Social cognition in multiple sclerosis

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Social cognition in multiple sclerosis
A systematic review and meta-analysis

ABSTRACT
Objective: To quantify the magnitude of deficits in theory of mind (ToM) and facial emotion recognition among patients with multiple sclerosis (MS) relative to healthy controls.

Methods: An electronic database search of Ovid MEDLINE, PsycINFO, and Embase was conducted from inception to April 1, 2016. Eligible studies were original research articles published in peer-reviewed journals that examined ToM or facial emotion recognition among patients with a diagnosis of MS and a healthy control comparison group. Data were independently extracted by 2 authors. Effect sizes were calculated using Hedges g.

Results: Twenty-one eligible studies were identified assessing ToM (12 studies) and/or facial emotion recognition (13 studies) among 722 patients with MS and 635 controls. Deficits in both ToM ($g = 0.71$, 95% confidence interval [CI] $-0.88$ to $-0.55$, $p < 0.001$) and facial emotion recognition ($g = -0.64$, 95% CI $-0.81$ to $-0.47$, $p < 0.001$) were identified among patients with MS relative to healthy controls. The largest deficits were observed for visual ToM tasks and for the recognition of negative facial emotional expressions. Older age predicted larger emotion recognition deficits. Other cognitive domains were inconsistently associated with social cognitive performance.

Conclusions: Social cognitive deficits are an overlooked but potentially important aspect of cognitive impairment in MS with potential prognostic significance for social functioning and quality of life. Further research is required to clarify the longitudinal course of social cognitive dysfunction, its association with MS disease characteristics and neurocognitive impairment, and the MS-specific neurologic damage underlying these deficits.

GLOSSARY
CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; ToM = theory of mind.

Cognitive dysfunction is present in up to 70% of patients with multiple sclerosis (MS) and has been reported at all stages and in all subtypes of the disease. Deficits are most commonly reported in attention, processing speed, memory, and executive function. However, comparatively little is known about the impact of MS on social cognition, the “mental operations that underlie social interactions.” Following pioneering work in autism, social cognitive impairment has been reported in a range of psychiatric, developmental, and neurodegenerative disorders. In this review, we focus on theory of mind (ToM) and facial emotion recognition, 2 core aspects of social cognition that have been the subject of recent research in MS. Deficits in these social cognitive domains are associated with reduced social and psychological quality of life in patients with MS, even after controlling for severity and duration of disease, age, and neurocognitive performance. ToM refers to the ability to infer the intentions, dispositions, and beliefs of others and is thought to comprise distinguishable but overlapping cognitive and affective components. Facial emotion recognition refers to an individual’s ability to identify and discriminate between the emotional states of others based on their facial expressions. Collectively these drive interpersonal skills such as empathy, and may have important
implications for social functioning. In this meta-analysis, we aimed to quantify the magnitude of deficits in ToM and facial emotion recognition among patients with MS relative to healthy controls. We also sought to explore the relationship between clinical, cognitive, and demographic factors and social cognitive performance.

METHODS This review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Study inclusion criteria. Eligible studies were original research articles published in peer-reviewed journals that examined ToM or facial emotion recognition among patients with a diagnosis of MS, as defined by the Poser or McDonald criteria. In order to be included, studies needed to include a healthy control comparison group and sufficient data to calculate an effect size. Where studies reported data from a subsample of patients from a larger study, only the larger study was included. No restrictions were placed on the age of patients or phenotype of MS for inclusion. Case studies, review articles, and non-English-language articles were excluded.

Search strategy. On April 1, 2016, we conducted an electronic database search of Ovid MEDLINE, PsycINFO, and Embase (from inception) using the following keyword search terms: “multiple sclerosis” and “social cognition” or “theory of mind” or “emotion.” In addition, a basic search of Google Scholar was conducted and the reference lists of retrieved articles were also reviewed to identify any additional relevant publications.

Study selection and data extraction. Two of the authors (J.C. and J.F.) independently screened articles for eligibility. There were no disagreements regarding the inclusion of studies in this review. A standardized data extraction spreadsheet was used for all eligible studies to record the following: (1) study characteristics (year of publication, country where the work was performed); (2) social cognitive domains assessed and measured used; (3) MS and control sample demographics (sample size, sex, age, years of education, disease duration, disease course, medication, depression, fatigue, and degree of physical disability); (5) study characteristics.

Statistical analysis. Data analyses were performed using Comprehensive Meta-Analysis version 3.0.18 Standardized mean differences (effect sizes) were calculated for both overall ToM and facial emotion recognition using Hedges’ g. This represents the difference between the means of the MS and healthy control comparison groups, divided by the pooled SD and weighted for sample size. For individual studies in which multiple measures were used to examine either ToM or facial emotion recognition, a pooled effect size and 95% confidence interval (CI) was calculated based on the mean of the effect sizes and corresponding standard errors for each task.

RESULTS Study characteristics. The study selection process is summarized in figure 1. We identified 21 eligible articles from 12 countries (table 1). Twelve studies examined ToM and 13 examined facial emotion recognition (4 examined both). One study reported outcome data separately for cognitively impaired and cognitively intact MS groups. As both groups had distinct clinical profiles, they were used and treated as separate data points in the meta-analyses. Another study included 8 patients with clinically definite MS and 12 with a clinically isolated syndrome suggestive of MS. This study was included in the relevant meta-analyses on the basis that a high proportion of patients with a clinically isolated syndrome go on to develop MS. However, additional sensitivity analyses were performed to examine the impact of this study on the results.

In total, 1,369 participants were included, 722 of whom had been diagnosed with MS, and 635 were healthy controls. The mean age of patients across samples was 39.9 years (range 16.3–52 years) and 67% were female. Control groups were generally well-matched to the MS groups with regards to age and sex and often for years of education and IQ, where reported. The mean disease duration was 8...
<table>
<thead>
<tr>
<th>Reference: Country</th>
<th>Social cognition tasks</th>
<th>Group</th>
<th>No. (F/M)</th>
<th>Age, y</th>
<th>Education, y</th>
<th>Disease duration, y</th>
<th>Disease course</th>
<th>EDSS</th>
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<tr>
<td>Banati et al.53; Hungary</td>
<td>ToM: RMitE, Faux Pas task, Adult Faces</td>
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<td>40 (29/11)</td>
<td>36.2 (9.4)</td>
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<td>HC</td>
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<td>Beatty et al.36; USA</td>
<td>FER: Ekman Faces</td>
<td>MS</td>
<td>21 (NR)</td>
<td>52</td>
<td>14</td>
<td>18.4</td>
<td>CP 21</td>
<td>6.6</td>
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<td>Berneiser et al.37; Germany</td>
<td>FER: FAB</td>
<td>MS</td>
<td>61 (44/17)</td>
<td>42.2</td>
<td>14</td>
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<td>RR 47, PP 3, SP 11</td>
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<td>HC</td>
<td>53 (33/20)</td>
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<td>NR</td>
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<tr>
<td>Cecchetto et al.38; Italy</td>
<td>FER: NimStim</td>
<td>MS</td>
<td>30 (21/9)</td>
<td>34.2 (6.2)</td>
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<td>9.1 (6.7)</td>
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<td>15.2 (3.1)</td>
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<td>Charvet et al.27; USA</td>
<td>ToM: RMitE, Faux Pas task, False Belief task</td>
<td>MS</td>
<td>28 (19/9)</td>
<td>16.29 (3.12)</td>
<td>NR</td>
<td>2.82 (2.51)</td>
<td>RR 28</td>
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<td>HC</td>
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<td>Genova et al.39; USA</td>
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<td>15 (11/4)</td>
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<td>Henry et al.28; Australia</td>
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<td>27 (18/9)</td>
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<td>MS</td>
<td>64 (50/14)</td>
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<td>38.6 (13.9)</td>
<td>12.4 (3.25)</td>
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<td>Jehna et al.45; Austria</td>
<td>FER: Ackerer face tasks</td>
<td>MS</td>
<td>20 (13/7)</td>
<td>36.4 (9.3)</td>
<td>13.65 (1.90)</td>
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<tr>
<td>Jehna et al.46; Austria</td>
<td>FER: BERT</td>
<td>MS</td>
<td>15 (10/5)</td>
<td>29.47 (9.61)</td>
<td>13.80 (2.91)</td>
<td>7.27 (6.46)</td>
<td>RR 15</td>
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<td>15 (10/5)</td>
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<td>Kraemer et al.34; Germany</td>
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<td>25 (15/10)</td>
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<td>Lenne et al.31; France</td>
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<td>55 (44/11)</td>
<td>39.84 (8.74)</td>
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<td>Ouellet et al.24; Canada</td>
<td>ToM: Faux Pas task, Strange stories, C&amp;B</td>
<td>MS −</td>
<td>26 (15/11)</td>
<td>45.2 (7.3)</td>
<td>13.7 (2.6)</td>
<td>10.2 (8.1)</td>
<td>RR 11, PP 3, SP 11, NR 1</td>
<td>3.8 (2.7)</td>
</tr>
<tr>
<td></td>
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<td>MS +</td>
<td>15 (12/3)</td>
<td>43.6 (8.3)</td>
<td>13.6 (2.0)</td>
<td>6.2 (4.6)</td>
<td>RR 11, PP 2, SP 2</td>
<td>2.8 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC</td>
<td>20 (10/10)</td>
<td>48.5 (8.2)</td>
<td>14.6 (1.9)</td>
<td>—</td>
<td>—</td>
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<td>Parada-Fernández et al.54; Spain</td>
<td>FER: FEEL</td>
<td>MS</td>
<td>45 (29/16)</td>
<td>49.44 (9.44)</td>
<td>NR</td>
<td>NR</td>
<td>RR 24, PP 10, SP 6, RP 5</td>
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<td>40 (20/20)</td>
<td>50.78 (10.08)</td>
<td>NR</td>
<td>—</td>
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<td>Passamonti et al.46; Italy</td>
<td>FER: Ekman Faces</td>
<td>MS</td>
<td>12 (7/5)</td>
<td>29.3 (8.1)</td>
<td>11.6 (2.8)</td>
<td>4.3 (2.8)</td>
<td>RR 12</td>
<td>1.5</td>
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Continued
**Table 1 Continued**

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<th>Reference, Country</th>
<th>Social cognition tasks</th>
<th>Group</th>
<th>No. (F/M)</th>
<th>Age, y</th>
<th>Education, y</th>
<th>Disease duration, y</th>
<th>Disease course</th>
<th>EDSS</th>
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<td>Phillips et al.11: UK</td>
<td>ToM: Video task</td>
<td>HC</td>
<td>33 (24/9)</td>
<td>44.4 (9.8)</td>
<td>16.7 (3.5)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Pinto et al.32: Portugal</td>
<td>FER: NimStim</td>
<td>MS</td>
<td>56 (32/24)</td>
<td>38.95 (10.34)</td>
<td>13.21 (4.48)</td>
<td>9.0 (6.2)</td>
<td>RR 48, PP 5, SP 3</td>
<td>2.47 (1.97)</td>
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<tr>
<td>Pöttgen et al.29: Germany</td>
<td>ToM: MASC</td>
<td>MS</td>
<td>45 (31/14)</td>
<td>42.42 (10.66)</td>
<td>14.16 (2.82)</td>
<td>8.46 (6.18)</td>
<td>RR 31, PP 6, SP 8</td>
<td>3.47</td>
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<tr>
<td>Prochnow et al.39: Germany</td>
<td>FER: Ekman Faces, PCFAE</td>
<td>MS</td>
<td>35 (12/23)</td>
<td>48.2 (10.2)</td>
<td>10.8 (2.7)</td>
<td>9.2 (8.4)</td>
<td>RR 5, PP 1, SP 29</td>
<td>6</td>
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<tr>
<td>Roca et al.35: Argentina</td>
<td>ToM: Faux Pas task</td>
<td>HC</td>
<td>16 (NR)</td>
<td>40.88 (9.99)</td>
<td>10.92 (7)</td>
<td>9.0 (9.4)</td>
<td>RR 18</td>
<td>0.58 (0.99)</td>
</tr>
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</table>

Abbreviations: BERT = Behavioral Emotion Recognition Test; C&I = Conversation and Insinuation task; CIS = clinically isolated syndrome; CP = chronic progressive; EDSS = Expanded Disability Status Scale; FAB = Florida Affect Battery; FER = Facial Emotion Recognition; FESST = Facial Expressions of Emotion Stimuli and Tests; FER = facial emotion recognition; HC = healthy controls; MASC = Movie for the Assessment of Social Cognition; MS = multiple sclerosis; MS CI = cognitively impaired group; MS CI = cognitively intact group; NR = not reported; PCFAE = Test of Perceptual Competence of Facial Affect Recognition; PP = progressive progressive; PR = relapsing-remitting; RR = relapsing-remitting; SP = secondary progressive; TAST = The Awareness of Social Inference Test; ToM = Theory of mind.

Values are means (SD) provided except where specified.
performance, though there were trend associations with EDSS score ($p = 0.066$) and disease duration ($p = 0.086$) (table e-1 and figure e-2). There was some evidence of low to moderate statistical heterogeneity in the overall facial emotion recognition effect size. The Egger regression test showed no evidence of publication bias for overall facial emotion recognition ($b = 0.778$, SE = 1.73, $p = 0.33$) (figure e-3). The fail-safe $N$ was 257. A sensitivity analysis excluding the only study to include patients with a clinically isolated syndrome had a negligible impact on the results.

Table 2 Mean weighted effect sizes, sample sizes, and heterogeneity statistics

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of studies</th>
<th>No. (MS)</th>
<th>No. (controls)</th>
<th>Hedges g</th>
<th>95% CI</th>
<th>Z</th>
<th>$p$</th>
<th>$I^2$ (95% CI)</th>
<th>$H^2$ (95% CI)</th>
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<tr>
<td>ToM (overall)</td>
<td>13</td>
<td>429</td>
<td>345</td>
<td>-0.71</td>
<td>-0.88 to -0.55</td>
<td>-8.38</td>
<td>$&lt;0.001$</td>
<td>23% (0–59.8)</td>
<td>1.30 (1.00–2.49)</td>
</tr>
<tr>
<td>Faux Pas</td>
<td>7</td>
<td>240</td>
<td>157</td>
<td>-0.26</td>
<td>-0.58 to 0.07</td>
<td>-1.56</td>
<td>0.119</td>
<td>61% (10.8–83.0)</td>
<td>2.56 (1.12–5.87)</td>
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<tr>
<td>RMitE</td>
<td>5</td>
<td>189</td>
<td>161</td>
<td>0.92</td>
<td>-1.15 to 0.70</td>
<td>-8.01</td>
<td>$&lt;0.001$</td>
<td>4% (0–80)</td>
<td>1.04 (1.00–5.01)</td>
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<td>Video task</td>
<td>6</td>
<td>158</td>
<td>138</td>
<td>-0.65</td>
<td>-0.92 to -0.37</td>
<td>-4.66</td>
<td>$&lt;0.001$</td>
<td>29% (0–70.9)</td>
<td>1.41 (1.00–3.44)</td>
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<tr>
<td>FER (overall)</td>
<td>13</td>
<td>473</td>
<td>423</td>
<td>-0.64</td>
<td>-0.81 to -0.47</td>
<td>-7.23</td>
<td>$&lt;0.001$</td>
<td>36% (0–66.9)</td>
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<td>Anger</td>
<td>8</td>
<td>344</td>
<td>301</td>
<td>-0.58</td>
<td>-0.81 to -0.36</td>
<td>-5.03</td>
<td>$&lt;0.001$</td>
<td>49% (0–77.3)</td>
<td>1.96 (1.00–4.40)</td>
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<td>Disgust</td>
<td>7</td>
<td>289</td>
<td>280</td>
<td>-0.24</td>
<td>-0.51 to 0.03</td>
<td>-1.72</td>
<td>0.086</td>
<td>62% (13.4–83.3)</td>
<td>2.63 (1.15–6.00)</td>
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<tr>
<td>Fear</td>
<td>8</td>
<td>344</td>
<td>301</td>
<td>-0.56</td>
<td>-0.81 to -0.32</td>
<td>-4.49</td>
<td>$&lt;0.001$</td>
<td>56% (3–80)</td>
<td>2.27 (1.03–5.01)</td>
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<tr>
<td>Happiness</td>
<td>8</td>
<td>244</td>
<td>301</td>
<td>-0.14</td>
<td>-0.35 to 0.07</td>
<td>-1.31</td>
<td>0.190</td>
<td>41% (0–73.9)</td>
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<td>Sadness</td>
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<td>344</td>
<td>301</td>
<td>-0.35</td>
<td>-0.54 to -0.17</td>
<td>-3.72</td>
<td>$&lt;0.001$</td>
<td>26% (0–86.5)</td>
<td>1.35 (1.00–3.00)</td>
</tr>
<tr>
<td>Surprise</td>
<td>7</td>
<td>289</td>
<td>280</td>
<td>-0.25</td>
<td>-0.50 to 0.01</td>
<td>-1.91</td>
<td>0.056</td>
<td>55% (0–80.7)</td>
<td>2.22 (1.00–5.18)</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; FER = facial emotion recognition; MS = multiple sclerosis; RMitE = Reading the Mind in the Eyes test; ToM = theory of mind.
Identification of specific emotional expressions. We performed additional analyses to examine the patients’ ability to identify each of the 6 specific basic emotional facial expressions (table 2). Effect sizes indicated deficits among the MS group in recognition of all types of emotional facial expressions; however, statistically significant deficits were identified only for anger, sadness, and fear. There were no statistically significant differences for labeling of happiness, disgust, or surprise.

Relationship with neurocognitive impairment, depression, and fatigue. Evidence to date suggests social cognitive dysfunction may occur both independently and secondary to neurocognitive deficits. There is evidence that social cognitive deficits are greater among...
patients with MS with more severe neurocognitive impairment. Significant positive correlations have also been reported between both ToM and facial emotion recognition task performance and neurocognitive measures of processing speed, working memory, and executive function. However, the strength and statistical significance of these associations was inconsistent, which may be at least partially attributable to differences in task demands. Studies have also reported that social cognition remained significantly impaired among patients with MS even after controlling for neurocognitive performance or after excluding those patients with cognitive impairment. Despite early work suggesting facial emotion recognition deficits were due to general problems discriminating between faces, more recent work indicated that these deficits also occurred in those with intact facial recognition, suggesting this deficit is due to a specific emotional rather than perceptual impairment.

Eleven of the studies in this review explicitly excluded patients with major depressive disorder. Though depressive symptoms were generally higher in the MS groups, no studies examining ToM reported associations between depressive symptoms and task performance and only 3 assessing facial emotion recognition did so. Similarly, fatigue was unrelated to performance on ToM tasks and evidence linking it to facial emotion recognition was inconsistent.

**DISCUSSION** Our results show significant deficits in the ability of patients with MS to identify and discriminate between the mental and emotional states of others relative to healthy controls. It is important to consider that these deficits were observed among a sample with a relatively young mean age (39.9 years), short disease duration (mean 8 years), mild to moderate degree of physical disability (median EDSS score 2.3), and predominantly relapsing-remitting course of illness (77%). Specific deficits were identified in the labeling of sad, fearful, and angry facial expressions. Among ToM tasks, patients with MS showed impairment in their ability to infer the mental states of others during visual tasks based on both images and videos. Deficits appeared to a degree independent of global neurocognitive impairment, though findings were inconsistent.

Previous reviews among patients with relapsing-remitting MS have reported global deficits in neurocognitive functioning (g = 0.58) relative to healthy controls, as well as domain-specific deficits in areas including memory (g = 0.60), attention and executive ability (g = 0.55), and verbal functions and language (g = 0.44). The findings of this review suggest that social cognitive deficits are similar or greater in magnitude to those observed in other aspects of cognition in this patient group. Deficits in ToM and facial emotion recognition among those with MS were not as severe as those identified in patients with schizophrenia (g = 0.88–0.96) or in other neurodegenerative disorders such as Parkinson disease (Cohen d = 0.83). However, they appear to be worse than those reported in attention-deficit/hyperactivity disorder (Cohen d = 0.44–0.45) and major depressive disorder (g = 0.16–0.51).

To date, social cognitive research in MS has consisted of small, cross-sectional studies, conducted primarily in patients with a relapsing-remitting disease course and modest level of physical disability. This earlier disease course is characterized by bouts of inflammation and periods of recovery and remyelination. When the disease advances to a progressive course, episodes of inflammation and demyelination become more infrequent, with a shift towards neurodegeneration and sustained damage. This has implications for the generalizability of these findings and highlights the need for research investigating the longitudinal course of social cognitive dysfunction. More research is needed in patients with a progressive course of illness and more severe physical disability to establish the extent to which the results of this review are generalizable to this patient group. This should ideally include repeated assessments over long-term follow-up and neuroimaging to permit more detailed examination of the relationship between disease characteristics and progression, tissue damage, and social cognitive dysfunction. The limited structural and functional imaging evidence among patients with MS to date suggests that social cognitive deficits may be due to abnormalities in the neural circuitry that underlie these processes. However, further analyses, particularly for ToM, are warranted to improve our understanding of social cognitive decline. Similarly, the relationship between social cognitive and neurocognitive deficits in MS remains unclear and would benefit from longitudinal evaluation.

Social cognitive research in MS has focused almost entirely on ToM and facial emotion recognition. Although studies have also investigated vocal and bodily affect recognition, in this patient group, there were too few to allow inclusion in the current review. In addition, only English-language articles were eligible for inclusion, which led to the exclusion of 2 non-English-language articles found in the electronic search. However, the large fail-safe N and lack of evidence suggestive of publication bias for both ToM and facial emotion recognition suggest that our findings were robust.

There was evidence of low to moderate statistical heterogeneity in the effect size estimates. This is likely
to have been driven by differences in the clinical and demographic characteristics of the study samples and the social cognitive tasks that were used. Facial emotion recognition tasks required individuals to label images of faces depicting up to 6 basic emotions. In contrast, ToM was assessed using a wide variety of tasks. Additional analyses investigating performance on the 3 most common types of ToM tasks indicated that patients with MS exhibited marked impairment in their ability to infer the mental states of others during visual tasks. However, nonsignificant deficits were found for performance on Faux Pas recognition tasks. High levels of heterogeneity in the effect size estimate for the Faux Pas recognition tasks may have been driven by alterations in these subtle tests due to translation, modification, or child versions being used. There was also some overlap between social cognitive domains. For example, the Reading the Mind in the Eyes test \(^1\text{9}\) was classed as a ToM measure as it requires the identification of complex mental states; however, it also includes emotion recognition items. Similarly, ToM video tasks typically require competence in emotion recognition and social knowledge. This tentatively suggests that the largest deficits in ToM are observed in those tasks with an affective component.

In addition to the meta-analysis, we conducted exploratory meta-regression analyses. These should be interpreted with caution. Although these provide a useful tool to visualize the relationship between social cognitive performance and each of the clinical and demographic variables, they are underpowered to detect anything but very large study-level effects since they only include aggregate data from a relatively small number of studies.

MS is a disease characterized by considerable patient heterogeneity in clinical presentation, lesion profiles, and cognitive dysfunction.\(^4\),\(^9\),\(^5\)\(^0\)\) Despite this variation, this review identified consistent deficits in the domains of ToM and facial emotion recognition. Individual studies suggested this was the case even among patients with early MS.\(^2\) Social cognitive deficits have been identified as potentially important predictors of quality of life among patients with MS,\(^1\) and warrant further attention. Further research is required to clarify the longitudinal course of social cognitive dysfunction, its association with MS disease characteristics and neurocognitive impairment, and the MS-specific neurologic damage underlying these deficits.

The results of this review emphasize the need to increase awareness among treating physicians of social cognitive dysfunction. They also support recent calls for monitoring of social cognition to be incorporated into routine neurologic assessments.\(^5\)\(^1\) Current cognitive test batteries developed for clinical use with MS include only neurocognitive tasks. Evidence from this review suggests that social cognitive deficits may be comparable in magnitude to or even exceed other neurocognitive impairments and should also be considered for inclusion. This raises the possibility of identifying early and subtle impairments and potentially intervening before deficits become more pronounced. This may be particularly important among patients with pediatric-onset MS. Social cognitive skills are likely to still be developing in these young people and early deficits may be more damaging for the development of social skills in the longer term. Social cognitive training has been shown to be effective in other disorders\(^5\)\(^2\) and it is hoped that the results of this review can potentially help inform the development of similar interventions for those with MS.

AUTHOR CONTRIBUTIONS

Jack Cotter: review concept and design, literature search, data extraction, statistical analyses, interpretation of data, drafting and revision of manuscript. Joseph Firth: data extraction, interpretation of data, critical revision of manuscript for intellectual content. Christian Enzinger: interpretation of data, critical revision of manuscript for intellectual content. Evangelos Kontopantelis: technical guidance with statistical analyses, interpretation of data, critical revision of manuscript for intellectual content. Alison Yang: interpretation of data, critical revision of manuscript for intellectual content. Rebecca Elliott: interpretation of data, critical revision of manuscript for intellectual content. Richard Drake: interpretation of data, critical revision of manuscript for intellectual content.

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DISCLOSURE

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