. Specifically, MS patients had significantly slower cognitive IPS on incongruent trials only; that is, trials in which there is conflict between the location of the stimulus and the required direction of movement. This reflects greater difficulty with the resolution of response conflict between an automatic and goal directed response, and which was further evidenced in the significantly larger Simon effect found for MS patients; this effect increased with increasing latency. Lastly, and most compellingly, SDMT performance did not correlate with cognitive IPS (adjusted incongruent latencies) in MS patients. This is despite correlating with unadjusted latencies which similarly represented a general measure of complex IPS. This highlights the limitations of the SDMT as a measure of cognitive IPS changes in patients with MS. Overall, these results suggest that cognitive IPS changes are dissociable from changes in sensorial and motor IPS, when a targeted approach is taken.

Increased latencies on incongruent trials, as demonstrated by MS patients, are thought to be due to reduced prefrontal cortex (PFC) inhibitory control. Dual-route models assert that two cognitive processing pathways are activated during conflict tasks: 1) a cortically controlled indirect pathway representing the stimulus-response (S-R) map formed on the basis of task instructions; 2) a direct, or automatic pathway activated by the presentation of a target, resulting in the generation of a motor program that corresponds with its spatial location, which occurs independently of S-R mapping (De Jong et al., 1994; Kornblum et al., 1990). Both pathways are activated during a trial, so that if the required response matches the automatically generated motor program (congruent trials), the motor program is released. However, if conflict exists between the response and the automatic motor program (incongruent trials), the direct pathway motor program must be cancelled in favour of the correct response, the retrieval and execution of which incurs a time cost corresponding as increased latency for incongruent trials (Ridderinkhof, 2002). The prefrontal cortex (PFC) is proposed to supervise the inhibition of the direct pathway which, for an incongruent trial, concomitantly facilitates the execution of the goal directed response. When PFC inhibition is reduced, a greater build-up of subthreshold activity within the direct pathway occurs, which the indirect pathway takes longer to overcome, producing even longer incongruent trial latencies than normal. Further, weak PFC inhibition has been shown to produce the pattern seen here for MS patients, of increased Simon effect with increasing latencies (Ridderinkhof, 2002).

The PFC is a key cognitive area responsible for the integration and manipulation of information, and the control of goal directed behaviour (Funahashi and Andreau, 2013). Increasingly, PFC changes are recognised as instrumental in the cognitive changes seen in MS. Indeed,

Table 3
Fixed effects, estimates of fixed effects and average Simon effects across quintiles and groups.

Fixed effects	Df	*F*	*p*
Intercept	1,42.34	3.83	.057
Group	1,42.34	9.21	.004*
Quintile	4, 162.14	2.00	.096
Group*quintile	4, 162.14	6.27	.00010**
Estimates of fixed effectsb	**Estimate**	p	**95% CI**
Intercept	188.53	8.23E-9***	127.50,249.55
Group: controls	−2537.24	1.11E-7***	−321.18, −153.31
20th Quintile	−157.45	.000008***	−224.71, −90.20
40th Quintile	−151.93	.000015***	−219.19, −84.68
60th Quintile	−148.02	.000031***	−216.16, −79.87
80th Quintile	−126.11	.0002**	−193.37, −58.85
Group*quintile: Control-20th quintile	207.17	.000021***	113.81, 300.52
Group*quintile: Control-40th quintile	193.44	.000063***	100.49, 286.39
Group*quintile: Control-60th quintile	181.73	.00018**	88.13, 275.33
Group*quintile: Control-80th quintile	167.21	.00050**	74.26, 260.17
	Controls	**MS**	**All**
	M(95% CI)	**M(95% CI)**	**M(95% CI)**
20th Quintile	1.00(−56.64,58.63)	31.07(−25.56, 87.71)	16.04(−24.37, 56.44)
40th Quintile	−7.21(−63.85, 49.43)	36.59(−20.05, 93.23)	14.69(−25.36, 54.74)
60th Quintile	−15.00(−71.64, 41.64)	40.51(−17.09, 98.12)	12.76(−27.64, 53.15)
80th Quintile	−7.61(−64.25, 49.03)	62.42(5.78, 119.06)	27.41(−12.65, 67.45)
100th Quintile	−48.71(−106.35, 8.29)	188.53(127.50, 249.55)	69.91(27.94, 111.86)

bAll comparison are made to the reference group; the highest designated level of a factor(all quintiles: 100th quintile; group*quintile: quintile-MS).
* Significant at $p < .05$.
** Significant at $p < .001$.
*** Significant at $p < .0001$.

MS patients consistently perform more poorly on cognitive tasks known to implicate PFC function: antisaccade (Clough et al., 2015; Fielding et al., 2009, 2012), task switching (Migliore et al., 2018; Clough et al., 2018), the Stroop task (Hughes et al., 2013; Macniven et al., 2008), cueing paradigms (Clough et al., 2015; Roth et al., 2015; Crivelli et al., 2012; Ishigami et al., 2013; Urbanek et al., 2010; Fielding et al., 2009). Further, changes within the functional connectivity of the PFC and associated networks have been reported in MS, even from the earliest stages of the disease (Roca et al., 2008; Wojtowicz et al., 2014; Pravata et al., 2016). However, there is currently a lack of reproducible and consistent evidence linking changes in PFC function to cognitive behavioural changes in MS. Conceivably, this may be due to the use of measures that are confounded by changes in efferent and afferent processing, and thus do not directly correspond with changes within the cognitive networks under investigation.

There are a few limitations of this study, most notably the small sample size and the early/mild disease. Replication of these results in a larger study, with patients at various disease stages is required both for validation of these results, and to determine whether conclusions are similarly relevant at more progressed stages of the disease.

In conclusion, this study has demonstrated that cognitive IPS changes are present independently and are dissociable from sensorial and motor processing changes in MS. Specifically, the pattern of results in MS suggest difficulty resolving conflict between automatic and goal driven behaviours, potentially due to a reduction in the integrity of PFC networks affecting top-down inhibitory control. Importantly, our measure of cognitive IPS was not related to SDMT performance, raising concerns about its use as an accurate measure of cognitive IPS in MS. These results have significant implications for future research. Firstly, the ability to dissociate cognitive IPS from other information processing impairments, improves our capacity to investigate the pathophysiological processes underlying cognitive deficits in MS, potentially providing a more direct comparison between behavioural performance and structural/functional changes. Secondly, the assessment of cognitive IPS might be best achieved through paradigms that interrogate PFC function, specifically those involving the resolution of response conflict. Lastly, and importantly, these results provide evidence that cognitive IPS changes are not necessarily a consequence of changes in afferent and efferent processing, an important consideration in the development of personalised therapies/rehabilitation strategies.

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Declaration of Competing Interest

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