Relationship between emotion recognition and cognition in multiple sclerosis: a meta-analysis protocol

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ABSTRACT

Introduction Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system characterised by a broad and unpredictable range of symptoms, including cognitive and socio-cognitive dysfunction. Alongside the well-known deficits in information processing speed (IPS), executive functioning and episodic memory, recent evidence also highlighted socio-cognitive impairments in MS, such as emotion-recognition deficits. Recently, several studies investigated the association between emotion-recognition and cognitive impairment to assess whether social cognition is parallel to (or even dependent on) general cognitive dysfunction. Yet, there have been inconsistent findings, raising the need for a meta-analysis of the literature.

Objectives The aim of the present paper is to outline the protocol for an upcoming meta-analysis we designed to clarify these conclusions.

Methods and analysis We plan to estimate combined effect sizes for the association between emotion-recognition and cognitive impairment in MS across three cognitive domains (IPS, executive functions and episodic memory) and 7 emotion scores of interests (total and by 6-basic emotions subscores). Further, we plan to investigate whether identified variables are the cause for heterogeneity in any combined association. To that end, we will conduct additional meta-regression analyses to explore whether overall correlations differ according to clinical characteristics of MS patients (ie, disease duration, MS-phenotype, severity of depression and disability). Ultimately, this study will provide support either for an association of these disorders (in which emotion-recognition deficits might result from more fundamental cognitive dysfunction), or for two distinct sets of symptoms which may occur independently, for targeted patient profiles.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cognitive dysfunction is prevalent in multiple sclerosis (MS), affecting up to 70% of patients, encompassing deficits in information processing speed, memory and executive functions.
⇒ Emotion recognition deficits, particularly for negative emotions, have been observed in persons with MS (pwMS) patients but the relationship between these deficits and general cognitive impairment is unclear.
⇒ Studies indicate a potential link between social cognition deficits and general cognitive impairment in MS, raising questions about their interdependence.

WHAT THIS STUDY ADDS

⇒ This study proposes an extensive meta-analysis to quantitatively assess the relationship between emotion recognition deficits and cognitive impairment in pwMS.
⇒ By taking into account demographic and clinical factors such as age, sex, disease duration, Expanded Disability Status Scale score, depression, anxiety, fatigue, metacognition and alexithymia, this research aims for a nuanced understanding of this association.
⇒ Estimate the significance and importance of this relationship while considering some variables may help to better understand mixed results in existing literature.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This research could enhance comprehension of socio-cognitive symptoms that are poorly managed in MS.
⇒ By accounting for demographic and clinical factors, the study may facilitate identification of pwMS subgroups prone to specific cognitive and socio-cognitive issues.
⇒ Better understanding of MS-related symptoms is the first step towards improving MS disease management.

INTRODUCTION
Background

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system characterised by multifocal destruction of myelin sheaths and axonal loss[1 2] and the most common cause of neurological disability in young adults.[3] This disease is characterised by a broad and unpredictable range of symptoms, including motor, visual, neuropsychiatric symptoms and cognitive decline.[4] These disturbances lead to significant functional impairment including difficulties in social functioning and employment.[5] Cognitive dysfunction, present in up

to 70% of persons with MS (pwMS), has been reported at all stages and in all subtypes of the disease,[6] and contributes to functional impairment in MS.[4 5] These disorders are, mainly, impairments in information processing speed (IPS),[6 7] learning and episodic memory, and executive functioning.[6 8] Besides cognitive dysfunction, recent studies have also highlighted social cognition deficits in MS,[9 10] including in early-stage disease and in patients with clinical isolated syndromes.[11–14]

Social cognition is a multi-component construct referring to a set of different processes aimed at recognising and interpreting signals from the environment, understanding self and others' behaviours, and adapting the response in a way that is consistent with the context.[15 16] Social-cognitive skills required for successful social interaction include social perception (eg, emotion recognition), mental state decoding (eg, theory of mind (ToM)), empathy and social behaviour.[16] In MS, two recent meta-analysis identified both ToM and emotion recognition deficits in patients.[9 17] If there is general consensus among studies that deficits in emotion recognition seems rather limited to negative emotions in pwMS,[9 17] the reason for these deficits are still under discussion. A few functional MRI studies investigated brain activation during an emotion recognition task in pwMS and suggested that emotion processing deficits (and more generally socio-cognitive deficits) in MS may result from alterations in the neural substrates underlining these processes.[14 18 19] Other studies proposed that such difficulties in recognising emotions in MS are related to a disconnection mechanism between cortical and subcortical networks due to demyelination or axonal loss (see Degraeve *et al*[20] for a review).

More recently, a growing body of research investigated if social cognition impairments were likely to be underpinned by general cognitive dysfunction or if there were susceptible to arise independently (for a review, see Giazkoulidou *et al*[21]). Indeed, a number of studies have investigated the association between emotion recognition and cognitive impairment to assess whether social cognition is parallel to (or even dependent on) general non-social cognitive dysfunction. Yet, there have been mixed findings. For example, some studies reported medium-sized correlations between social-cognitive and cognitive deficits.[10 22] However, other studies found no such correlations. Instead, they argued in favour of two distinct sets of symptoms, suggesting that emotion recognition deficits in MS may not merely be an epiphenomenon of more basic cognitive dysfunction but could arise independently.[23 24] Given that these mixed findings could be related to the low statistical power, a meta-analysis can be helpful to increase statistical power and clarify these conclusions.

Objectives
The association between emotion recognition and cognitive impairment have yielded mixed results, raising the need for a meta-analytic analysis of the literature. To our knowledge, no meta-analytic review has been performed

to quantify and test the significance of the overall correlation between emotion recognition and cognitive impairment in MS. Further, it is unclear for *whom* this association could be relevant.

Therefore, we plan to systematically review and statistically aggregate the magnitude of the association between emotion recognition and cognitive impairment in MS, across 7 emotion scores of interests (total and by 6-basic emotions subscores) and three cognitive domains (IPS, executive functions and episodic memory). Given that negative emotions were found to be more difficult to process than positive ones[25] and that emotion recognition deficits were found to be rather limited to negative emotions in pwMS (specifically anger, fear and sad[9 17]), we believe that it is important to take emotion type into account in planned analyses.

Furthermore, given that emotion recognition is likely to co-occur with particular non-social cognitive abilities, we believe that it is also important to take cognitive domains into account in the analyses. For example, several studies showed positive associations between emotion recognition and executive performances in pwMS.[10 12 26 27] Other studies found positive correlations between emotion recognition and episodic memory and IPS.[28 29] We believe that it is important to take cognitive domain into account in planned analyses because not all cognitive domains are necessarily impaired in pwMS depending on several clinical characteristics.[30 31] Indeed, the prevalence as well as intensity of cognitive deficits may vary depending on cognitive domain.[32]

Finally, to clarify *for whom* such associations might be relevant, we plan to explore whether overall correlations differ according to demographic and clinical characteristics of pwMS (ie, age, sex, disease duration, Expanded Disability Status Scale (EDSS) score, severity of depression, severity of anxiety, fatigue, metacognition and alexithymia). Indeed, the prevalence and intensity of both cognitive and emotion recognition deficits may vary according to such characteristics. As some authors showed that cognitive impairment tends to extend with disease duration,[30] we plan to explore the role of disease duration. In addition, because of the specific pathological mechanisms they involve, we plan to explore the role of MS-phenotypes (Clinically Isolated Syndrome (CIS) · Relapsing-remitting MS (RRMS) · Secondary progressive MS (SPMS) · Primary progressive MS (PPMS)).[31] Indeed, literature pointed toward the presence of different patterns and severity levels of neurocognitive (as well as social-cognitive) deficits among MS-phenotypes.[10 30 33] To that end, we will conduct additional meta-regression analyses.

To summarise, we will assess overall associations between emotion recognition and cognitive impairment in MS. We will also examine the impact of some key potential moderators to help explain any variability between studies and better identify the potential factors that accentuate or diminish the relationship between emotion recognition and cognitive deficits in pwMS. Ultimately, this study

will provide support either for an association of these disorders (in which emotion recognition deficits might result from more fundamental cognitive dysfunction), or for two distinct sets of symptoms which may occur independently, for targeted patient profiles.

METHODS
Protocol design and registration
The present protocol will be registered within the Open Science Framework and is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement[34 35] (see checklist in online supplemental file 1).

Eligibility criteria
Criteria for inclusion
We will conduct a systematic review of the literature to identify all potential eligible published and unpublished studies. Relevant variables will be coded in each eligible study, and effect sizes will be extracted for quantitative synthesis. Studies will be included if they met the following criteria:

1. Studies including (adult) patients diagnosed with MS. Considering that (a) social cognition continues to develop with increased age into adulthood[36] and (b) that significant neural development and hormonal changes were shown to influence social cognition at puberty,[37] it is not clear whether potential interactions between nonsocial and social cognition are comparable from childhood to adulthood. For this reason, only studies including *adult* MS patients (ie, aged 18 and over) will be included.
2. Studies assessing both emotion recognition and at least one cognitive domain.
3. Studies using standardised and/or recognised measures to assess both emotion recognition and cognitive dysfunction.
4. Studies (or authors) providing correlational measures between emotion recognition and cognition in pwMS (ie, Pearson or Spearman correlations).
5. Studies published in a peer-reviewed journal in English.
6. Unpublished studies will only be included if their samples were substantively different from a potential published one. Intervention studies will only be included if authors reported baseline or preintervention data.

Criteria for exclusion
Studies will be excluded at the full-text screening stage if they met the following criteria:

1. Studies not including an (adult) MS patient group. Case studies and studies including paediatric MS patients (ie, aged >18) will be excluded.
2. The publication is not an empirical original type, such as: research protocols, letters, conference abstracts, reviews and editorials.
3. Studies with patient samples overlapping with another one with a larger sample size. Indeed, where studies reported data from a subsample of patients from a larger study, only the larger study will be included.

Sample of studies
Data sources
A comprehensive search strategy will be implemented in an attempt to identify, retrieve and code the entire population of eligible studies using three electronic databases (PsycARTICLES, PubMed, ScienceDirect). In order to ascertain the feasibility of the meta-analysis, we carried out an initial search until 7 January 2023 (see figure 1). Additionally, we conducted a search using Google Scholar and reviewed the reference lists of included articles to identify any additional relevant publications that may not be directly indexed in such sources. This search will be updated at the start of the study to verify the eligibility of any additional studies published after 7 January.

Search strategy and study selection
We will search all studies of emotion recognition in MS to see if associations between recognition performance and cognitive performance are reported, using the following keyword search terms: "multiple sclerosis" AND "social cognition" OR "emotion" OR "emotion recognition". No date restrictions will be placed on any searches. There will be no restrictions of the age of patients (>18 years) or phenotype of MS for inclusion.

This search strategy will result in an initial pool of studies to be screened. A two-stage selection process will be adopted consisting of an initial screening based on title and abstract only, followed by a full-text review of non-excluded items. First, we will review titles and abstracts from the initial pool of studies: any ineligible study will be eliminated. Studies having any potential to be included will be moved on to stage two (full-text review). For each stage, two of the authors will independently screen articles for eligibility in accordance with predetermined inclusion and exclusion criteria. Any inconsistencies (uncertainty, disagreement) in the study exclusion process will be referred to a third author for resolution. The process of selecting literature for our initial search is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (see figure 1). The final search results will be exported into a standardised data extraction spreadsheet in which all duplicates will be detected and eliminated.

Data collection and analysis
Data management
A standardised data extraction spreadsheet will be used to record data from full-text articles and other sources which meet the eligibility criteria. Specifically, we will extract the following information:

1. Study characteristics (authors, publication year, title and journal).
2. MS sample characteristics (sample size, sex, age).
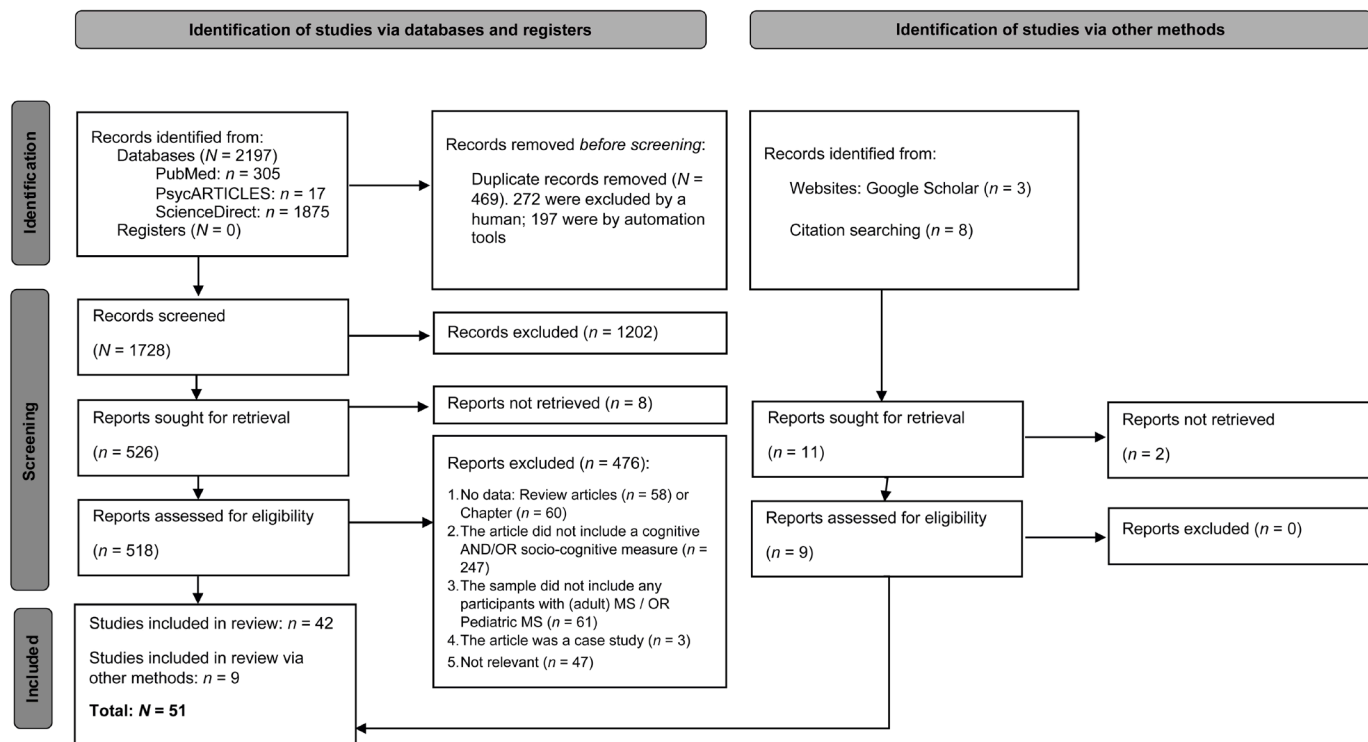
Figure 1 Meta-analysis flow diagram in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Adapted from Page et al.[46] http://www.prisma-statement.org/.

3. MS disease characteristics (disease duration, EDSS score, severity of depression, severity of anxiety, fatigue, metacognition and alexithymia). Regarding disability, we will extract EDSS (Kurtzke, 1983) scores.[38] EDSS is a widely used clinician-administered assessment that quantifies the severity of disability, increasing from 0 (no disability) to 10 (death due to MS) in increments of 0.5 units.

4. Correlational data provided between emotion recognition performance and cognitive performance in pwMS (ie, Pearson or Spearman correlations).

5. The type of cognitive and socio-cognitive measures used for each retrieved association (cognitive domain, tasks names).

Where necessary, we contacted study authors for unreported data in order to calculate effect sizes.

Data items
All variables and any preplanned data assumptions are listed and defined in table 1.

DATA SYNTHESIS AND STATISTICAL ANALYSIS
Data synthesis
Combined effects will be computed using jamovi and the MAJOR module.[39] Jamovi is a Graphical User Interface (GUI) version of R, and MAJOR is based on the commonly used R package, Metafor.[40] The mean effect size (r) and 95% CIs will be used to assess the combined association between emotion recognition and cognition in patients. For missing data, we will try to contact the first or corresponding authors of the included studies via

email to acquire relevant information that is not available in the study. All retrieved correlations will be transformed using Fisher's z transformation prior to synthesis in order to reduce the bias associated with synthesising r coefficient effect sizes.[41]

Assessment of heterogeneity
We will assess the heterogeneity by using the I^2 index,[42] with $I^2 < 50$ indicating low heterogeneity.[43] A random-effects model will be employed in view of anticipated high heterogeneity across studies.[44]

Assessment of publication bias
We will use funnel plots to detect publication bias. If the analysis includes ≥10 studies in meta-analysis, a test for funnel plot asymmetry using Egger method will be conducted.[45]

Subgroup and meta-regression analyses
We will perform separate subgroup analyses (as listed in table 1) to investigate associations between emotion recognition (7 scores of interests: total score and by 6-basic emotions subscores) and three prespecified cognitive domains. Additionally, for each subgroup of analyses, we will conduct random-effects meta-regression analyses to investigate prespecified moderating effects of additional identified variables (as listed in table 1), on moderate associations where 10 or more studies were available.[41] Specifically, meta-regression analyses will be conducted to investigate whether demographic and clinical variables (including age, sex, disease duration, EDSS score, severity of depression, severity of anxiety, fatigue, metacognition

Table 1 Definition of all variables for which data will be sought

Variable	Definition
Population	The population of interest was (adult) patients diagnosed with MS
Primary outcomes measures	Primary outcomes consist of correlation coefficients between emotion recognition and cognitive performance in patients. An emotion recognition task is defined as one requiring participants to discriminate the emotion being expressed by static or dynamic faces depicting basic (anger, disgust, fear, happiness, surprise and sadness) or complex (eg, pride, shame …) emotions
Subgroup analyses	Separate subgroup analyses will be conducted to investigate associations between emotion recognition across 7 scores of interests: total score and by 6-basic emotions subscores) in three prespecified cognitive domains (severity of processing speed, executive and episodic memory deficits). Subscores of the emotion recognition task: we identified 7 scores of interests: total score and by 6-basic emotions subscores. Cognitive domains assessed by the cognitive measure: we identified three cognitive domains of interests: information processing speed; executive functions, episodic memory. Combining the type of score of the emotional task and the assessed cognitive domain, 21 separate analyses will be performed (total score and 6-basic emotions subscores *three cognitive domains). For these analyses, a minimum of 10 relevant data is required[47]
Additional outcomes (moderators)	Meta-regression analyses will be conducted in each of these 21 subgroup analyses to investigate whether additional identified variables are the cause for heterogeneity. These identified potential moderators include demographic and clinical variables (including age, sex, disease duration, EDSS score, severity of depression, severity of anxiety, fatigue, metacognition and alexithymia). For these analyses, a minimum of 10 relevant data will also be required[47]

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

and alexithymia) are the cause for heterogeneity in any combined subgroup associations. We will investigate mean age, sex (ratio of female patients in the MS group), disease duration, EDSS scores as continuous moderators using meta-regression. Regarding severity of depression, anxiety, fatigue, metacognition and alexithymia, we will classify studies according to accepted cut-off scores of the used rating scales (no symptoms=0, mild symptoms=1, moderate symptoms=2, severe symptoms=3).

DISCUSSION

We will conduct a systematic review and meta-analysis to characterise the association between emotion recognition and cognitive impairment in MS. Additionally, we will examine potential moderators to identify the potential factors that may moderate this relationship. Ultimately, this study will provide support either for an association of these disorders (in which emotion recognition deficits might result from more fundamental cognitive dysfunction), or for two distinct sets of symptoms which may occur independently, for targeted patient profiles. This meta-analysis will contribute to enhancing our understanding of MS-related disorders. Our results may emphasise the need to increase awareness among clinicians of social-cognitive dysfunction that may appear independent of more fundamental cognitive dysfunction in targeted pwMS. Conversely, if those two sets of deficits seem to be associated, this may raise questions about how to address them. This work will help us provide recommendations for future clinical trials. Finally, a better understanding of MS-related symptoms is the first step towards improving MS disease management. In particular, socio-cognitive symptoms remain poorly managed in MS despite their high prevalence and burden.

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