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Social Cognitive Disruptions in Multiple Sclerosis: The Role of Executive (Dys)Function

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Objective: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, resulting in a range of potential motor and cognitive impairments. The latter can affect both executive functions that orchestrate general goal-directed behavior and social cognitive processes that support our ability to interact with others and maintain healthy interpersonal relationships. Despite a long history of research into the cognitive symptoms of MS, it remains uncertain if social cognitive disruptions occur independently of, or reflect underlying disturbances to, more foundational executive functions. The present preregistered study investigated this directly. ***Method:*** Employing an experimental design, we administered a battery of computerized tasks online to a large sample comprising 134 individuals with MS and 134 age- and sex-matched healthy controls (HCs). Three tasks measured elements of executive function (working memory, response inhibition, and switching) and two assessed components of social cognition disrupted most commonly in MS (emotion perception and theory of mind). ***Results:*** Individuals with MS exhibited poorer working memory ($d = .31$), response inhibition ($d = -.26$), emotion perception ($d = .32$), and theory of mind ($d = .35$) compared with matched HCs. Furthermore, exploratory mediation analyses revealed that working memory performance accounted for approximately 20% of the group differences in both measures of social cognition. ***Conclusions:*** Disruptions to working memory appear to serve as one of the mechanisms underpinning disturbances to social cognition in MS. Future research should examine if the benefits of cognitive rehabilitation programs that incorporate working memory training transfer to these social cognitive processes.

Key Points

Question: This study investigated the potential causes of difficulties shown frequently by individuals with multiple sclerosis (MS) in understanding what others are thinking ("theory of mind") and feeling ("emotion perception"), which can hinder their ability to develop and maintain healthy interpersonal relationships. ***Findings:*** Our results indicate that these social difficulties are driven partly by nonsocial impairments—in particular, a poorer ability to update their memory of rapidly changing information ("working memory"). ***Importance:*** This suggests that common social difficulties experienced by individuals with MS are manifestations of disruptions to more general nonsocial capacities, which should guide cognitive rehabilitation programs and self-management strategies. ***Next Steps:*** Future research should build on these findings by evaluating the effectiveness of training working memory as a potential strategy to improve these social cognitive processes.

Keywords: multiple sclerosis, social cognition, executive function, working memory

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The data are available at https://osf.io/2bhmy/.

The experimental materials are available at https://osf.io/2bhmy/.

The preregistered design is available at https://osf.io/shukw.

continued

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that affects more than 2.8 million people worldwide (Walton et al., 2020). As a result of widespread neurodegeneration, MS is characterized by highly variable symptoms that can include both physical (motor) and cognitive impairment. Although physical symptoms can impose direct constraints on individuals' mobility, cognitive symptoms can also impinge profoundly upon quality of life. This is true especially for cognitive disturbances that interfere with individuals' ability to maintain meaningful interpersonal relationships and, in turn, a healthy social environment. The present study set out to provide a precise characterization of the cognitive disturbance(s) occurring in MS that might underpin such negative psychosocial outcomes.

Cognitive symptoms can occur in all clinical phenotypes of MS, with estimated prevalence rates between 20% and 75% (Benedict et al., 2020; Johnen et al., 2017). Disruptions to cognitive processing speed and executive functions have been reported most frequently, perhaps reflecting the historical focus of research (Chiaravalloti & DeLuca, 2008; Sumowski et al., 2018). Executive functions refer collectively to mental operations that orchestrate adaptive and goal-directed behavior (Diamond, 2013), and their disruption is likely to interfere with activities of daily living. In addition to these foundational cognitive systems, however, disturbances to social cognition are reported in 20%–40% of individuals with MS (Islas & Ciampi, 2019)—that is, the collection of cognitive processes that allow us to interact effectively with others and conduct ourselves appropriately in interpersonal contexts (C. D. Frith & Frith, 2012; Happé et al., 2017). In particular, two core components of social cognition have been shown repeatedly to become impaired in all MS phenotypes: our ability to process others' emotional states from their facial expressions (referred to herein as "emotion perception") and our capacity to attribute mental states to others (e.g., beliefs, intentions; for reviews, see Bora et al., 2016; Cotter et al., 2016; Lin et al., 2021). The latter is referred to as theory of mind (ToM; C. Frith & Frith, 2005; Premack & Woodruff, 1978) and considered essential for social interaction; understanding that others have beliefs independent of our own allows us to understand, predict, and even manipulate their behavior. In this light, disruptions to these two elements of social cognition in MS could impede individuals' ability to develop and maintain interpersonal relationships with friends, family members, colleagues, and health care providers, thereby compromising their overall quality of life (Islas & Ciampi, 2019; Topcu et al., 2020).

A long-standing yet still unanswered question is whether social cognitive disturbances in MS occur independently or reflect manifestations of disruptions to more foundational executive functions that guide behavior in both social and nonsocial contexts (see Doskas et al., 2021). Several studies have reported that the performance of individuals with MS on tasks designed to measure emotion perception or ToM correlate positively with their performance on neurocognitive tests of working memory (e.g., Genova et al., 2015; Lenne et al., 2014) and other executive functions (e.g., Ciampi et al., 2018; Dulau et al., 2017; J. D. Henry et al., 2009; Kraemer et al., 2013). The presence of such associations is highly inconsistent, however, likely reflecting the underpowered samples and/or heterogeneous methods employed typically in this research domain (e.g., A. Henry et al., 2011; Kraemer et al., 2013). Further, some studies report that the impaired performance of individuals with MS compared with matched healthy control (HC) samples on tasks measuring emotion perception and ToM remain significant after controlling for performance on neurocognitive assessments (Genova et al., 2020; Pöttgen et al., 2013; Raimo et al., 2017; for a review, see Cotter et al., 2016) and can occur independently of disturbances to executive functions in some individuals (A. Henry et al., 2022). Perhaps more importantly, none of these studies provide insights into the causal relationships among measures of these seemingly discrete cognitive systems. As such, it remains unclear if and how disturbances to emotion perception and/or ToM are underpinned by disruptions to more foundational executive functions.

A similar debate is found in the broader field of social cognitive research, wherein some scholars conceptualize components of social cognition as particular instantiations of foundational cognitive processes deployed in both social and nonsocial domains (e.g., Binney & Ramsey, 2020; Ramsey & Ward, 2020). Certain executive functions should play a particularly pivotal role in supporting social cognition: These include *working memory* (monitoring and updating memory representations), *response inhibition* (intentionally overriding automatic or involuntary behavior that is inappropriate in the current context), and *switching* (switching flexibly between multiple tasks/mental sets; see Darda et al., 2020; Shaw et al., 2020). Emotion perception and ToM are cases in point: To infer another's emotional and/or mental state at any given moment, we must continuously process available social cues (e.g., their eye gaze and facial expressions) and update our working memory representations accordingly, inhibit our own emotional and mental state to avoid egocentric misattributions ("decentering"; Bukowski, 2018; Lamm et al., 2016), and switch flexibly between self- and other-directed mentation (inferring another's state often requires us to consider how we ourselves might think or feel in their position; see Samson, 2009). In this light, disruptions to emotion perception and ToM might represent manifestations of disturbances to one or more of these underpinning executive functions.

In the present preregistered study, we investigated if and how disturbances to emotion perception and/or ToM in MS might reflect underlying disruptions to working memory, response inhibition and/or switching components of executive function. First, we created a neuropsychological test battery comprising computerized versions of experimental tasks used frequently to assess each element of these cognitive systems. For executive functions, working memory was assessed with the keep track task (KTT), response inhibition with the Stroop task, and switching with the color-shape switching task (CSS; Friedman et al., 2009; Miyake et al., 2000). We measured emotion perception with the reading the mind in the eyes test (RMET; Baron-Cohen et al., 2001), given meta-analytic evidence of reliable performance deficits on this task in individuals with MS (see Bora

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et al., 2016; Cotter et al., 2016; Lin et al., 2021). Although the RMET has been used extensively as a measure of ToM in studies investigating social cognition into MS, formal assessments of its factorial structure, construct validity and associations with other tasks suggest that it more likely measures the accuracy with which emotions are perceived (Higgins et al., 2022; Kittel et al., 2022; Oakley et al., 2016; Quesque & Rossetti, 2020; Schurz et al., 2021). To measure ToM, we utilized another tool employed commonly in this area of research—the faux pas test (FPT; Gregory et al., 2002). This is considered as an advanced test of ToM ability that requires social sensitivity; to correctly detect the occurrence of a faux pas among fictional characters in social situations, respondents must appreciate that each character has a different mental (e.g., belief) state that can be influenced by another's statements. Employing a battery of tasks used most frequently to assess these specific components of social cognition and executive function in MS allowed us to not only draw comparisons with previous research findings but also identify interrelationships and dependencies among these cognitive systems that might provide further mechanistic insights into their co-occurring disruptions. To overcome the small sample sizes recruited typically in previous studies, which are likely to have obfuscated true relationships among social and domain-general cognitive processes, we administered this battery online using a crowdsourcing platform. This allowed us to acquire data from a sample of individuals with MS powered sufficiently to detect small-to-medium effect sizes while also capturing the heterogeneity of this patient population that is seldom considered in existing research. Moreover, this approach allowed us to recruit an equally sized group of HCs matched closely on various demographics.

Driven by meta-analyses that synthesize vast corpora of research studies into disrupted executive function (Islas & Ciampi, 2019; Johnen et al., 2017; Sumowski et al., 2018) and social cognitive impairments in MS (Bora et al., 2016; Cotter et al., 2016; Lin et al., 2021), we hypothesized that individuals with MS would perform worse than HCs across all measures of executive function and social cognition. For those measures of executive functions on which the MS group exhibited impairment relative to the HC group, we then performed exploratory mediation analyses to quantify the extent to which performance on that measure accounted for between-group differences on the RMET and FPT. In doing so, we examined whether disruptions to specific executive functions might underpin the disturbances to social cognitive processes.

Method

Transparency and Openness

This study was preregistered on the Open Science Framework prior to data collection and analyses (https://osf.io/shukw/) and any necessary deviations are outlined within this report. All materials and data are available publicly (https://osf.io/2bhmy). This report of the study follows the Journal Article Reporting Standards for quantitative research.

Participants

The sample size was determined using an a priori power analysis conducted with G*Power (Faul et al., 2007), as described fully in the preregistration. In brief, we estimated the sample size required to detect between-group differences with an effect size of $d = .305$ at 80% power and $\alpha = .05$ for pairwise comparisons following significant analyses of variance (ANOVAs). The effect size of interest was the smallest mean difference between an independent group of MS and HC samples in a previous study (Czekóová et al., 2019). A sample size of 268 individuals was required with $n = 134$ in each group. This defined our target sample size *after* any exclusions (e.g., failed attention checks; see below).

Volunteers were recruited online through Prolific Academic (https://www.prolific.co/), which has been shown to yield higher quality data than other online recruitment platforms (Peer et al., 2017). All participants were required to be aged 17–75 years, fluent in English, and report no history of mild cognitive impairment or dementia and no known psychiatric or neurological conditions (other than MS in the MS group). Although initial inclusion criteria specified that participants must have English as their first language, this was extended to include those who were fluent in English to enable us to achieve our planned sample of individuals with MS.

Individuals with a formal diagnosis of MS were recruited in three steps: first, prescreening criteria on Prolific were used to selectively recruit individuals who reported a diagnosis of MS when signing up to this platform; second, a formal diagnosis of MS was stated as one of the inclusion criterion in the study advert before volunteers progressed to the procedure; third, the demographics survey asked participants to confirm explicitly that they had a formal diagnosis of MS but no other form of neurological or psychiatric diagnoses. Participants were also asked a series of questions concerning their diagnosis: their specific type of MS (e.g., secondary or primary progressive), disease duration, current treatment, and recent history of relapses.

After excluding six participants due to technical issues ($n = 3$), careless responding ($n = 2$; failed attention checks, poor data), and misreporting their diagnosis ($n = 1$), the target sample of 268 participants was achieved. Of this sample, 134 reported a formal diagnosis of MS and 134 were age- and sex-matched HCs. Table 1 summarizes participant demographics (see supplemental Table S1 for more detailed information).

All participants provided written informed consent, and the study was approved by Aston University's research ethics committee (ref. 1791). Participation was recompensed at £7.50/hr.

Procedure

Demographic data and consent were acquired through Qualtrics (Provo, Utah, United States; https://www.qualtrics.com), after which participants were redirected to Pavlovia (https://pavlovia.org; Peirce et al., 2019) to complete five experimental tasks administered in a fully randomized order. The two social cognition tasks were selected on the basis of meta-analytic data (Bora et al., 2016; Cotter et al., 2016; Lin et al., 2021), and the three executive function tasks were selected from the seminal article by Friedman et al. (2009). Figure 1 presents a schematic of these five tasks. Two attention checks were embedded in the first and second half of the experiment: First, participants were asked "Which planet do you live on?" and were required to select from four possible answers ("EARTH," "SATURN," "MERCURY," and "MARS"); in the second half of the procedure, participants were asked to type the word "purple" into a free-response box. These questions were chosen as ethically viable attention checks, as recommended by Prolific guidelines, and only

Table 1
Sample Demographics

Demographics	MS	HC	Total
Gender (M:F)	36:98	36:98	72:196
Age (*M*) [*SD*, range]	39.66 [12.57, 19–71]	39.49; [12.47, 20–74]	39.58; [12.50, 19–74]
Ethnicity			
White	108	100	208
African/Black American	6	25	31
Residency			
United Kingdom	56	82	138
MS diagnosis			
Clinically isolated	8	—	—
Relapse–remitting	97	—	—
Secondary progressive	8	—	—
Primary progressive	7	—	—
Undetermined	13	—	—
Disease duration (*SD*)	9.88 (9.42)	—	—
Treatment[a]			
Yes	87	—	—

Note. Values represent (majority) frequencies or means (*SD*). MS = multiple sclerosis; HC = healthy control; M = male; F = female.
[a] A breakdown of this anonymized data is provided at https://osf.io/2bhmy.

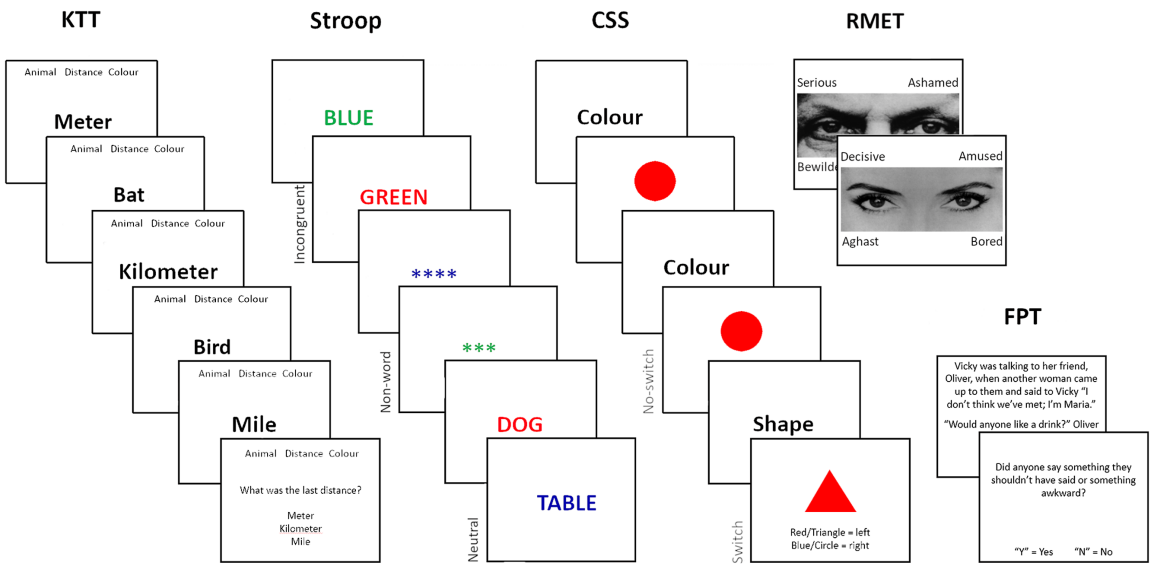
participants who passed both of these checks were included in the analysis.

Measures of Executive Function

KTT

The KTT (adapted from Yntema & Mueser, 1960) was administered as a measure of updating. On each of 12 trials, participants were first presented with two, three, or four target categories (four trials each; *metal, country, distance, relative, color* or *animal*). Fifteen words were then presented sequentially, each for 1,500 ms, including two to three exemplars of each target category. Participants were instructed to remember the last (most recent) word belonging to each of the target categories; when all the words had been presented, they were asked to indicate with a button press which of two, three, or four exemplar words was the last to be presented for a specific target category. A participant's data were excluded if they achieved <60% accuracy.

Figure 1
Experimental Tasks



Note. KTT = keep track task (memory updating); Stroop = Stroop task (response inhibition); CSS = color-shape switching task (switching); RMET = reading the mind in the eyes test (emotion perception); FPT = faux pas test (ToM); ToM = theory of mind. See the online article for the color version of this figure.

An index of working memory was computed by calculating response accuracy across all 36 questions in the trials, with higher accuracy reflecting better working memory ability.

Stroop Task

The Stroop task (Stroop, 1935) was employed as a measure of response inhibition. In each trial, a fixation cross was presented for 500 ms and then replaced immediately by one of three color words or a string of asterisks displayed in red, green, or blue. Participants were asked to indicate the color in which the words or asterisks were presented by pressing one of three response keys. After each response, a blank screen was presented for 1,000 ms before the next trial began. Participants' reaction time (RT) was recorded only for correct responses. The task consisted of three trial types: (a) 60 nonword trials, comprising strings of three to five asterisks presented in one of the three colors; (b) 60 incongruent trials, in which a word for one of the three colors was printed in a different color font (e.g., "RED" printed in blue); and (c) 60 filler trials, whereby a neutral (noncolor) word was printed in one of the three colors (e.g., "cow" presented in red font). Three practice trials were also administered, but were discarded from subsequent analyses. Trial order was pseudorandomized so that the same trial type was presented on no more than three consecutive occurrences, and color words or fonts were different to that of the preceding trial. There were four blocks of trials, with each trial type presented 15 times per block. Individual participant data sets were excluded in full if their response accuracy was below 60%, and individual trials were omitted if RTs were ±3 *SD* of their mean score. An *interference effect* was computed by subtracting the mean RT of correct nonword trials from those of correct incongruent trials. A lower interference effect was used as an index of better response inhibition.

CSS

The CSS (Miyake et al., 2004) was administered as a measure of switching. At the start of each trial, participants were shown a fixation cross for 350 ms, followed by the word cue "Shape" or "Color" presented for 150 ms. A triangle or circle was then presented in red or blue with the cue remaining on the screen. The word cue instructed participants how they should respond on each trial: If "Color" was presented, they were required to indicate whether the shape was red or blue; if "Shape" was presented, they were required to indicate whether it was a circle or triangle. Participants gave their response via the left and right arrow keys, respectively. There were two types of trials: On no-switch trials, the word cue was the same as the previous trial; on switch trials, the word cue changed from the previous trial (e.g., a "Color" trial followed by a "Shape" trial). There were two blocks of 48 trials, each with 24 no-switch and 24 switch trials presented in a pseudorandom order that ensured the same trial type was presented on no more than three consecutive occurrences. Again, a participant's data were excluded in full if their response accuracy was below 60%, and individual trials were omitted if RTs were ±3 *SD* of each participant's mean. A switch cost was computed by subtracting the mean RT of correct no-switch trials from correct switch trials, and a lower switch cost indexed better switching ability.

Measures of Social Cognition

RMET

The RMET (Baron-Cohen et al., 2001) was administered to measure individuals' accuracy in emotion perception. This task consisted of 36 trials, each presenting a photograph of a person's eyes portraying an emotional state. Each photograph was presented with four words of different emotions, and participants were required to indicate which word best described the emotion being portrayed by clicking on it with their computer mouse. Trials (photographs) were presented in a fixed order. Participants were encouraged to keep a dictionary to hand during this task to ensure they understood the meaning of infrequent emotion words (e.g., aghast). An index of emotion perception was computed by calculating accuracy across all 36 trials.

FPT

The FPT (Gregory et al., 2002) was administered as a measure of ToM. This task consisted of 20 trials, each presenting a vignette that described a social encounter between two or more characters. In 10 of the stories, a social faux pas occurred through the verbal or nonverbal behavior of a character (experimental trials); a faux pas is defined as a situation in which a speaker says something without considering if the listener wants to hear it, and which has negative consequences that the speaker did not intend. In the other half of stories, no such faux pas occurred (control trials). After each story, participants were first asked if a faux pas had occurred ("Did anyone say something they shouldn't have said?") to which they responded by selecting either "yes" or "no." If they reported to have detected a faux pas, they were then asked to identify the culprit ("Who said something they shouldn't have said or something awkward?") by typing a free response. Together, these two questions measured faux pas detection. Participants who detected a faux pas were then asked an additional four questions to assess their understanding of the source of the faux pas: why a faux pas had occurred, why someone had said something inappropriate or awkward, and how the faux pas had made the victim feel. Free-response answers to these three questions assess different aspects of social awareness, and were not considered in subsequent analyses. Finally, regardless of whether they had detected a faux pas, participants were asked two open-ended questions that assessed their comprehension of the story (e.g., "Who arrived late for the meeting?"), to which they provided a free response. A faux pas detection score was calculated as a ratio of experimental trials in which the participant correctly detected the presence of a faux pas *and* comprehended the story, to control trials in which they correctly detected the absence of a faux pas *and* comprehended the story (1.0 = perfect accuracy). Higher faux pas detection scores were used as an index of better ToM.

Task Reliability

Permutation-based split-half reliability estimates were calculated for each of the dependent measures of interest using the *splithalf* package in R (Version 0.8.2; Parsons, 2021), whereby the results of 5,000 random splits were averaged. Although reliability estimates are continuous, and arbitrary thresholds may therefore hinder their utility, to facilitate interpretation we adopt Koo and Li's (2016)

guideline categories of <.50 (poor), .50–.75 (moderate), .75–.90 (good), and >.90 (excellent).

Data Analysis Strategy

As described above, participants' data on each measure of executive function were excluded if their response accuracy was below 60% (KTT = 19, Stroop = 5, CSS = 3). For tasks utilizing RT as the primary measure, scores ±3 *SD* of the entire sample mean were considered outliers and were also excluded (Stroop = 4, CSS = 3, RMET = 2, faux pas = 6). For the final data set, each of the five dependent variables were *z*-scored to permit direct comparisons among the different units of measurement. Data were analyzed with the Statistical Package for the Social Sciences (V.26; IBM Corp, 2019). To examine if individuals with MS exhibited disruptions in executive function and/or social cognition compared with the HC group, two mixed-design ANOVA tests were conducted: a 2 (group: MS, HC) × 3 ($task_{Executive}$: KTT, Stroop, CSS), and a 2 (group: MS, HC) × 2 ($task_{Social}$: RMET, FPT). For both these ANOVAs, task was a repeated-measures factor that assessed specific differences between task performance, and group was a between-measures factor that assessed differences between MS and HCs. Bonferroni corrections were applied to pairwise comparisons.

Exploratory mediation analyses were then conducted using ordinary least-squares path analysis (PROCESS V.3.5; Hayes, 2013) to assess if measures of executive function that differed between the groups mediated group differences on measures of social cognition. While some scholars contend that mediation analyses are only appropriate for longitudinal data, in which a mediator transmits the influence of a predictor on an outcome variable in a clear temporal order, others suggest that such analyses are appropriate for cross-sectional data if (a) there is a theoretically driven prediction and (b) the measured variables reflect nearly instantaneous processes (see Fairchild & McDaniel, 2017). The use of mediation analyses in the present study satisfies both of these criteria; as outlined above, current theories predict that social cognitive disruptions are (instantaneous) manifestations of disturbances to foundational executive functions. Therefore, mediation analyses allowed us to explore if common or specific disruptions to executive functions account for a significant proportion of disturbances to social cognitive processes. A necessary component of mediation is a statistically and practically significant indirect effect (Preacher & Hayes, 2004). Indirect effects were assessed with 10,000 bias-corrected bootstrap 95% confidence intervals (CIs; see Preacher & Hayes, 2004, 2008); CIs that do not overlap with zero indicate a significant mediation model. Percent mediation is reported, which is the ratio of the indirect to the total effect (*ab*/*c*; Preacher & Kelley, 2011).

Results

With listwise deletion, participants with outlier scores on any measure of executive function or social cognition were removed from each ANOVA analysis. The lowest sample size was 238 participants, comprising 114 individuals with MS and 124 HCs. Sensitivity power analyses indicated that across all analyses, effect sizes of $d > .32$ could be detected with 80% power at $\alpha = .05$.

The split-half reliability estimates for the dependent measures calculated from these participants in each task are shown in Table 2.

Table 2
Task Reliability

Task	MS	HC	Overall
KTT	.45 [.29, .58]	.56 [.44, .67]	.52 [.43, .60]
Stroop	.53 [28, .69]	.51 [.28, .68]	.52 [.35, .65]
CSS	.31 [−.08, .57]	.27 [−.11, .54]	.29 [.02, .49]
RMET	.62 [.52, .71]	.68 [.60, .75]	.66 [.60, .72]
FPT			
Experimental	63 [.51, .73]	.68 [.54, .80]	.51 [.37, .62]
Control	.37 [.15, .54]	.58 [.39, .71]	.66 [.57, .73]

Note. Values with square brackets present upper and lower 95% confidence intervals. MS = multiple sclerosis; HC = healthy control; KTT = keep track task; CSS = color-shape switching task; RMET = reading the mind in the eyes test; FPT = faux pas test.

This shows moderate reliability for all measures except the switch cost, which was poor.

Table 3 presents correlations among the dependent measures computed from each task, participant age, and self-reported disease duration (both expressed in years) for the MS group. Of particular interest, this shows that among the two measures of social cognition, accuracy on the RMET was correlated positively with that achieved on the FPT (increases in emotion perception were associated with increases in ToM); among the measures of executive function, accuracy on the KTT was correlated negatively with the interference effect shown on the Stroop task but *positively* with switch costs on the CSS task (increases in working memory associated with increases in response inhibition but decreases in switching), while Stroop and CSS task performance were not correlated significantly; and between measures of social cognition and executive function, a significant positive correlation was observed between accuracy on the RMET and performance on the KTT. Age was correlated positively with disease duration, and both age and disease duration were correlated positively with interference effects on the Stroop task, but both age and disease duration were correlated *negatively* with switch costs on the CSS task (increases in age and disease duration associated with decreases in response inhibition but increases in switching). To investigate this unexpected pattern of associations with switch costs, we performed a closer inspection of performance on the CSS task. This revealed that switch costs gradually disappeared and eventually reversed with the longer response latencies expressed by older adults in both the MS and HC groups. This opposes the pattern for interference effects, explaining these unexpected correlations (see supplemental Figure S1).

The first ANOVA identified neither a significant main effect of group, $F(1, 236) = 1.85$, $p = .176$, $\eta_p^2 = .01$, nor a significant effect of $task_{Executive}$, $F(2, 472) = .16$, $p = .850$, $\eta_p^2 = .001$. However, there was a significant Group × $Task_{Executive}$ interaction, $F(2, 472) = 4.86$, $p = .008$, $\eta_p^2 = .02$. Pairwise comparisons revealed that the MS group performed worse than the HC group on the KTT ($M = -.17$, $SD = .96$ and $M = .14$, $SD = 1.01$, respectively; $p = .015$, $d = .31$) and the Stroop ($M = .05$, $SD = .90$ and $M = -.15$, $SD = .64$, respectively; $p = .048$, $d = -.26$), but there were no significant differences on the CSS task ($M = -.07$, $SD = 1.01$ and $M = .07$, $SD = .83$, respectively; $p = .222$, $d = .15$).

The second ANOVA identified neither a main effect of $task_{Social}$, $F(1, 258) = .37$, $p = .546$, $\eta_p^2 = .001$, nor a significant Group × $Task_{Social}$ interaction, $F(1, 258) = .01$, $p = .905$, $\eta_p^2 < .001$. However,

Table 3
Correlations Among Dependent Measures for the MS Group (n = 112)

Variable	Age	Duration	KTT	Stroop	CSS	RMET	FPT
Age	—						
Duration	.65** [.51, .76]	—					
KTT	−.15 [−.32, .02]	−.14 [−.29, .02]	—				
Stroop	.29** [.10, .48]	.20* [−.01, .42]	−.25** [−.43, −.04]	—			
CSS	−.40** [−.54, −.23]	−.25** [−.42, −.05]	.22* [.05, .38]	−.17 [−.34, .001]	—		
RMET	.03 [−.13, .21]	.04 [−.12, .20]	.24* [.02, .43]	−.16 [−.36, .04]	−.02 [−.18, .15]	—	
FPT	.10 [−.08, .26]	.03 [−.12, .17]	.13 [−.08, .35]	−.01 [−.18,. .14]	−.07 [−.23, .09]	.23* [.06, .40]	—

Note. $N = 112$. Values present Pearson correlation coefficients, with square brackets containing upper and lower 95% confidence intervals. Correlation analyses were performed among z-scored accuracy scores for RMET, FPT, and KTT and z-scored differences in reaction time between experimental and control conditions for the Stroop ("interference effect") and CSS tasks ("switch cost"; see text for details). MS = multiple sclerosis; KTT = keep track task; CSS = color-shape switching task; RMET = reading the mind in the eyes test; FPT = faux pas test.
* $p < .05$. ** $p < .01$ (two-tailed).

there was a significant main effect of group, $F(1, 258) = 10.83$, $p = .001$, $\eta_p^2 = .04$. Follow-up pairwise comparisons revealed that the MS group was significantly less accurate on the RMET relative to the HC group ($M = -.11$, $SD = .91$ and $M = .19$, $SD = .97$, respectively; $p = .011$, $d = .32$) and achieved significantly lower faux pas detection on the FPT compared with HCs ($M = -.06$, $SD = .86$ and $M = .23$, $SD = .81$, respectively; $p = .006$, $d = .35$). Figure 2 illustrates this pattern across the five dependent measures.

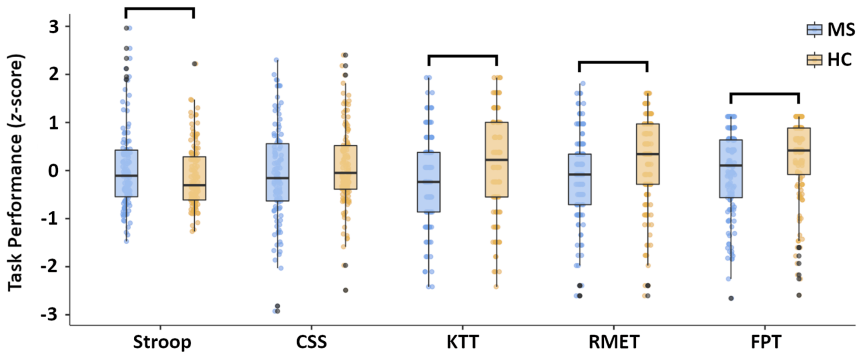
Exploratory Mediation Analyses

Since the MS group demonstrated poorer working memory and response inhibition relative to the HCs, two multimediator models were performed to assess the mediating effect of both executive functions on emotion perception and ToM. The first of these models revealed a significant indirect effect of KTT performance on the group difference in accuracy on the RMET ($ab = .07$, $SE = .04$, 95% CI [.01, .15]), indicating that working memory ability mediated poorer emotion perception for the MS group relative to HCs. This mediator accounted for 23% of the total (group) effect. The indirect effect of Stroop performance on the group difference in emotion perception was not significant ($ab = .005$, $SE = .02$, 95% CI [−.03, .05]), and this mediator (response inhibition) accounted for only 2% of the total effect. The second model revealed a significant indirect effect of KTT performance on the group difference in FPT accuracy ($ab = .04$, $SE = .02$, 95% CI [.002, .09]), revealing that working memory ability mediated the difference in ToM between the MS group relative to HCs. This mediator accounted for 20% of the total effect. Again, the indirect effect of Stroop performance on this group difference in ToM was not significant ($ab = -.007$, $SE = .01$, 95% CI [−.04, .02]), and this mediator accounted for only 4% of the total effect. Figure 3 illustrates these results.

Discussion

The present study investigated if the disturbance(s) to social cognition reported frequently in MS are underpinned by disruptions to executive functions. In line with our preregistered hypotheses and previous meta-analyses (Cotter et al., 2016; Johnen et al., 2017; Lin et al., 2021), a large sample of individuals reporting a diagnosis of MS showed poorer performance on measures of emotion perception, as measured with the RMET, and ToM relative to a group of age- and

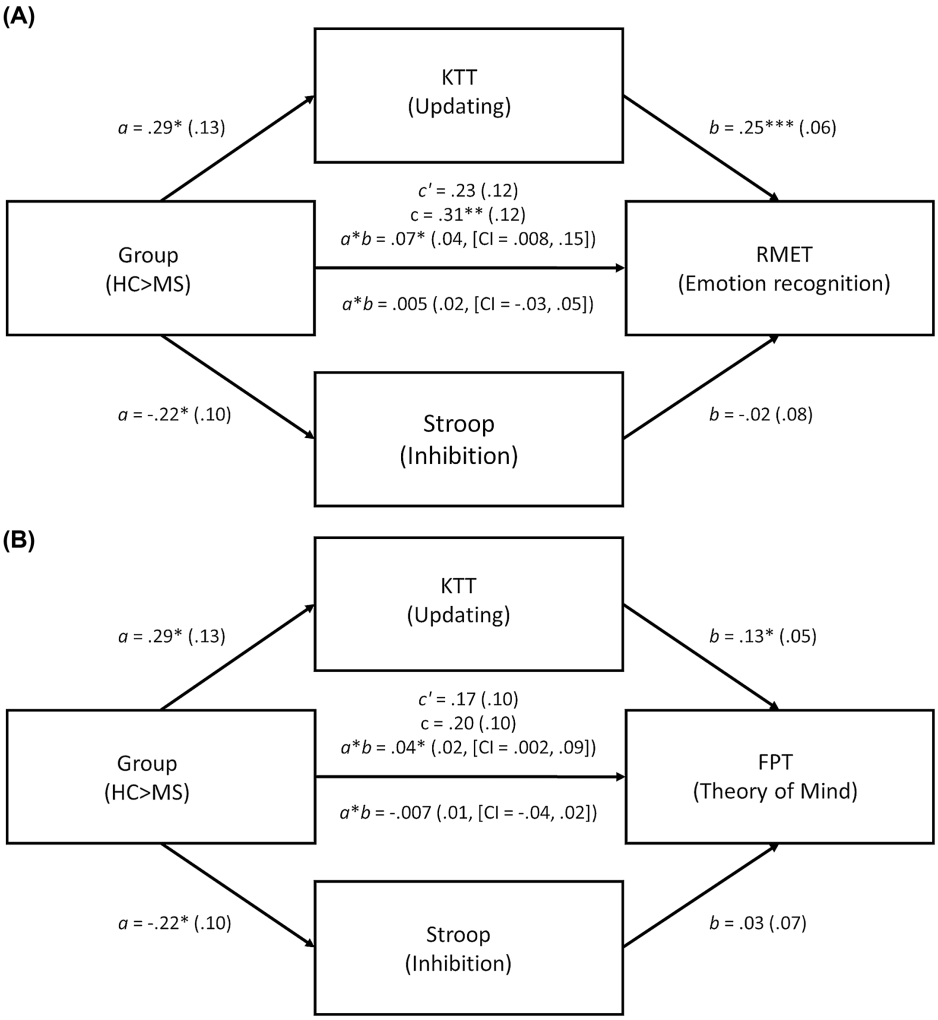
Figure 2
A Box Plot Showing Group Performance on Each Task



Note. Middle lines present medians, and error bars depict upper and lower quartiles. Horizontal lines indicate tasks on which performance differed significantly between the two groups. MS = multiple sclerosis; HC = healthy control; CSS = color-shape switching task; KTT = keep track task; RMET = reading the mind in the eyes test; FPT = faux pas test. See the online article for the color version of this figure.

Figure 3

The Mediating Effects of Working Memory and Response Inhibition on Social Cognition



Note. Panel A shows that performance on the KTT, but not the Stroop task, mediates the group difference in accuracy on the RMET. Panel B shows that performance on the KTT, but not the Stroop task, mediates the group difference in accuracy on the FPT. KTT = keep track task; HC = healthy control; MS = multiple sclerosis; RMET = reading the mind in the eyes test; FPT = faux pas test; CI = confidence interval.
* $p < .05$. ** $p < .01$. *** $p < .001$.

sex-matched HCs. Furthermore, the MS group also displayed impairments in two measures of executive function—namely, working memory and response inhibition. Exploratory mediation analyses revealed that working memory performance accounted for a considerable portion of the between-group difference in both emotion perception and ToM, but response inhibition did not. This indicates that disruptions to working memory in MS might serve as one of the mechanisms underpinning those observed in social cognition, supporting the notion that social cognitive impairments in MS are instantiations of alterations to fundamental executive processes.

This study is certainly neither the first to reveal disruptions to the working memory and response inhibition components of executive function, emotion perception, and ToM aspects of social cognition nor relationships among these sets of cognitive processes in MS (e.g., Drew et al., 2008; Dulau et al., 2017; Genova et al., 2015; J. D. Henry et al., 2009; Kraemer et al., 2013; Neuhaus et al., 2018; Ouellet et al., 2010; Raimo et al., 2017; for reviews, see Chiaravalloti & DeLuca, 2008; Islas & Ciampi, 2019; Langdon, 2011; Prakash et al., 2008; Sumowski et al., 2018). However, the present results extend these earlier findings by identifying a potential causal relationship; disruptions to working memory, but not response inhibition mediated group differences in emotion perception and ToM, accounting for approximately 20% of the effects. Although we acknowledge that other factors are likely to explain additional variance in such group effects, such as education level that was not measured in the present study (e.g., Ciampi et al., 2018; A. Henry et al., 2022), this finding could inform future research and clinical practice. Considerable variability exists in the measures employed to

assess neurocognitive functioning in MS, for both individual tests and multidomain batteries (Elwick et al., 2021). Although memory span is assessed commonly, working memory *updating* is rarely considered. As such, common neurological assessments will be unable to detect this specific domain of disruption—one that might interfere with a host of daily activities and, as we have shown, has the potential to impact negatively on cognitive systems supporting interpersonal behavior. Given the ease with which the KTT can be administered, and the resulting data can be analyzed, we encourage researchers and clinicians to incorporate this test into their routine neurological assessments. Furthermore, the present findings should guide future evaluations of cognitive rehabilitation programs. A number of such programs incorporate working memory training and have demonstrated their effectiveness in enhancing performance on outcome measures that require working memory updating, such as the Paced Auditory Serial Attention Test (for a review, see Sokolov et al., 2018). If disruptions to working memory updating do indeed contribute to impairments in social cognitive processes, the beneficial effects of working memory training should transfer to measurable improvements in emotion perception and ToM.

Unlike previous studies that have shown poorer switching ability in individuals with MS compared with HCs (e.g., Ciampi et al., 2018; Drew et al., 2008), we observed no such performance detriments on the CSS. This might reflect the poor reliability of switch cost measurements that we acquired with this task, which have also been reported elsewhere (e.g., Sicard et al., 2022). In the present study, reliability may have been further compromised as a result of the pattern of responses expressed by our sample; switch costs gradually disappeared and eventually reversed with the longer response latencies expressed by older adults. With longer response latencies, switch costs will become more variable as a result of various subprocesses; for example, greater response-to-stimulus intervals permit longer preparation times, which are known to influence switch costs substantially (Monsell, 2003). Increases in measurement error such as these can obscure true effects. This emphasizes the importance of future studies reporting reliability estimates for the cognitive behavioral tasks they employ to permit comparisons with other research findings (see Parsons et al., 2019).

An explosion of research into MS over the past few decades has examined emotion perception and ToM abilities. Meta-analyses of this literature have reached conflicting conclusions with regard to the individual tests employed to assess these core components of social cognition; while Cotter et al. (2016) and Bora et al. (2016) report impaired performance in individuals with MS compared with HCs on the RMET but not the FPT, Lin et al. (2021) report a reliable difference in the performance of these groups on both measures. Importantly, however, both Cotter et al. (2016) and Bora et al. (2016) report small but potentially meaningful effects with regard to the FPT (Cohen's $d \approx .26$). The present study observed that an effect size of similar magnitude was mediated fully by working memory performance, providing the first insight into possible mechanisms driving this small, but potentially impactful social cognitive disturbance. Even subtle disruptions to our capacity to infer others' beliefs, intentions, motivations, and perspectives on the world are likely to influence our behavior in interpersonal situations and, in turn, our social environment.

The link we have observed between working memory, response inhibition, and social cognition in MS is perhaps unsurprising when we consider their putative neural substrates. The dynamic updating of memory engages a frontoparietal brain network that transiently connects neural systems spanning dorsolateral prefrontal and parietal cortices (e.g., Menon & D'Esposito, 2022; Nee & Jonides., 2013; Uddin et al., 2019). Interestingly, then, meta-analytic data indicate that inferences about others' mental (e.g., intentional) states are supported by a partially overlapping network encompassing medial and lateral prefrontal and parietal cortices (Molenberghs et al., 2016; Schurz et al., 2013, 2021). Altered functional connectivity among nodes of the frontoparietal network is reported frequently in MS (for reviews, see Chard et al., 2021; Tahedl et al., 2018), likely resulting from widespread demyelination among constituent white matter tracts. Damage to the nodes and connecting tracts shared by networks supporting working memory processes and mental state inferences will have concomitant effects in these cognitive functions. Future research should investigate this by building on our behavioral data and assessing whether signatures of functional brain connectivity elicited during working memory updating, emotion perception, and/or ToM processes resemble one another, and if they are similarly (dis)connected in MS. This would go some way toward identifying biomarkers for the effects we have observed.

The method of online participant recruitment and data collection that we employed in the present study permitted us to not only acquire data from a well-powered sample, thereby overcoming the limitations of underpowered samples employed frequently in clinical studies (Lin et al., 2021), but also to capture the natural distribution of different MS disease courses. In the MS group, 80% reported relapse–remitting, 12% secondary- *or* primary progressive, and 7% clinically isolated syndrome. This converges with formal prevalence estimates (e.g., Benedict et al., 2020; Engelhard et al., 2022; Nazareth et al., 2018), which is important when we consider differences in the prevalence of cognitive symptoms presented in these phenotypes; estimates are 30%–45% in relapsing–remitting, 50%–75% in secondary-progressive MS, 20%–25% in clinically and radiologically isolated syndrome (Benedict et al., 2020). Similarly, 73% of our MS sample were female, converging with global ratios (Walton et al., 2020). Furthermore, correlations (or lack thereof) among demographic, clinical, and performance variables in the present sample align closely with those reported in clinical studies: Self-reported disease duration was unrelated to either measure of social cognition (e.g., Drew et al., 2008; Dulau et al., 2017; Neuhaus et al., 2018; for reviews, see Cotter et al., 2016; Lin et al., 2021), but age and disease duration were correlated with response inhibition and switching (Ciampi et al., 2018; but see Drew et al., 2008), likely reflecting the reliance on processing speed in the Stroop and CSS tasks (for a review, see Vallesi et al., 2021). Finally, through this method of recruitment, we were able to acquire data from individuals with MS residing across 20 different European (e.g., Ireland and Germany) and non-European countries (e.g., the United States and South Africa), and a range of ethnicities. Although the vast majority of our MS and HC samples reported to be White, somewhat limiting the generality of the present findings, this demonstrates the utility of online methodology for research into cognitive function in MS.

We are not, of course, claiming that self-report data acquired online present an alternative to controlled clinical assessments. Although we restricted our analyses to data acquired from participants who passed two separate attention checks administered at different points of the procedure and excluded from our analyses any data that might indicate careless responding (i.e., outliers), it is important to acknowledge some potential limitations of this approach to data acquisition. First, we cannot know about the conditions in which participants complete tasks administered online. It is entirely

possible that environmental distractions could have influenced participants' performance, though this is unlikely to have exerted a systematic influence on the between-group differences we have observed. Second, in the sample of individuals with MS that we recruited, 10% were unwilling or unable to state their current diagnosis, and without clinical records, we are unable to verify the reports of those who did declare this information. This data acquisition method also prevented us from collecting objective measurements of disease severity or depressive symptoms. Although several studies have reported that neither clinical characteristics is reliably correlated with executive functions (Ciampi et al., 2018; A. Henry et al., 2022; Johnen et al., 2017; Raimo et al., 2017; but see Dulau et al., 2017) nor social cognition (Dulau et al., 2017; J. D. Henry et al., 2009; Kraemer et al., 2013; Neuhaus et al., 2018; for reviews, see Bora et al., 2016; Cotter et al., 2016; Lin et al., 2021), it is important that these clinical data are collected and reported if we are to eventually develop precise characterizations of cognitive syndromes that can occur at different disease stages. Furthermore, although we used prescreening criteria on Prolific to ensure that the study was available only to individuals who reported no "mild cognitive impairment/dementia," this did not preclude volunteers with preclinical dementia. The accurate identification of such individuals requires sensitive global cognitive screening assessments. For these reasons, we stress that the findings of this study should be treated as preliminary and in need of replication in studies that administer our publicly available assessment battery under tightly controlled experimental conditions and on individuals for whom clinical records and screening assessments are available.

Rather than focusing on isolated deficits, in the present study, we administered a broad battery of experimental tasks that allowed us to explore multiple aspects of executive function and social cognition as well as their interrelationships and dependencies simultaneously in a within-subject manner. To build upon previous research on social cognitive disruptions in MS and guide future studies, we measured each executive function and social cognitive process with tasks and performance indices (i.e., relative response times and accuracies) used commonly in the literature. However, such crude metrics can only offer limited insights into each of these seemingly complex cognitive operations. This is true especially when examining accuracy across all items of the RMET; recent meta-analyses have shown this task to have a multidimensional structure, in which subsets of items appear to assess different aspects of social cognition (Higgins et al., 2022). Similarly, responses to subsets of items on the FPT task can be combined to assess different dimensions of social awareness (e.g., understanding others' intentions and empathic awareness). To achieve even more precise characterizations of the social cognition disturbances and underpinning disruptions to executive functions in MS, future studies should build upon our findings and assess dependencies among the constituent dimensions of these and other tasks measuring components of cognitive function.

Conclusion

Consistent with a growing body of research, our findings from an online sample show that MS can result in disruptions to core social cognitive capacities crucial for maintaining a healthy social environment; specifically, poorer emotion perception and ToM. Moreover, we provide preliminary evidence that such impairments to social cognition are underpinned partly by disruptions to a specific executive function—working memory. These results should guide further research into the interdependent and possibly causal relationships between this and other executive functions and social cognitive processes.

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