Brain Connectivity

DOI: 10.1089/brain.2021.0104

A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis

Abbreviated title: Connectivity changes in multiple sclerosis

Danka Jandric[1]*, Anisha Doshi[2]*, Richelle Scott[1], David Paling[3], David Rog[4], Jeremy Chataway[2], Menno M. Schoonheim[5], Geoff Parker[1,6], Nils Muhlert[1†]

* Joint first authors

† Corresponding author

Author email addresses:

danka.jandric@manchester.ac.uk

anisha.doshi@ucl.ac.uk

richelle.scott@student.manchester.ac.uk

david.paling@nhs.net

david.rog@srft.nhs.uk

j.chataway@ucl.ac.uk

m.schoonheim@amsterdamumc.nl

geoff.parker@ucl.ac.uk

nils.muhlert@manchester.ac.uk

Author affiliations:

[1]Division of Neuroscience & Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Zochonis Building, Oxford Road, Manchester M13 9PT, UK

[2]Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, Faculty of Brain Sciences, University College London WC1B 5EH, UK

[3]Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield S10 2JF, UK

[4]Salford Royal Hospital, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK

[5]Department of Anatomy and Neurosciences, MS Center Amsterdam, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 117, Amsterdam, The Netherlands.

[6]Centre for Medical Image Computing, Department of Computer Science and Department of Neuroinflammation, Queen Square Institute of Neurology, University College London, London WC1B 5EH, UK

Corresponding author:

Dr Nils Muhlert, Division of Neuroscience & Experimental Psychology, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Zochonis Building, Oxford Road, Manchester M13 9PT, UK, email: nils.muhlert@manchester.ac.uk, tel: +44 (0) 161 275 2691

Keywords

Multiple sclerosis, Cognitive impairment, Resting state functional MRI, Functional connectivity, Brain connectivity

Abstract

Introduction: Cognitive impairment in multiple sclerosis (MS) is increasingly being investigated with resting state functional MRI (rs-fMRI) functional connectivity (FC) . However, results remain difficult to interpret, showing both high and low FC associated with cognitive impairment. We conducted a systematic review of rs-fMRI studies in MS to understand whether the direction of FC change relates to cognitive dysfunction, and how this may be influenced by the choice of methodology.

Methods: Embase, Medline and PsycINFO were searched for studies assessing cognitive function and rs-fMRI FC in adults with MS.

Results: Fifty-seven studies were included in a narrative synthesis. Of these, 50 found an association between cognitive impairment and FC abnormalities. Worse cognition was linked to high FC in 18 studies, and to low FC in 17 studies. Nine studies found patterns of both high and low FC related to poor cognitive performance, in different regions or for different MR metrics. There was no clear link to increased FC during early stages of MS and reduced FC in later stages, as predicted by common models of MS pathology. Throughout, we found substantial heterogeneity in study methodology, and carefully consider how this may impact on the observed findings.

Discussion: These results indicate an urgent need for greater standardisation in the field – in terms of the choice of MRI analysis and the definition of cognitive impairment. This will allow us to use rs-fMRI FC as a biomarker in future clinical studies, and as a tool to understand mechanisms underpinning cognitive symptoms in MS.

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Impact statement

We present the first systematic review of resting state fMRI functional connectivity studies to investigate cognitive impairment in multiple sclerosis. We assess whether this MR metric is a suitable biomarker of cognitive decline in MS. We demonstrate that while there is a strong link between functional connectivity abnormalities and cognitive impairment, the direction of abnormalities varies considerably across studies. We also demonstrate that there is substantial methodological heterogeneity across studies, which makes results difficult to interpret. From this, we highlight the urgent need for more standardisation in functional connectivity studies in MS, and offer potential ways forward to achieve this.

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Abbreviations

BICAMS - Brief International Cognitive Assessment for Multiple Sclerosis

BMS – Benign Multiple Sclerosis

BOLD - Blood-Oxygenation-Level-Dependent

CI – Cognitively Impaired

CIS – Clinically Isolated Syndrome

CP – Cognitively Preserved

DMN – Default Mode Network

EDSS - Expanded Disability Status Scale

FC – Functional Connectivity

ICA – Independent Component Analysis

MACFIMS - Minimal Assessment of Cognitive Function in Multiple Sclerosis

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

PASAT - Paced Auditory Serial Addition Test

PPMS – Primary Progressive Multiple Sclerosis

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO - International Prospective Register of Systematic Reviews

ROI – Region Of Interest

RRMS – Relapsing-Remitting Multiple Sclerosis

Rs-fMRI Resting State Functional MRI

RSN – Resting State Network

SCA – Seed Based Connectivity Analysis

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

SDMT - Symbol Digit Modalities Test

SPMS – Secondary Progressive Multiple Sclerosis

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Introduction

Multiple sclerosis (MS) is a chronic immune mediated disorder of the central nervous system that predominantly affects young adults (Dobson and Giovannoni, 2019; Filippi et al., 2018; Thompson et al., 2018). Inflammatory demyelination is pathognomonic with neurodegeneration insidiously dominating over time (Lassmann, 2018).

Cognitive impairment is common in all MS phenotypes (Benedict, 2020; Benedict et al., 2020; Charcot, 1888) with an estimated prevalence of 43-70% dependent on factors including phenotype and the cognitive diagnostic criteria used (Fischer et al., 2014; Sumowski et al., 2018). Cognitive impairment is associated with several adverse outcomes including a higher risk of depression, unemployment and reduced quality of life (Ruet et al., 2013b; Strober et al., 2014; Sumowski et al., 2018). A more progressive MS phenotype and longer disease duration have been shown to be associated with greater cognitive impairment (Baird et al., 2019; Connick et al., 2013; Johnen et al., 2019, 2017; Patti et al., 2010). There are currently no licensed treatments for cognitive symptoms in MS, however exercise (Motl and Sandroff, 2020) and behavioural therapy show promise (Sandroff and DeLuca, 2020). Disease modifying therapies show positive outcomes on cognitive dysfunction in MS, despite no routine evaluation in phase 3 clinical trials currently. However, effects are small and at present understudied, and there are to date no approved pharmaceutical treatments for cognitive symptoms (Benedict et al., 2020; Landmeyer et al., 2020).

Gaining an understanding of the underlying pathophysiology of cognitive dysfunction is essential for diagnosing, monitoring and developing treatments for this debilitating aspect of MS. The ‘clinico-radiological’ paradox highlights the mismatch of MS cognitive symptoms and conventional Magnetic Resonance Imaging (MRI) measures, such as lesion volumes (Rocca et al., 2015). It is widely accepted that cognitive function is supported by a complex network of structurally interconnected brain regions supporting a highly dynamic functional network, which is researched with advanced MRI tools such as resting state functional MRI (rs-fMRI), in MS and other neurodegenerative diseases (Battle et al., 2017; Castellazzi et al., 2014; Mori et al., 2011; Rocca et al., 2015; Schoonheim et al., 2015b).

The main measure derived from rs-fMRI is the functional connectivity (FC) metric. It is a measure of the statistical correlation of blood-oxygenation-level-dependent (BOLD) signal time course between any selection of voxels. The underlying assumption is that voxels with similar BOLD time courses are connected in the performance of a function (Bijsterbosch et al., 2017), see Figure 1. FC has the potential to be an imaging biomarker of cognitive performance in neurodegenerative disease (Hohenfeld et al., 2018) and is the subject of a growing research field in MS (Benedict et al., 2020). Such a marker could offer a fast, non-invasive way to detect imminent cognitive decline, which is often underdiagnosed on routine neurological examinations (Romero et al., 2015). For a measure to be suitable as a clinical biomarker, it needs to be able to identify those with cognitive dysfunction from those without it, and to show acceptable repeatability and reproducibility across studies. In some diseases, like Alzheimer's disease, the rs-fMRI literature shows consistently low FC in the default mode network (DMN) (Badhwar et al., 2017), yet a recent review of rs-fMRI studies in several neurodegenerative diseases, including Alzheimer's, argued that the evidence is not yet strong enough for rs-fMRI FC measures to be suitable biomarkers (Hohenfeld et al., 2018). This review cited a lack of standardised protocols as a challenge in the field.

The rs-fMRI FC literature on cognition in MS has not yet been subject to systematic review, and so the specificity and reliability of FC as a marker of cognitive dysfunction has not been established. Correlations between FC metrics and cognition have been frequently reported (Hawellek et al., 2011; Lin et al., 2020; Schoonheim et al., 2012; Tona et al., 2014), but in studies comparing FC between cognitively impaired (CI) and cognitively preserved (CP) patients, results have shown both high and low FC linked with worse cognitive function (Basile et al., 2014; Bonavita et al., 2011; Cruz-Gómez et al., 2014; Faivre et al., 2012; Rocca et al., 2018). A common interpretation of increases in any type of brain function is that of functional "reorganisation": a compensatory mechanism that enables the functioning of networks in the presence of structural damage, hence delaying clinical progression. This compensatory mechanism is thought to be sustainable only up to a critical point, at which the structural damage becomes too great to compensate for, leading to the hypothesized "network collapse", manifested as decreases in FC and clinical

progression (Schoonheim et al., 2015b; Schoonheim et al., 2017). In support of this, several studies indicate different patterns of FC changes at different disease stages, such as high FC in clinically isolated syndrome (CIS), the earliest stage of MS, and low FC in progressive MS (Basile et al., 2014; Cocozza et al., 2018; Rocca et al., 2010; Roosendaal et al., 2010a; Roosendaal et al., 2010b). However, high FC has also been related to the severity of impairment (Hawellek et al., 2011), casting doubt on the beneficial nature of these changes. As such, it is not yet clear whether the pattern of results from rs-fMRI studies consistently fits the predictions of this model. This may be complicated by the heterogeneity in methodological aspects of studies which could influence the direction of findings (Tewarie et al., 2018).

In this study we carry out a systematic review of rs-fMRI FC studies of cognitive dysfunction in MS to outline the state of the field and provide a critical analysis of findings to date. We considered directionality of results and the influence of methodological aspects on findings of FC alterations. Through doing so we offer key points that need to be addressed in order to develop a parsimonious account of why FC may change in MS and what it may mean for clinical practice.

Method

Protocol and Registration

The design of the systematic review and manuscript preparation were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2015). The systematic review protocol was developed in advance and, in accordance with PRISMA guidelines, registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 18 May 2020, and last updated on 31/8/2020 (registration number CRD42020154415).

Information sources and search strategy

Literature searches were conducted in Embase (accessed through the Ovid interface, 1974 onwards), Medline (accessed through Ovid, 1946 onwards), and PsycINFO (accessed through Ovid, 1806 onwards) on 31st October 2019, with no limits imposed on the searches. The search strategy used terms for ‘multiple sclerosis’ ‘functional connectivity’

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

and 'cognition' and was tailored for each database to use both controlled terms where available and uncontrolled keywords in order to capture any synonym, abbreviation and related term of the keywords of interest. The searches were repeated on 22nd October 2020 to capture any studies published since the original searches. The same search strategy was used, but limits were added to capture only results which had been added or updated in the period 1st November 2019 – 22nd October 2020. The full search strategy used in each database is available in Supplementary Table 1.

Study eligibility and selection

Records returned by each search were imported into the Mendeley reference management software v 1.19.4, and duplicates were removed using the tool's de-duplication function. Titles and abstracts were then manually screened by two independent reviewers (DJ and RS). Full text publications were obtained for all papers chosen for full text review by one or both reviewers and assessed for inclusion in the review against pre-defined eligibility criteria. Any disagreements about study inclusion were resolved through discussion and reasons for study exclusion were recorded. This process was then repeated for the search conducted on 22nd October 2020. The results at each stage, for the combined two searches, are presented in Figure 2.

Eligibility criteria were: original peer-reviewed research studies reporting on cognitive function and FC metrics derived from rs-fMRI in adult MS patients. Review articles, book chapters and conference abstracts were excluded, as were any original research studies in a paediatric population, on diseases other than MS, studies which had not measured cognitive function and/or functional connectivity, studies focusing on cognitive rehabilitation, studies which had assessed social cognition only, and any articles which were not available in English.

Data collection and synthesis

Data extraction was performed by DJ and RS and the following data items were recorded: 1) study characteristics (authors, year of publication, journal); 2) aims of the study; 3) Participant details (MS subtype, control group, sample size, disease duration of MS sample, Expanded Disability Status Scale (EDSS) score of MS sample); 4) MR methodology

(scanner field strength, MR metrics); 5) FC analysis (data pre-processing, method for analysis, whether analysis was global or regional [and if so, which regions], use of covariates); 6) cognitive testing (cognitive test(s) used, definition of cognitive impairment, number of cognitively impaired/preserved patients if applicable); 7) results from FC analysis and from other MR metrics).

To understand whether there might be a link between methodological aspects and FC results, we examined whether a particular feature was commonly present in studies that report links between worse cognition and either high or low FC. The features we examined were the MS subgroup studied, the average disease duration of patient samples, the rs-fMRI analysis method and the brain region or resting state network (RSN) investigated. Because the studies included were too heterogeneous for a meta-analysis, data synthesis was done by tallying the number of studies sharing a specific methodological feature or FC result.

Assessment of study quality

A quality assessment approach was chosen over a risk of bias tool because most articles for inclusion in this review were expected to be cross-sectional. The AXIS tool was designed for cross-sectional studies across a range of scientific disciplines (Downes et al., 2016) and was therefore selected to judge the quality of the evidence included in the review. The AXIS tool is a 20 item checklist which asks 'yes/no' questions about important elements of a study. Three of the 20 items in the tool were not relevant for the studies selected for this review, as they refer to responding to an intervention, so quality assessment was based on the remaining 17 items. The items of the AXIS tool are not scored, but instead recorded in a similar way to the Cochrane risk of bias tool (Higgins et al., 2011), allowing review authors to make an overall assessment of the quality of the study based on the presence or absence of reporting of the items covered by the tool.

Results

Study selection and quality assessment

The systematic review process is outlined in Figure 2. The database searches yielded 2061 results, and in addition 6 were identified from other sources. After removal of duplicates

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

1697 remained, which were screened for eligibility until 177 remained for full-text assessment. At this point 120 records were excluded, most of which were conference abstracts (see Figure 1 for reasons for exclusion). Fifty-seven studies met eligibility criteria and were included in the review. These studies are summarised in Table 1. All studies were of high quality, as measured by the AXIS tool (Downes et al., 2016). Eighteen studies did not include clear details of where participants were recruited from for the study, and very few studies (5/57) had a justification for the sample size used.

Participant characteristics

The studies that were included differed in the clinical and demographic details of the MS samples used. The majority of studies used a mixed sample of different MS phenotypes (29/57 studies), and slightly over a third used a sample of relapsing-remitting MS (RRMS) patients only (22/57 studies). The remaining six studies used either a primary progressive MS (PPMS) sample (1/57), CIS sample (2/57), a benign MS (BMS) sample (1/57) or did not specify the MS subtype (2/57). See Table 1 for details on the cohort of each study.

The average disease duration ranged from as little as 4.2 months (Koubiyr et al., 2019) to 21.9 years (Lin et al., 2019) from either time from first symptom or from diagnosis, and median EDSS ranging from 1 (Faivre et al., 2012; Koubiyr et al., 2019) to 6.5 (Manca et al., 2019).

Most studies (54/57) used healthy volunteers as a control group. In one study normative data from age-matched healthy controls was used for neuropsychological assessments, but no control group was used for comparisons of MRI metrics (Manca et al., 2019). In one study no control group was specified (Leavitt et al., 2014), and in one longitudinal study no control group was used (Petsas et al., 2019). Out of the studies using healthy controls, many did not report matching groups on any demographic variables (18/54) while some reported matching groups but not on which variables (3/54) and one reported not matching the groups. Of the studies reporting the variables groups were matched on, most were on age and sex (15/54), followed by age, sex and education (10/54), age only (2/54), sex only (2/54) or age, sex, education and premorbid IQ (1/54). In this review we have

interpreted the words ‘sex’ and ‘gender’ to both refer to sex, given that MS is a disease characterised by sex differences in prevalence (Krysko et al., 2020; Thompson et al., 2018).

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Neuropsychological assessment

Most studies (34/57) looked at relationships between cognitive test performance and MR metrics through correlations or regressions, and 19 studies examined group differences in MR metrics between patients who met criteria for cognitive impairment and those who did not. Of the remaining four studies, one looked at FC only in MS patients with intact spatial memory (Roosendaal et al., 2010b), and three did not directly assess the relationship between cognition and FC. Despite this, they were included in the review for the following reasons: the authors of one study expressed intentions to correlate FC measures with clinical measures, but did not because the FC measure did not show any abnormalities in MS patients (Romascano et al., 2015); two studies indirectly explored the relationship between FC and cognition and did not meet any exclusion criteria (van Geest et al., 2018, 2017).

To assess cognitive function most studies used either the Brief Repeatable Battery of Neuropsychological tests (BRB-N), which has been validated for use in MS (Amato et al., 2006), alone or in combination with other tests (20/57), or a collection of individual tests (22/57). The remaining studies used either another cognitive battery; Brief International Cognitive Assessment for MS (BICAMS) n=2 (Langdon et al., 2012), Minimal Assessment of Cognitive Function in MS (MACFIMS) n=2 (Benedict et al., 2002), or a single test; Paced Auditory Serial Addition Test (PASAT) n=6, Symbol Digit Modalities Test (SDMT) n=1, Location Learning Test n=1, Short test of mental status n=1, the computerised test of information processing n=1) or a cognitive reserve index (n=1). See figure 3A for an overview of the tests used across the reviewed studies. The specific battery or tests used by each study are summarised in Table 1.

Within the 19 studies that split the MS sample into cognitively impaired and cognitively preserved sub-samples, there were 12 different definitions of cognitive impairment. Some definitions are likely guided by the test(s) used to assess cognition, but even amongst studies using the BRB-N, there were five different definitions of cognitive impairment (see

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Figure 3B). These include: ≥1.5 SD below normative values on ≥1 test (n=1); ≥1.5 SD below controls scores on ≥2 tests (n=5, but note that four used this definition of a mildly cognitively impaired group), ≥2 SD below normative values on ≥1 test (n=1); ≥2 SD below normative values on ≥2 tests (n=9); performance in the 5th percentile of scores on either the Selective Reminding Test or Spatial Recall Test compared to normative data (n=1).

Functional connectivity analysis

Half of all studies (28/57) used a seed-based connectivity analysis (SCA) method for assessing FC. In this category we have included studies which used one or a few specific regions of interests (ROIs; regional SCA) or divided the whole brain into ROIs and created a connectivity matrix (global SCA). The second most common method was independent component analysis (ICA) (14/57), and the remaining studies either calculated graph theory metrics (7/45), used a principal component analysis (1/45) or used a combination of SCA and graph theory (1/45) or ICA and graph theory (1/45). See Table 1 for the design and rs-fMRI analysis method of each study.

A wide range of regions and RSNs were investigated, either as a priori defined areas of interest, or as patterns emerging from a data-driven analysis, of which the most common were the DMN (21/57), thalamus and thalamic networks (9/57), the fronto-parietal network (FPN), including the right, left, dorsal and ventral FPNs (7/57). Other RSNs and regions investigated include the attentional network including left, right, dorsal, ventral variants, the salience network, the executive network, the working memory network, the motor network, the sensorimotor network, the visual processing network, the auditory network, the auditory and language processing network, visual processing networks, including medial and lateral variants, the cerebellar network, the medial prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, precuneus, basal ganglia, hippocampus and cerebellum. Ten studies conducted a whole-brain analysis and did not report regional FC changes.

Functional connectivity results

The main result of the relationship between FC and cognition of each study is summarised in Table 1 and Figure 4A. Overall, 18 studies found worse cognition to be linked with high

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

FC and 17 found it to be associated with low FC. Nine studies found patterns of both high and low FC to be associated with cognitive impairment, in different regions or for different MR metrics, and seven studies found no significant relationship between cognitive and FC measures. Six studies had a methodology which did not measure the direction of FC change in relation to cognitive impairment.

When grouping studies based on methodological and clinical features to assess whether one direction of FC change associated with worse cognition is more commonly seen in studies with that feature, we found no trend to suggest that one FC direction change associated with worse cognition is more commonly seen in studies using a specific method or studying a specific type of sample. This includes grouping studies based on the RSN or network assessed. For example, of the 21 studies measuring FC in the DMN, 10 found worse cognition to be associated with low FC, 6 with high FC, 1 with both high and low FC, 3 obtained a negative result, and one study did not test the relationship directly. See Figure 4B and Supplementary Table 2 for a full overview of study results by regions investigated.

We also considered the role of disease phenotype, however, most studies used either a mixed sample consisting of several phenotypes or a sample of RRMS patients only. Of the 22 studies which used a RRMS sample, eleven reported worse cognition to be associated with high FC and ten with low FC. Three studies reported a negative result and one had a study method which does not inform about the direction of FC changes. Similarly, within the mixed sample studies almost half of studies reported worse cognition to be associated with high FC (13/29) and more than half with low FC (16/29). Some studies reported both high and low FC to be associated with worse cognitive function and have therefore been counted twice. See Figure 4C for an overview. In seven of the studies with mixed phenotype samples subgroup analyses were conducted to compare FC changes between different MS phenotypes in the sample, but only two included cognition in these analyses. One found a stronger positive correlation between FC in the DMN and errors on the PASAT in secondary progressive MS (SPMS) compared to RRMS, while another found differences between RRMS and SPMS in the spatial location of FC abnormalities that corelated with cognitive test performance.

Finally, we ordered studies by the average reported disease duration of the sample used, to see if patterns of FC changes differ from early to late in the disease and found no such trend, see Figure 5 and Supplementary Table 3.

Discussion

In this systematic review we examined the consistency and direction of findings of studies investigating associations between rs-fMRI FC measures and cognition in MS. Overall, the studies reviewed support the notion of FC alterations associated with cognitive dysfunction in MS (Filippi and Rocca, 2013). Although most changes were related to cognitive dysfunction, the direction of FC changes varied considerably between studies and was not clearly linked to any methodological factors. There was substantial heterogeneity in clinical and rs-fMRI methodology, as has previously been noted in non-imaging cognition studies in MS (Benedict et al., 2020; Sumowski et al., 2018). We therefore consider ways in which the field can reflect on what has been learned to date and improve future study designs to more clearly understand the mechanisms and consequences of changes in rs-fMRI FC. Specifically, we propose that future studies should consider the following points which are the source of much heterogeneity identified in this review: 1) the possibility of different network degeneration patterns in different MS clinical and cognitive phenotypes; 2) the role of disease duration and aging processes; 3) the definition and measurement of cognitive impairment; 4) the spatial topography of brain regions of resting state networks of interest; 5) the investigation of the mechanisms of FC abnormalities. A discussion of each follows below.

Models of network changes in MS

To consider how FC should relate to cognitive function in MS, and what results to expect from rs-fMRI studies, a model of the relationship is useful. The most commonly used model for understanding FC changes in MS is the 'network collapse' model, which postulates three main stages (Schoonheim et al., 2015b). In the first, early stage network efficiency remains normal, at this point structural damage can be compensated by increases in local activation. This predicts early increases in FC, reflecting these compensatory processes. The second stage is where structural damage accrues to a critical point, at which compensatory processes become less effective. Finally, in the third stage

structural damage exceeds the critical point with associated 'network collapse', and concomitant decreases in FC. Computational modelling of empirical data on FC in MS supports this model (Tewarie et al., 2018). Similarly, longitudinal studies demonstrate a reorganisation of structural and functional networks in early stages of MS (i.e. CIS) despite intact cognitive performance, suggesting compensatory processes are at work (Koubiyr et al., 2019). Cross-sectional task-related fMRI studies also indicate increasing deviation from healthy control patterns of brain activation during cognitive tasks, consistent with functional reorganization, as patients progress from CIS to RRMS to secondary progressive MS (Loitfelder et al., 2011). Together, these theories predict early adaptive reorganization of functional networks, followed by a failure of effective network organization in MS over time (see also Chard *et al.*, 2021).

Role of clinical phenotype, disease duration and age

In our review, when ordering studies by the average disease duration of the sample, we did not observe a trend in the direction of FC findings from early to advanced MS, as predicted by the network collapse model and as observed in some studies (e.g. Castellazzi et al., 2018). We therefore consider whether the lack of fit to the model relates to the particular samples or methods of analysis employed. Many of the studies included in this review used samples of mixed clinical phenotypes. MS phenotype has previously been reported to influence resting network FC alterations, so the inclusion of mixed MS samples could contribute to the lack of consistency in findings. However, in our review only two studies assessed the relationship between FC, phenotype and cognition, and these found both abnormally increased (Meijer et al., 2018a) and abnormally decreased (Rocca et al., 2018) FC in patients with progressive MS. This suggests that even in specific MS subgroups, there remains considerable variability in the direction of findings. More evidence is needed in order to determine whether FC changes vary between phenotypes, and whether any model of network changes has different explanatory power for the different phenotypes. A further important consideration is the effect of disease duration and how it may mediate the relationship between FC, phenotype and cognition. Longer disease duration in RRMS is associated with FC changes in attentional, executive, and default mode networks (Castellazzi et al., 2018). This suggests that disease duration may have an important

influence on FC changes associated with cognitive impairment, possibly due to increased structural damage with longer disease duration. While we did not find such a trend in our review, our analysis of disease duration was confounded by samples of mixed phenotypes, the study of many different spatial regions of the brain, and the vast number of definitions of cognition. Therefore, the effect of disease duration should be formally tested in studies in which other variables, such as neuropsychological tests and spatial regions, are kept constant. Those studying patients with longer disease duration (such as those with SPMS) will also have to account for age-related atrophy in these samples (Azevedo et al., 2019), which will be exacerbated when studying those patients with relapsing as well as progressive subtypes of MS.

Cognitive tests and definition of cognitive impairment

We also considered whether the direction of FC change relates to definitions of cognitive impairment and choice of FC analysis. Studies of cognition in MS use a vast array of definitions of cognitive impairment (Benedict et al., 2020; Fischer et al., 2014; Sumowski et al., 2018), as reflected in this review. For example, of the studies using the BRB-N to assess cognitive function, most use a more conservative definition of cognitive impairment of at least 2 SDs below controls on 2 or more tests (Bonavita et al., 2011; d'Ambrosio et al., 2017; d'Ambrosio et al., 2020; Eijlers et al., 2017; Eijlers et al., 2019; Meijer et al., 2018a; Meijer et al., 2017; Rocca et al., 2018; Schoonheim et al., 2015a), but other, less conservative definitions are used too (Cruz-Gómez et al., 2018, 2014; Eijlers et al., 2018). The definition of cognitive impairment has been shown to have effects on underlying FC alterations of MS CI by the classification used (Doshi et al., 2019). A few studies have compared different thresholds of cognitive impairment and found the greatest FC abnormalities in those participants meeting the more conservative thresholds (i.e., more than 2 standard deviations from controls on 2 or more tests). In contrast, less clear FC abnormalities were observed in samples performing between 1.5 and 2 SDs below controls on 2 tests ("mild cognitive impairment") (Doshi et al., 2019; Eijlers et al., 2017; Meijer et al., 2017; Schoonheim et al., 2015a). This demonstrates the possible effect of the definition of cognitive impairment on FC findings and the arbitrary nature of these thresholds. Such findings highlight the importance of using a consistent measure of

cognitive dysfunction and definition of impairment across studies. As a further challenge there is no consistency in use of specific cognitive tests or batteries for defining cognitive dysfunction in MS, with many studies using impairments on multiple separate tests to assess global cognitive function. There are documented phenotypic differences in impairments by test and domain (Chan et al., 2017; Connick et al., 2013; Johnen et al., 2017; Ruet et al., 2013a), yet very few studies have looked at network alternations associated with deficits in specific cognitive domains, such as information processing speed or memory, and those that have used a range of cognitive tests to probe the same domain, further complicating comparisons. The use of consistent measures of cognition and definitions of cognitive impairment, and possibly conducting sub-group analyses of different cognitive domains, should therefore be an aim for future studies.

Spatial topography

Separately, we found scant evidence to support a consistent direction of FC change in cognitively impaired patients when using model-based (e.g., seed) or data driven (e.g., ICA) approaches, or when considering specific resting state networks. Indeed, the default mode network, the most commonly studied RSN across the literature, showed both increases and decreases in cognitively impaired MS patients. One explanation of increases in FC is that processing moves from local networks to hub regions when the former accumulate structural damage (Meijer et al., 2017; Stam, 2014; Tahedl et al., 2018), but this explanation fails to account for the findings in this review. Attempting to understand these findings is complex. The role of disease stage in the samples studied could influence the FC directions reported, in line with the network collapse model. Another consideration is the spatial location of the regions investigated. It must be remembered that the default mode network consists of several key 'hub' regions, which are heavily interconnected and involved in several additional networks. For example, the anterior cingulate cortex is also a key hub in the salience network. Moreover, the regions making up a network can vary between studies, often depending on the analysis method used. In a seed-based connectivity study the extent of the network of interest will depend on how and where the seed is defined. The idea that different networks or even subregions of a network hub have different patterns of connectivity is evidenced by the thalamus, a network hub which

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

has shown both hypo- and hyperconnectivity in MS, depending on the thalamic nucleus and pathways investigated (Lin et al., 2019). Despite this, the topography of a network might not be the full explanation of the inconsistent results observed. A meta-analysis of mild cognitive impairment prodromal to Alzheimer's disease did not find consistent FC abnormalities even when using a voxel-wise analysis to assess the same spatial regions, suggesting that directional inconsistencies of FC findings cannot be fully explained by the spatial extent of the region(s) studied (Eyler et al., 2019). Nevertheless, to rule out the potential influence of topography, and enable comparisons between studies, care should be taken to define a specific region consistently with previous research.

Mechanisms of FC changes

There also needs to be a greater understanding of the mechanisms through which FC changes in MS. The 'network collapse' model suggests that network efficiency reduction is a function of accumulation of structural damage. In support of this, work focusing on structural connectivity in MS has found consistent evidence for structural network alterations associated with cognitive dysfunction (Llufriu et al., 2019, 2017; Solana et al., 2018). However, these studies have considered white matter in isolation, so conclusions about the effect of anatomical network changes including grey matter on functional connectivity cannot be drawn. In contrast, multimodal MRI studies of diffusion-weighted MRI (DWI) and rs-fMRI can assess the relationship between changes in structural and functional connectivity. Those that have been conducted support the influence of alterations in white matter linked to FC abnormalities in MS, and fit the predictions of the 'network collapse' model (Enzinger et al., 2016; Lowe et al., 2008; Patel et al., 2018; Tewarie et al., 2018, 2014). Future multimodal studies using DWI and rs-fMRI can test the predictions of the 'network collapse' model further and to develop this or new models as needed to better characterise progression and the influence of pathology in MS brains, in order to develop clinically useful disease markers. In addition, there is evidence of physiological abnormalities in MS that are associated with cognitive dysfunction, such as cerebral hypoperfusion and sodium accumulation in the grey and white matter (Lapointe et al., 2018; Maarouf et al., 2017; Paling et al., 2013), and additional proton spectroscopic changes (Solanky et al., 2020). Considering how these are related to network changes can

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

help us understand the mechanisms of network abnormalities and aid in the search for a biomarker of cognitive impairment.

FC as a biomarker of cognitive impairment in MS?

This systematic review provides a call to arms for the need to standardize the study of cognitive impairment in MS, but also the use of specific rs-fMRI methodology and interpretations of results. Eleven years ago Fox and Greicius (2010) identified inconsistent results of FC changes across rs-fMRI studies as a barrier to the clinical applicability of this modality, and suggested a set of guidelines for rs-fMRI studies of clinical populations (Fox and Greicius, 2010). Despite this, heterogeneity in study methodology seems to be a challenge across neurodegenerative diseases investigated by rs-fMRI, and the rs-fMRI derived FC measure is not yet suitable as a biomarker of disease (reviewed by Hohenfeld *et al.*, 2018). Even in Alzheimer's disease, where there is evidence of consistent hypoconnectivity compared to controls, there is a problem of inconsistent directional results in the prodromal stages (i.e. mild cognitive impairment) of this disease (Badhwar et al., 2017; Eyler et al., 2019). A recent systematic review and meta-analysis found inconsistent results across 56 studies in mild cognitive impairment and concluded that while FC changes may be a marker of Alzheimer's disease, at present the evidence for FC to be a biomarker of the risk of developing Alzheimer's disease is limited (Eyler et al., 2019). In this review we have shown that, similarly, the FC measure is not yet a suitable biomarker for cognitive impairment in MS. Unlike Alzheimer's disease, the use of rs-fMRI in MS has not been the subject of many systematic reviews, and so we do not at present know whether FC results become more consistent at a certain stage of the disease. In this review we found considerable variability in the study of cognitive impairment in MS by rs-fMRI, both in study methods and findings, which pose a challenge for the interpretation of results.

Standardisation of FC studies of cognition in MS and future directions

The FC measure shows promise; most studies suggest that FC alterations are a key pathological feature. Therefore, we argue that standardisation of study methods and more model-driven research would lay a clearer path towards understanding directional FC

changes, and thereby clinical utility of the FC metric and the potential use as a biomarker of MS disease state. First, clinical studies using the rs-fMRI method should ensure that the guidelines suggested by Fox and Greicius (2010) are followed: "(1) *A priori* hypotheses regarding a region or network with abnormal [rs-fMRI FC] and clear criteria for selecting this region or network; (2) *A priori* hypothesis and demonstration of a region or network with normal [rs-fMRI FC] to serve as a control; (3) Correlation with clinical variables whenever possible; (4) Stringent correction for multiple comparisons; (5) An analysis of movement in patients and control subjects; (6) An analysis of the differential impact of pre-processing in patients and control subjects; (7) A discussion of how current findings relate to prior [rs-fMRI FC] findings." In the studies considered in this systematic review, point 3 is necessarily met. Points 4, 5 and 6 are typically met. Points 1, 2 and 7 are occasionally met.

Going forward, research using FC as a marker of cognitive impairment in MS should consider the following to meet points 1, 2 and 7: 1) studying different clinical and cognitive phenotypes of a disease separately to identify phenotype specific influences; 2) controlling for age and disease duration, where this is known to have an influence on the clinical symptom of interest; 3) using well-established and validated measures of the symptom of interest for the disease being investigated; 4) defining regions of interest consistently with previous research; 5) conducting model-led research to understand the underlying pathophysiological basis of any alterations in FC, for example in MS this might involve multimodal diffusion MRI and rs-fMRI studies to test the network collapse model and its prediction of FC being driven by structural changes.

The studies so far have been useful to establish that effects do exist and that there is an association with cognitive impairment, but what is needed now is the equivalent of a well powered multi-site phase 3 trial to establish that the effect is robust. This will help to determine whether functional connectivity measures can indeed be used as biomarkers of cognitively relevant network degeneration in MS.

Limitations

This review is the first to systematically summarise the rs-fMRI functional connectivity literature on cognitive impairment in MS. However, there are some limitations to consider. First, rs-fMRI is not the only imaging modality for studying functional connectivity. While they were outside the scope of this review, electroencephalography and magnetoencephalography studies may offer additional insights into FC changes associated with cognitive impairment in MS. Similarly, there are other network measures that can be derived from rs-fMRI in addition to FC, such as dynamic FC and graph theory measures. At present the number of studies reporting these measures is small and so we did not consider them separately, but rather grouped them with the FC measure for the purposes of the review. Nevertheless, these metrics provide somewhat different information to the FC metric, which has not been captured in detail in this review. In addition, we compared results from studies which looked at the same networks or regions of interest, but using different analysis methods, and vice versa. It could be argued that differences in methods and spatial topography of networks limit the information that can be gained from this approach, however, grouping studies which shared similarities on several methodological variables, such as networks studied and analysis method, would have created very small groups from which it would have been difficult to infer anything with confidence. Previous systematic reviews of rs-fMRI FC changes in mild cognitive impairment find inconsistent directions of altered FC in patient groups even when using a voxel-wise analysis (Eyler et al., 2019). This suggests that the findings of inconsistency in FC results are not entirely due to variation in networks studied or spatial topography. Finally, we did not carry out a formal statistical meta-analysis of the studies in this review. Instead, due to low numbers of homogeneous studies we were limited to tallying the number of studies with a specific feature. As studies start to become more consistent in their use of methods it will become easier to determine across the field whether the hypotheses including disease-specific effects, such as the ‘network collapse’ model, can suitably explain the patterns of associations that are observed.

Conclusion

In conclusion, this systematic review shows that cognitive impairment in MS is associated with both high and low FC, indicating that any network change seems related to poorer functioning. This is an important finding that shows that rs-fMRI FC is sensitive to cognitively relevant brain changes. However, because of the inconsistencies in the direction of FC results this measure needs further exploration in consistently designed studies in order to become a suitable biomarker of cognitive impairment in MS. To better understand the relationship between worsened cognitive function and FC abnormalities, including directional FC changes, there must be standardisation in the field of the definition and measurement of CI, rs-fMRI methodology, and correction and allowances for MS phenotype, and non-MS related pathology from ageing. We have outlined five recommendations to this effect for future research, based on the sources of heterogeneity we have identified in literature, and welcome a discussion of these with our colleagues in this field.

Appendix

Supplementary material associated with this article can be found in the online version at [doi TBC].

Acknowledgements

This article has been published on preprint server medRxiv, DOI 10.1101/2021.03.18.21253878, and is available on the following weblink: https://www.medrxiv.org/content/10.1101/2021.03.18.21253878v1

Author Contributions

AD and DJ contributed to the conception and design of the study. The data was acquired and analysed by AD, DJ and RS. All authors contributed to drafting and reviewing the text and figures.

Declarations of Interest

The authors report no potential competing interests relating to this work.

Funding Sources

This work was funded by grants held by DJ and AD. DJ was supported by a Medical Research Council Doctoral Training Partnership grant (MR/N013751/11). AD was supported by the Multiple Sclerosis Progressive Multi-arm Randomisation Trial, an investigator-led project sponsored by University College London.

References

Aschenbrenner, S., Tucha, O., Lange, K. Regensburger Wortflüssigkeits-Test : RWT ; Handanweisung, 2000, Hogrefe, Verl. für Psychologie, Göttingen.

Amato, M., Portaccio, E., Goretti, B. The Rao's Brief Repeatable Battery version B: Normative values with age, education and gender corrections in an Italian population. Mult. Scler. 2006;12:787–793.

Azevedo, C.J., Cen, S.Y., Jaberzadeh, A. Contribution of normal aging to brain atrophy in MS. Neurol. Neuroimmunol. Neuroinflammation 2019;6.

Badhwar, A.P., Tam, A., Dansereau, C. Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. 2017:8;73–85.

Baird, J.F., Cederberg, K.L.J., Sikes, E.M. Changes in Cognitive Performance With Age in Adults With Multiple Sclerosis. Cogn. Behav. Neurol. 2019:32;201–207.

Basile, B., Castelli, M., Monteleone, F. Functional connectivity changes within specific networks parallel the clinical evolution of multiple sclerosis. Mult. Scler. 2014:20;1050–1057.

Basso, A., Capitani, E., Laiacona, M. Raven's coloured progressive matrices: normative values on 305 adult normal controls. Funct. Neurol. 1987;2:189–194.

Batlle, M., Alahmadi, A., Collorone, S. Resting state functional networks and cognitive performance in clinically isolated syndromes. Mult. Scler. J. 2017:23;813, 7th Joint ECTRIMS-ACTRIMS, MSPARIS2017. France.

Benedict, R. Brief Visuospatial Memory Test–Revised Professional Manual. 1997. Psychological Assessment Resources, Odessa, Florida.

Benedict, R.H.B., Schretlen, D., Groninger, L. Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. Clin. Neuropsychol. 1998;12:43–55.

Benedict, R.H.B., DeLuca, J., Phillips, G. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult. Scler. 2017;23:721–733.

Benedict, R.H.B. Cognition in multiple sclerosis: Charcot was right. Lancet Neurol. 2020:19;810.

Benedict, R.H.B., Amato, M.P., DeLuca. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020:19;860–871.

Benedict, R.H.B., Fischer, J.S., Archibald, C.J. Minimal neuropsychological assessment of MS patients: A consensus approach. Clin. Neuropsychol. 2002:16;381–397.

Benton, A., Hamsher, S., Sivan, A. Multilingual aplasia examination, 2nd ed. ed. 1983a. AJA Associates, Iowa City.

Benton, A., Hamsher, K., Varney, N. Contributions to Neuropsychological Assessment: A Clinical Manual. 1983b. Oxford, New York.

Bijsterbosch, J., Smith, S., Beckmann, C. Introduction to Resting State fMRI Functional Connectivity. 2017. Oxford University Press, Oxford.

Bizzo, B.C., Arruda-Sanchez, T., Tobyne, S.M. Anterior Insular Resting-State Functional Connectivity is Related to Cognitive Reserve in Multiple Sclerosis. J. Neuroimaging 2021;31:98-102.

Blair, J., Spreen, O. Predicting premorbid IQ: A revision of the National Adult Reading Test. Clin. Neuropsychol. 1989;3:129–136.

Bonavita, S., Gallo, A., Sacco, R.. Distributed changes in default-mode resting-state connectivity in multiple sclerosis. Mult. Scler. J. 2011a:17;411–422.

Bucks, R.S., Willison, J.R. Development and validation of the Location Learning Test (LLT): A test of visuo-spatial learning designed for use with older adults and in dementia. Clin. Neuropsychol. 1997;11:273–286.

Caffarra, P., Vezzadini, G., Dieci, F. Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol. Sci. 2002;22:443–447.

Carotenuto, A., Wilson, H., Giordano, B. Impaired connectivity within neuromodulatory networks in multiple sclerosis and clinical implications. J. Neurol. 2020;267:2042–2053.

Castellazzi, G., Debernard, L., Melzer, T.R. Functional connectivity alterations reveal complex mechanisms based on clinical and radiological status in mild relapsing remitting multiple sclerosis. Front. Neurol. 2018:9;1–15.

Castellazzi, G., Palesi, F., Casali, S. A comprehensive assessment of resting state networks: bidirectional modification of functional integrity in cerebro-cerebellar networks in dementia. Front. Neurosci. 2014:8;1-18.

Chan, D., Binks, S., Nicholas, J.M. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. Lancet Neurol. 2017:16;591–600.

Charcot, J.M. Lectures on the disease of the nervous system, Second. ed. 1888. J E Adlard.

Chard, D.T., Alahmadi, A.A.S., Audoin, B. Mind the gap: from neurons to networks to outcomes in multiple sclerosis. Nat. Rev. Neurol. 2021:17;173–184.

Cocozza, S., Pontillo, G., Russo, C. Cerebellum and cognition in progressive MS patients: functional changes beyond atrophy? J. Neurol. 2018:265;2260–2266.

Connick, P., Chandran, S., Bak, T.H. Patterns of cognitive dysfunction in progressive MS. Behav. Neurol. 2013:27;259–265.

Cruz-Gómez, Á.J., Aguirre, N., Sanchis-Segura, C. Subcortical grey matter structures in multiple sclerosis: What is their role in cognition? Neuroreport 2018:29;547–552.

Cruz-Gómez, Á.J., Ventura-Campos, N., Belenguer, A. The link between resting-state functional connectivity and cognition in MS patients. Mult. Scler. J. 2014:20;338–348.

d'Ambrosio, A., Hidalgo de la Cruz, M., Valsasina, P. Structural connectivity-defined thalamic subregions have different functional connectivity abnormalities in multiple sclerosis patients: Implications for clinical correlations. Hum. Brain Mapp. 2017:38;6005–6018.

d'Ambrosio, A., Valsasina, P., Gallo, A. Reduced dynamics of functional connectivity and cognitive impairment in multiple sclerosis. Mult. Scler. J. 2020:26;476–488.

Delis, D., Kramer, J., Kaplan, E. California Verbal Learning Test, 2nd ed. ed. 2000. Psychological Corporation, San Antonio, Texas.

Dobson, R., Giovannoni, G. Multiple sclerosis – a review. Eur. J. Neurol. 2019:26;27–40.

Doshi, A., Castellazzi, G., Muhlert, N. COGNITIVE DIAGNOSTIC CRITERIA LEAD TO DISTINCT PATTERNS OF FUNCTIONAL CONNECTIVITY IN SECONDARY PROGRESSIVE MS. J. Neurol. Neurosurg. Psychiatry 2019:90;2019.

Downes, M.J., Brennan, M.L., Williams, H.C. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open 2016:6;e011458.

Eijlers, A.J.C., Meijer, K.A., Wassenaar, T.M. Increased default-mode network centrality in cognitively impaired multiple sclerosis patients. Neurology 2017:88;952–960.

Eijlers, A.J.C., Meijer, K.A., van Geest, Q. Determinants of Cognitive Impairment in Patients with Multiple Sclerosis with and without Atrophy. Radiology. 2018:288(2);552-55

Eijlers, A.J.C., Wink, A.M., Meijer, K.A. Reduced Network Dynamics on Functional MRI Signals Cognitive Impairment in Multiple Sclerosis. Radiology 2019:292;449–457.

Enzinger, C., Pinter, D., Rocca, M.A. Longitudinal fMRI studies: Exploring brain plasticity and repair in MS. Mult. Scler. 2016:22;269–278.

Eshaghi, A., Riyahi-Alam, S., Saeedi, R. Classification algorithms with multi-modal data fusion could accurately distinguish neuromyelitis optica from multiple sclerosis. NeuroImage Clin. 2015:7;306–314.

Eyler, L.T., Elman, J.A., Hatton, S.N. Resting State Abnormalities of the Default Mode Network in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. J. Alzheimer's Dis. 2019:70;107–120.

Faivre, A., Rico, A., Zaaraoui, W. Assessing brain connectivity at rest is clinically relevant in early multiple sclerosis. Mult. Scler. J. 2012:18;1251–1258, 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon France.

Fan, J., McCandliss, B.D., Sommer, T. Testing the efficiency and independence of attentional networks. J. Cogn. Neurosci. 2002;14:340–347.

Filippi, M., Rocca, M.A. Present and future of fMRI in multiple sclerosis. Expert Rev. Neurother. 2013:13;27–31.

Filippi, M., Bar-Or, A., Piehl, F. Multiple sclerosis. Nat. Rev. Dis. Prim. 2018:4;43.

Fischer, M., Kunkel, A., Bublak, P. How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis? J. Neurol. Sci. 2014:343;91–9.

Folstein, M.F., Folstein, S.E., McHugh, P.R. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 1975;12:189–198.

Fox, M.D., Greicius, M. Clinical applications of resting state functional connectivity. Front. Syst. Neurosci. 2010:4;1–13.

Fuchs, T.A., Benedict, R.H.B., Bartnik, A. Preserved network functional connectivity underlies cognitive reserve in multiple sclerosis. Hum. Brain Mapp. 2019;40:5231–5241.

Gabilondo, I., Rilo, O., Ojeda, N. The influence of posterior visual pathway damage on visual information processing speed in multiple sclerosis. Mult. Scler. 2017;23:1276–1288.

Gao, F., Yin, X., Edden, R.A.E. Altered Hippocampal GABA and Glutamate Levels and Uncoupling from Functional Connectivity in Multiple Sclerosis. Hippocampus 2018;28:813–823.

Has Silemek, A.C., Fischer, L., Pöttgen, J. Functional and structural connectivity substrates of cognitive performance in relapsing remitting multiple sclerosis with mild disability. NeuroImage Clin. 2020;25:102177.

Hawellek, D.J., Hipp, J.F., Lewis, C.M. Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. Proc. Natl. Acad. Sci. U. S. A. 2011:108;19066–19071.

Helmstaedter, C., Durwen, H.F. The Verbal Learning and Retention Test. A useful and differentiated tool in evaluating verbal memory performance. Schweiz. Arch. Neurol. Psychiatr. 1990;141:21–30.

Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

Hohenfeld, C., Werner, C.J., Reetz, K. Resting-state connectivity in neurodegenerative disorders: Is there potential for an imaging biomarker? NeuroImage Clin. 2018:18;849–870.

Holdnack, H. Wechsler Test of Adult Reading. 2001. The Psychological Corporation, San Antonio, Texas.

Hugonot-Diener, L., Barbeau, E., Michel, B. GREMOIRE: Tests et echelles de la maladie d'Alzheimer et des syndromes apparentes. 2008. Solal, Marseille.

Hulst, H.E., Schoonheim, M.M., Van Geest, Q. Memory impairment in multiple sclerosis: Relevance of hippocampal activation and hippocampal connectivity. Mult. Scler. 2015;21:1705–1712.

Janssen, A.L., Boster, A., Patterson, B.A. Resting-state functional connectivity in multiple sclerosis: An examination of group differences and individual differences. Neuropsychologia 2013;51:2918–2929.

Johnen, A., Landmeyer, N.C., Bürkner, P.C. Distinct cognitive impairments in different disease courses of multiple sclerosis—A systematic review and meta-analysis. Neurosci. Biobehav. Rev. 2017:83:568-578.

Johnen, A., Burkner, P.-C., Landmeyer, N.C. Can we predict cognitive decline after initial diagnosis of multiple sclerosis? Results from the German National early MS cohort (KKNMS). J. Neurol. 2019:266;386–397.

Jones, D.T., Mateen, F.J., Lucchinetti, C.F. Default mode network disruption secondary to a lesion in the anterior thalamus. Arch. Neurol. 2011;68:242–247.

Karavasilis, E., Christidi, F., Velonakis, G. Hippocampal structural and functional integrity in multiple sclerosis patients with or without memory impairment: a multimodal neuroimaging study. Brain Imaging Behav. 2019;13:1049–1059.

Kaufman, A., Lichtenberger, E. Assessing Adolescent and Adult Intelligence. 2005. Wiley, New York.

Koenig, K.A., Lowe, M.J., Lin, J. Sex differences in resting-state functional connectivity in multiple sclerosis. Am. J. Neuroradiol. 2013;34:2304–2311.

Kokmen, E., Smith, G.E., Petersen, R.C. The Short Test of Mental Status: Correlations With Standardized Psychometric Testing. Arch. Neurol. 1991;48:725–728.

Koubiyr, I., Besson, P., Deloire, M. Dynamic modular-level alterations of structural-functional coupling in clinically isolated syndrome. Brain 2019;142:3428–3439.

Krysko, K.M., Graves, J.S., Dobson, R. Sex effects across the lifespan in women with multiple sclerosis. Ther. Adv. Neurol. Disord. 2020;13:1–30.

Landmeyer, N.C., Bürkner, P.-C., Wiendl, H. Disease-modifying treatments and cognition in relapsing-remitting multiple sclerosis: A meta-analysis. Neurology 2020;94:e2373–e2383.

Langdon, D., Amato, M., Boringa, J. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult. Scler. J. 2012;18:891–898.

Lapointe, E., Li, D.K.B., Traboulsee, A.L. What Have We Learned from Perfusion MRI in Multiple Sclerosis? Am. J. Neuroradiol. 2018;39:994–1000.

Lassmann, H. Multiple sclerosis pathology. Cold Spring Harbor Perspect. Med. 2018;8: 1–16.

Leavitt, V.M., Paxton, J., Sumowski, J.F. Default network connectivity is linked to memory status in multiple sclerosis. J. Int. Neuropsychol. Soc. 2014;20:937–944.

Lehrl, S. Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B). 2nd ed, 1991. Straube, Erlangen, Germany.

Lezak, M. Neuropsychological assessment. 3rd ed, 2004. Oxford University Press, New York.

Lin, S.J., Vavasour, I., Kosaka, B. Education, and the balance between dynamic and stationary functional connectivity jointly support executive functions in relapsing-remitting multiple sclerosis. Hum. Brain Mapp. 2018;39:5039–5049.

Lin, F., Zivadinov, R., Hagemeier, J. Altered nuclei-specific thalamic functional connectivity patterns in multiple sclerosis and their associations with fatigue and cognition. Mult. Scler. J. 2019;25:1243–1254.

Lin, S.J., Kolind, S., Liu, A. Both Stationary and Dynamic Functional Interhemispheric Connectivity Are Strongly Associated With Performance on Cognitive Tests in Multiple Sclerosis. Front. Neurol. 2020;11:407.

Llufriu, S., Martinez-Heras, E., Solana, E. Structural networks involved in attention and executive functions in multiple sclerosis. NeuroImage. Clin. 2017;13:288–296.

Llufriu, S., Rocca, M.A., Pagani, E. Hippocampal-related memory network in multiple sclerosis: A structural connectivity analysis. Mult. Scler. J. 2019;25:801–810.

Loitfelder, M., Fazekas, F., Petrovic, K. Reorganization in cognitive networks with progression of multiple sclerosis: insights from fMRI. Neurology 2011;76:526–533.

Loitfelder, M., Filippi, M., Rocca, M. Abnormalities of resting state functional connectivity are related to sustained attention deficits in MS. PLoS One 2012;7:e42862.

Lowe, M.J., Beall, E.B., Sakaie, K.E. Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. Hum. Brain Mapp. 2008:29;818–827.

Louapre, C., Perlbarg, V., García-Lorenzo, D. Brain networks disconnection in early multiple sclerosis cognitive deficits: An anatomofunctional study. Hum. Brain Mapp. 2014;35:4706–4717.

Maarouf, A., Audoin, B., Pariollaud, F. Increased total sodium concentration in gray matter better explains cognition than atrophy in MS. Neurology 2017;88:289–295.

Manca, R., Mitolo, M., Stabile, M.R. Multiple brain networks support processing speed abilities of patients with multiple sclerosis. Postgrad. Med. 2019;131:523–532.

Meijer, K.A., Eijlers, A.J.C., Douw, L. Increased connectivity of hub networks and cognitive impairment in multiple sclerosis. Neurology 2017;88:2107–2114.

Meijer, K.A, Eijlers, A.J.C., Geurts, J.J.G. Staging of cortical and deep grey matter functional connectivity changes in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 2018a;89:205–

Meijer, K.A., van Geest, Q., Eijlers, A.J.C. Is impaired information processing speed a matter of structural or functional damage in MS? NeuroImage. Clin. 2018b;20:844–850.

Moher, D., Shamseer, L., Clarke, M. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 2015;4.

Mori, F., Rossi, S., Sancesario, G. Cognitive and cortical plasticity deficits correlate with altered amyloid-beta CSF levels in multiple sclerosis. Neuropsychopharmacology 2011;36:559–568.

Motl, R.W., Sandroff, B.M. Current Perspectives on Exercise Training in the Management of Multiple Sclerosis. Expert Rev. Neurother. 2020;20:855–866.

Paling, D., Solanky, B.S., Riemer, F. Sodium accumulation is associated with disability and a progressive course in multiple sclerosis. Brain 2013;136:2305–2317.

Pasqua, G., Tommasin, S., Bharti, K. Resting-state functional connectivity of anterior and posterior cerebellar lobes is altered in multiple sclerosis. Mult. Scler. J. 2020:1–10.

Patel, K.R., Tobyne, S., Porter, D. Structural disconnection is responsible for increased functional connectivity in multiple sclerosis. Brain Struct. Funct. 2018;223:2519–2526.

Patterson, J. F-A-S Test BT - Encyclopedia of Clinical Neuropsychology, in: Kreutzer, J.S., DeLuca, J., Caplan, B. (Eds.), 2011, Springer New York, New York, NY, pp. 1024–1026.

Patti, F., Amato, M.P., Bastianello, S. Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing-remitting multiple sclerosis. Mult. Scler. 2010;16:68–77.

Petracca, M., Saiote, C., Bender, H.A. Synchronization and variability imbalance underlie cognitive impairment in primary-progressive multiple sclerosis. Sci. Rep. 2017;7:46411.

Petsas, N., De Giglio, L., González-Quintanilla, V. Functional Connectivity Changes After Initial Treatment With Fingolimod in Multiple Sclerosis. Front. Neurol. 2019;10:153.

Rao, S. A manual for the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis. 1990. National Multiple Sclerosis Society, New York.

Riccitelli, G.C., Pagani, E., Meani, A. Cognitive impairment in benign multiple sclerosis: a multiparametric structural and functional MRI study. J. Neurol. 2020:8–10.

Robinson, A., Heaton, R., Lehman, R. The utility of the Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. J. Consult. Clin. Psychol. 1980;48:605–614.

Rocca, M.A., Valsasina, P., Absinta, M. Default-mode network dysfunction and cognitive impairment in progressive MS. Neurology 2010;74:1252–1259.

Rocca, M.A., Amato, M.P., De Stefano, N. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. Lancet Neurol. 2015;14:302–417.

Rocca, M.A., Valsasina, P., Meani, A. Impaired functional integration in multiple sclerosis: a graph theory study. Brain Struct. Funct. 2016;221:115–131.

Rocca, M.A., Valsasina, P., Leavitt, V.M. Functional network connectivity abnormalities in multiple sclerosis: Correlations with disability and cognitive impairment. Mult. Scler. J. 2018;24:459–471.

Romascano, D., Meskaldji, D.-E., Bonnier, G. Multicontrast connectometry: a new tool to assess cerebellum alterations in early relapsing-remitting multiple sclerosis. Hum. Brain Mapp. 2015;36:1609–1619.

Romero, K., Shammi, P., Feinstein, A. Neurologists' accuracy in predicting cognitive impairment in multiple sclerosis. Mult. Scler. Relat. Disord. 2015;4:291–295.

Roosendaal, S.D, Schoonheim, M.M., Hulst, H.E. Resting state networks change in clinically isolated syndrome. Brain 2010a;133:1612–1621.

Roosendaal, S.D., Hulst, H.E., Vrenken, H. Structural and functional hippocampal changes in multiple sclerosis patients with intact memory function. Radiology 2010b;255:595–604.

Ruet, A., Deloire, M., Charré-Morin, J. Cognitive impairment differs between primary progressive and relapsing-remitting MS. Neurology 2013a;80:1501–1508.

Ruet, A., Deloire, M., Hamel, D. Cognitive impairment, health-related quality of life and vocational status at early stages of multiple sclerosis: A 7-year longitudinal study. J. Neurol. 2013b;260:776–784.

Ruet, A., Deloire, M., Charré-Morin, J. A new computerised cognitive test for the detection of information processing speed impairment in multiple sclerosis. Mult. Scler. J. 2013c;19:1665–1672.

Salthouse, T.A., Babcock, R.L., Shaw, R.J. Effects of adult age on structural and operational capacities in working memory. Psychol. Aging. 1991;6:118-127.

Salthouse, T.A. Selective influences of age and speed on associative memory. Am. J. Psychol. 1995;108:381–396.

Sanchis-Segura, C., Cruz-Gomez, A.J., Belenguer, A. Increased regional gray matter atrophy and enhanced functional connectivity in male multiple sclerosis patients. Neurosci. Lett. 2016;630:154–157.

Sandroff, B.M., DeLuca, J. Will behavioral treatments for cognitive impairment in multiple sclerosis become standards-of-care? Int. J. Psychophysiol. 2020;154:67–79.

Sbardella, E., Tona, F., Petsas, N. Functional connectivity changes and their relationship with clinical disability and white matter integrity in patients with relapsing-remitting multiple sclerosis. Mult. Scler. 2015;21:1681–1692.

Sbardella, E., Upadhyay, N., Tona, F. Dentate nucleus connectivity in adult patients with multiple sclerosis: Functional changes at rest and correlation with clinical features. Mult. Scler. J. 2017;23:546–555.

Schoonheim, M.M., Hulst, H.E., Landi, D. Gender-related differences in functional connectivity in multiple sclerosis. Mult. Scler. J. 2012;18:164–173.

Schoonheim, M.M., Geurts, J., Wiebenga, O.T. Changes in functional network centrality underlie cognitive dysfunction and physical disability in multiple sclerosis. Mult. Scler. 2014;20:1058–1065.

Schoonheim, M.M., Hulst, H.E., Brandt, R.B. Thalamus structure and function determine severity of cognitive impairment in multiple sclerosis. Neurology 2015a;84:776–783.

Schoonheim, M.M., Meijer, K.A., Geurts, J.J.G. Network collapse and cognitive impairment in multiple sclerosis. Front. Neurol. 2015b;6:82.

Schoonheim, M.M., Penner, I.K., Aktas, O. Functional reorganization is a maladaptive response to injury - COMMENTARY. Mult. Scler. J. 2017;23:194–196.

Soares, J.M., Conde, R., Magalhães, R.R.R.R. Alterations in functional connectivity are associated with white matter lesions and information processing efficiency in multiple sclerosis. Brain Imaging Behav. 2021;15:375-388.

Solana, E., Martinez-Heras, E., Martinez-Lapiscina, E.H. Magnetic resonance markers of tissue damage related to connectivity disruption in multiple sclerosis. NeuroImage. Clin. 2018;20:161–168.

Solanky, B.S., John, N.A., DeAngelis, F. NAA is a marker of disability in secondary-progressive MS: A proton MR spectroscopic imaging study. Am. J. Neuroradiol. 2020;41:2209–2218.

Stam, C.J. Modern network science of neurological disorders. Nat. Rev. Neurosci. 2014:15; 683–695.

Strober, L.B., Rao, S.M., Lee, J.C.C. Cognitive impairment in multiple sclerosis: An 18 year follow-up study. Mult. Scler. Relat. Disord. 2014;3:473–481.

Stroop, R. Studies of interference in serial verbal reactions. J. Exp. Psychol. 1935;18.

Sumowski, J.F., Benedict, R., Enzinger, C. Cognition in multiple sclerosis: State of the field and priorities for the future. Neurology 2018;90:278–288.

Tahedl, M., Levine, S.M., Greenlee, M.W. Functional connectivity in multiple sclerosis: Recent findings and future directions. Front. Neurol. 2018:9;1–18.

Tewarie, P., Steenwijk, M.D., Tijms, B.M. Disruption of structural and functional networks in long-standing multiple sclerosis. Hum. Brain Mapp. 2014;35:5946–5961.

Tewarie, P., Steenwijk, M.D., Brookes, M.J. Explaining the heterogeneity of functional connectivity findings in multiple sclerosis: An empirically informed modeling study. Hum. Brain Mapp. 2018;39:2541–2548.

Thompson, A.J., Baranzini, S.E., Geurts, J. Multiple sclerosis. Lancet 2018;391:1622–1636.

Tombaugh, T.N. Trail Making Test A and B: Normative data stratified by age and education. Arch. Clin. Neuropsychol. 2004;19:203–214.

Tombaugh, T., Rees, L. Computerized Test of Information Processing. 2008. Multi-Health System Inc, Toronto.

Tona, F., Petsas, N., Sbardella, E. Multiple sclerosis: Altered thalamic resting-state functional connectivity and its effect on cognitive function. Radiology 2014;271:814–821.

Van der Elst, W., Van Boxtel, M.P.J., Van Breukelen, G.J.P. The Concept Shifting Test: adult normative data. Psychol. Assess. 2006a;18:424–432.

van der Elst, W., van Boxtel, M.P.J., van Breukelen, G.J.P. The Letter Digit Substitution Test: Normative Data for 1,858 Healthy Participants Aged 24–81 from the Maastricht Aging Study (MAAS): Influence of Age, Education, and Sex. J. Clin. Exp. Neuropsychol. 2006b;28:998–1009

van Geest, Q., Westerik, B., van der Werf, Y.D. The role of sleep on cognition and functional connectivity in patients with multiple sclerosis. J. Neurol. 2017;264:72–80.

van Geest, Q., Douw, L., van 't Klooster, S. Information processing speed in multiple sclerosis: Relevance of default mode network dynamics. NeuroImage. Clin. 2018;19:507–515.

Wechsler, D. Wechsler memory scale administration and scoring manual. 1997. Psychological Corporation.

Wechsler, D. Test of Premorbid Functioning. 2011. The Psychological Corporation, San Antonio, Texas.

Welton, T., Constantinescu, C.S., Auer, D.P. Graph Theoretic Analysis of Brain Connectomics in Multiple Sclerosis: Reliability and Relationship with Cognition. Brain Connect. 2020;10:95–104.

Wojtowicz, M., Mazerolle, E.L., Bhan, V. Altered functional connectivity and performance variability in relapsing-remitting multiple sclerosis. Mult. Scler. 2014;20:1453–1463.

Zhao, Q., Lv, Y., Zhou, Y. Short-Term Delayed Recall of Auditory Verbal Learning Test Is Equivalent to Long-Term Delayed Recall for Identifying Amnestic Mild Cognitive Impairment. PLoS One 2012;7:e51157.

Zhou, F., Gong, H., Chen, Q. Intrinsic functional plasticity of the thalamocortical system in minimally disabled patients with relapsing-remitting multiple sclerosis. Front. Hum. Neurosci. 2016;10:2.

Zimmermann, P., Fimm, B. A test battery for attentional performance, in: Applied Neuropsychology of Attention. Theory, Diagnosis and Rehabilitation. 2002. pp. 110–151.

Table 1. Study characteristics, cognitive assessment and relationship between cognition and functional connectivity

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Study	Cohort (n)	Design	Cognitive measures	FC-cognition analysis outcome	Direction of FC result
Rocca et al. 2010 (Rocca et al., 2010)	SPMS (33) PPMS (24) HC (24)	Cross-sectional ICA	PASAT3, TMT, SST, WLT, RCFT, VFT	Lower ACC FC within the DMN in MS patients compared to HC, but more pronounced reductions in cognitively impaired MS patients.	↓
Roosendaal et al. 2010 (Roosendaal et al., 2010a)	CIS (14) RRMS (31) HC (41)	Cross-sectional ICA	Stroop, LLT, LDST	No correlations between FC metrics and cognitive measures.	-
Roosendaal et al. 2010 (Roosendaal et al.,	CIS (5) RRMS (18) SPMS (2)	Cross-sectional Seed	LLT	Lower FC in hippocampus bilaterally in MS patients with intact spatial memory	-

2010b)	HC (30)			compared to HC.	
Bonavita et al. 2011 (Bonavita et al., 2011)	RRMS (36) HC (18)	Cross-sectional ICA	BRB-N, Stroop	Lower ACC and PCC FC in cognitively impaired and cognitively preserved RRMS compared to HC. Lower PCC FC in cognitively impaired patients compared to cognitively preserved.	↓
Hawellak et al 2011 (Hawellek et al., 2011)	CIS (2) RRMS (12) MS* (2) HC (16) *Subtypes not specified.	Cross-sectional PCA	PASAT, SDMT, TMT, Digitspan, Verbal Intelligence Test 'Mehrfachwortschatztest-B," COWAT, subtests of TAP	High FC in DMN correlated with low cognitive efficiency.	↑
Jones et al 2011	MS NOS (1)	Case study	The short test of mental status	Single patient with cognitive	↓

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

(Jones et al., 2011)	HC (10)	ICA		symptoms showed lower FC in PCC, precuneus and left inferior parietal lobe of DMN compared to HC.	
Faivre et al. 2012 (Faivre et al., 2012)	RRMS (13) HC (14)	Cross-sectional ICA	BRB-N	High FC in DMN correlated with decreased performance in semantic fluency task. High FC in dorsal FPN and right ventral FPN correlated with worse PASAT scores.	↑
Loitfelder et al. 2012 (Loitfelder et al., 2012)	CIS (10) RRMS (16) SPMS (5) HC (31)	Cross-sectional Seed	BRB-N, WCST	Better cognitive performance correlated with high FC from ACC to cerebellum, middle temporal gyrus, occipital pole and	↓

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

				angular gyrus.	
Schoonheim et al. 2012 (Schoonheim et al., 2012)	RRMS (26) SPMS (4) HC (30)	Cross-sectional SCA GT	LLT, LDST	Low FC and network efficiency in male MS correlated with visuospatial memory.	↓
Janssen et al. 2013 (Janssen et al., 2013)	RRMS (28) HC (28)	Cross-sectional ICA	PASAT3, letter comparison and pattern comparison tasks	No correlations between FC in any network and processing speed measure.	-
Koenig et al 2013 (Koenig et al., 2013)	RRMS (30) SPMS (2) HC (32)	Cross-sectional SCA	CVLT-II, BVMT-R, PASAT, SDMT, COWAT	No correlations between FC metrics and cognitive measures.	-
Basile et al. 2014 (Basile et al., 2014)	RRMS (34) SPMS (14) HC (25)	Cross-sectional ICA	PASAT3, SDMT, RCFT	Positive correlation between ACC FC and PASAT3 mistakes in patients.	↑
Cruz-Gomez et	RRMS (60)	Cross-sectional	BRB-N	Lower FC in DMN, LFPN,	↓

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

al. 2014 (Cruz-Gómez et al., 2014)	HC (18)	ICA		RFPN and SN in cognitively impaired MS compared to cognitively preserved patients.	
Leavitt et al 2014 (Leavitt et al., 2014)	RRMS (33) PPMS (4) SPMS (6)	Cross-sectional SCA	HVLT-R, BVMT-R, Digitspan, COWAT, PASAT, SDMT, JoLO, WTAR, Stroop	Higher FC in DMN in memory intact compared to memory impaired patients. Higher FC correlated with better memory performance.	↓
Louapre et al 2014 (Louapre et al., 2014)	RRMS (35) HC (20)	Cross-sectional ICA	Mattis Dementia Rating Scale, PASAT, TMT, verbal fluency, Digitspan, SPART	Lower FC in cognitively impaired compared to cognitively preserved in DMN and ATT.	↓
Schoonheim et al. 2014 (Schoonheim et al.,	RRMS (112) PPMS (7) SPMS (9)	Cross-sectional GT	BRB-N, CST, Stroop, MCT	Low eigenvector centrality mapping values in the ventral stream	↓

2014)	HC (50)			correlated with worse cognition.	
Tona et al. 2014 (Tona et al., 2014)	RRMS (48) HC (24)	Cross-sectional SCA	PASAT3	Inverse correlation of thalamo-cortical resting state functional connections with PASAT3 score.	↑
Wojtowicz et al 2014 (Wojtowicz et al., 2014)	RRMS (18) HC (16)	Cross-sectional SCA	The computerised test of information processing	Better cognitive task performance associated with high FC in DMN regions.	↓
Hulst et al 2015 (Hulst et al., 2015)	RRMS (40) SPMS (17) HC (28)	Cross-sectional SCA	Dutch equivalent of CVLT, LLT, Digit Span, WLG, LDST	Memory impairment was predicted by (among other variables) high hippocampal FC.	↑
Romascano et al 2015 (Romascano et al., 2015)	RRMS (28) HC (16)	Cross-sectional GT	BRB-N	Relationship between FC and cognition not assessed.	-

Sbardella et al 2015 (Sbardella et al., 2015)	RRMS (30) HC (24)	Cross-sectional ICA	Mini Mental State Examination, PASAT	FC of executive control and medial visual networks correlated inversely with PASAT scores.	↑
Schoonheim et al. 2015 (Schoonheim et al., 2015a)	RRMS (133) PPMS (15) SPMS (9) HC (47)	Cross-sectional SCA	BRB-N, Stroop, CST, MCT	Higher thalamic FC in severely cognitively impaired patients compared to cognitively preserved patients.	↑
Rocca et al. 2016 (Rocca et al., 2016)	RRMS (121) BMS (45) SPMS (80) HC (55)	Cross-sectional GT	PASAT3	Abnormal network properties in cognitively impaired compared to cognitively preserved patients: lower mean network degree, global efficiency and hierarchy,	↓

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

				higher path length, fewer hubs in left frontal cortex and thalamus.	
Sanchis-Segura et al 2016 (Sanchis-Segura et al., 2016)	RRMS (56) HC (63)	Cross-sectional SCA	BRB-N	Positive correlation between FC and cognitive performance.	↓
Zhou et al 2016 (Zhou et al., 2016)	RRMS (20) HC (20)	Cross-sectional SCA	PASAT	No correlations between FC metrics and cognitive measures.	-
D'Ambrosio et al 2017 (d'Ambrosio et al., 2017)	RRMS (136) PPMS (9) SPMS (42) HC (94)	Cross-sectional SCA	BRB-N	Higher thalamic FC in cognitively impaired compared to cognitively preserved patients.	↑
Eijlers et al. 2017 (Eijlers et al., 2017)	RRMS (243) SPMS (53) PPMS	Cross-sectional GT	BRNB, SRT, WLG, SDMT, Stroop, MCT	Widespread high DMN network centrality in cognitively	↓↑

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

	36) HC (96)			impaired compared to cognitively preserved patients. Some low centrality in CI, in occipital and sensorimotor areas.	
Gabilondo et al 2017 (Gabilondo et al., 2017)	RRMS (22) PPMS (1) SPMS (7) HC (28)	Cross-sectional SCA	TMT, Salthouse Perceptual Comparison Test, SDMT	Low visual processing speed correlated with both low and high FC, in the medial visual component.	↓↑
Meijer et al 2017 (Meijer et al., 2017)	RRMS (243) PPMS (36) SPMS (53) HC (96)	Cross-sectional ICA	BRB-N	Higher FC in cognitively impaired compared to cognitively preserved patients in DMN and FPN.	↑
Petracca et al 2017 (Petracca	PPMS (25)	Cross-sectional	MACFIMS	Pattern of both lower and higher FC in	↓↑

et al., 2017)	HC (20)	SCA		cognitively impaired compared to cognitively preserved patients.	
Sbardella et al 2017 (Sbardella et al., 2017)	RRMS (54) HC (24)	Cross-sectional SCA	PASAT	Positive correlation between FC of dentate nuclei and PASAT performance.	↓
Van Geest et al 2017 (van Geest et al., 2017)	RRMS (52) SPMS (18) HC (40)	Cross-sectional SCA	Dutch equivalent of CVLT, LLT, Digitspan, WLG, LDST	Lower FC in sleep disturbed patients, but sleep disturbed patients did not differ from normally sleeping in cognitive test performance. (No direct analysis of FC at rest and cognition.)	-
Cocozza et al 2018 (Cocozza	Progressive MS* (29)	Cross-sectional	BICAMS	Inverse relationship between	↑

et al., 2018)	HC (22) *Number of PPMS relative to SPMS not reported	SCA		cerebellar FC and BVMT scores.	
Cruz-Gomez et al 2018 (Cruz-Gómez et al., 2018)	RRMS (36) HC (18)	Cross-sectional SCA	BRB-N	Higher FC in cognitively impaired compared to cognitively preserved patients between right caudate and bilateral orbitofrontal cortex.	↑
Eijlers et al 2018 (Eijlers et al., 2018)	RRMS (239) PPMS (35) SPMS (53) HC (96)	Cross-sectional GT	BRB-N	Higher network centrality in PCC in cognitively impaired compared to cognitively preserved patients regardless of	↑

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

				presence of GM atrophy.	
Gao et al 2018 (Gao et al., 2018)	RRMS (29) HC (29)	Cross-sectional SCA	Auditory verbal learning test, RCFT, SDMT, TMT	No correlations between FC metrics and cognitive measures in MS group.	-
Lin et al 2018 (Lin et al., 2018)	RRMS (27) HC (15)	Cross-sectional SCA	Digit span, arithmetic, letter-numbering sequencing, symbol search, coding subtests from the WAIS IV, VFT, WCST, TMT.	Better executive functions and processing speed correlated with higher dynamic and stationary FC.	↓
Meijer et al. 2018 (Meijer et al., 2018a)	RRMS (241) SPMS (53) HC (96)	Cross-sectional SCA	BRB-N, CST, MCT, Stroop	High within-DGM and DGM-cortex FC correlated to worse cognition.	↑
Meijer et al 2018 (Meijer et al., 2018b)	RRMS (243) PPMS (36) SPMS (51)	Cross-sectional SCA	BRB-N	Higher FC in patients with impaired information processing speed compared to those with	↑

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

	HC (96)			preserved.	
Rocca et al. 2018 (Rocca et al., 2018)	RRMS (119) PPMS (13) SPMS (41) BMS (29) CIS (13) HC (98)	Cross-sectional SCA	BRB-N	Lower FC in DMN and DAN in cognitively impaired compared to cognitively preserved patients. Higher FC in thalamic network in cognitively impaired compared to cognitively preserved patients.	↓↑
Van Geest et al. 2018 (van Geest et al., 2018)	MS* (29) HC (19) *Subtypes not specified.	Cross-sectional SCA	LDST, SDMT, Stroop	Information processing task performance predicted by difference in dynamic FC between task and rest states. (No direct analysis of FC at rest and	-

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

				cognition.)	
D'Ambrosio et al 2019 (D'Ambrosio et al., 2019)	RRMS (62) HC (65)	Cross-sectional ICA	BRB-N, WCST	Lower dynamic FC in the subcortical and default mode networks in cognitively impaired compared to cognitively preserved patients. Static FC showed pattern of both lower and higher FC in cognitively impaired compared to cognitively preserved patients.	↓↑
Eijlers et al 2019 (Eijlers et al., 2019)	RRMS (197) PPMS (23) SPMS (47)	Cross-sectional GT	BRB-N	Lower dynamic FC in cognitively impaired compared to cognitively preserved patients in DMN	↓

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

	HC (96)			regions.	
Fuchs et al 2019 (Fuchs et al., 2019)	RRMS (48) PPMS (2) SPMS (24) HC (29)	Cross-sectional ICA	BICAMS, North American Adult Reading Test	Cognitive reserve predicted preservation of functional connectivity describe accumulation of GM atrophy and additionally attenuated structural network disruption.	-
Karavasilis et al 2019 (Karavasilis et al., 2019)	CIS (16) RRMS (15) HC (16)	Cross-sectional SCA	BRB-N	Compared to memory impaired patients, memory preserved patients showed higher FC between left hippocampus and right temporo-occipital fusiform/lingual	↓↑

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

				gyrus, and lower FC between left hippocampus and right supramarginal gyrus.	
Koubiyr et al 2019 (Koubiyr et al., 2019)	CIS (52) HC (20)	Longitudinal GT	TAP, PASAT3, SRT, BVMT-R, Stroop test, WLG, computerised speed cognitive test, SDMT alertness test	No significant correlations between structural-functional coupling and neuropsychological variables at either baseline or 1 year follow up.	-
Lin et al 2019 (Lin et al., 2019)	RRMS (37) PPMS (3) SPMS (24) HC (26)	Cross-sectional ICA	SDMT, CVLT, BVMT-R, PASAT	Negative correlation between SDMT scores and FC in MS group. No other cognitive measures correlated with FC.	↑

Manca et al 2019 (Manca et al., 2019)	RRMS (40) SPMS (25)	Cross-sectional ICA	Mini Mental State Examination, Raven's Coloured Progressive Matrices, TMT, Stroop, Semantic and Phonemic Fluency Tests	FC correlated positively with cognitive test performance in LFPN, and negatively in SN and DMN. No correlations in RFPN.	↓↑
Petsas et al 2019 (Petsas et al., 2019)	RRMS (32)	Longitudinal SCA	PASAT 2 and 3 sec	Low resting state FC before a task (baseline FC) over a 6 month period was inversely related to PASAT 3 performance, but not PASAT 2. No relationships were found for the resting state FC metric obtained after a task.	↑
Bizzo et al 2020 (Bizzo et	RRMS (28) HC (28)	Cross-sectional SCA	Cognitive reserve index created by combining premorbid	Intrinsic FC within the left dorsal anterior	↑

al., 2020)			IQ measured with the Test of Premorbid Function, leisure activities, and education level	insula and left occipital cluster was inversely correlated with cognitive reserve index values.	
Carotenuto et al 2020 (Carotenuto et al., 2020)	RRMS (29) HC (24)	Cross-sectional SCA, GT	SDMT	Both positive and negative correlations between SDMT scores and FC and graph theory metrics in neuromodulatory networks.	↓↑
Lin et al 2020 (Lin et al., 2020)	RRMS (25) HC (41)	Cross-sectional SCA	SDMT, PASAT 3 sec	Static FC analysis showed that high interhemispheric connectivity across homologous regions predicts performance on the SDMT and PASAT. Dynamic FC analysis	↓↑

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

				showed a negative correlation between interhemispheric connectivity changes and PASAT scores.	
Pasqua et al 2020 (Pasqua et al., 2020)	RRMS (91) SPMS (28) HC (42)	Cross-sectional SCA	PASAT 2 and 3 sec	FC of cerebellar ROIs correlated positively with PASAT score.	↓
Riccitelli et al 2020 (Riccitelli et al., 2020)	BMS (37) HC (50)	Cross-sectional ICA	BRB-N	No significant correlations between cognitive impairment index and FC abnormalities.	-
Has Simelek et al 2020 (Has Silemek et al., 2020)	RRMS (33) HC (29)	Cross-sectional GT	PASAT3, SDMT, Verbal Learning and Memory task, Block Tapping Task of the WMS, BVMT, Regensburger Word Fluency Task	No relationship between global functional graph metrics and cognitive tests. Some significant associations between	↑

				cognitive tests and nodal functional graph measures, predominantly negative.	
Soares et al 2020 (Soares et al., 2020)	RRMS (21) HC (17)	Cross-sectional ICA, GT	MACFIMS, PASAT	Whole brain connectome FC correlated positively with information processing efficiency composite. For specific RSNs, there were positive correlations between information processing efficiency and FC of the DMN, precuneus, sensorimotor and ventral attentional networks.	↓

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Welton et al 2020 (Welton et al., 2020)	RRMS (22) SPMS (15) HC (23)	Longitudinal, GT	PASAT 3 sec, SDMT, attention network test	FC graph theory network metrics were significantly predictive for the PASAT3 and SDMT, but not for the attention network test. Worse performance on the PASAT was predicted by increased clustering and modulatory, longer average path lengths and less small worldness. Worse performance on the SDMT was predicted by less small worldness, lower global efficiency and longer average path lengths.	-

↑arrow up indicates that high FC is associated with worse cognition, ↓ arrow down indicates that low FC is associated with worse cognition, - dash indicates negative result or that the study did not assess directionality in the relationship between FC and cognition

Abbreviations: FC=functional connectivity, ICA=independent component analysis, SCA=Seed based connectivity analysis, GT=graph theory, MS=multiple sclerosis, RRMS=relapsing-remitting multiple sclerosis, PPMS=primary progressive multiple sclerosis, SPMS=secondary progressive multiple sclerosis, CIS=clinically isolated syndrome, BMS=benign multiple sclerosis, HC=healthy controls, ACC=anterior cingulate cortex, PCC=posterior cingulate cortex, DGM=deep grey matter, DMN=default mode network, FPN=frontoparietal network, LFPN=left FPN, RFPN=right FPN, SN=salience network, ATT=attentional network, DAN=dorsal attention network

Abbreviations and references of cognitive measures: Attention network test (Fan et al., 2002); Auditory verbal learning test (Zhao et al., 2012); BICAMS=Brief International Cognitive Assessment for MS (Langdon et al., 2012); BRB-N=Brief Repeatable Battery of Neuropsychological tests (Rao, 1990); BVMT-R=Brief Visuospatial Memory Test-Revised (Benedict, 1997); Computerised speed cognitive test (Ruet et al., 2013c); COWAT=Controlled Oral Words Association Test (Benton et al., 1983a); CST=Concept Shifting Test (Van der Elst et al., 2006a); CVLT=California Verbal Learning Test (Delis et al., 2000); Digitspan (Kaufman and Lichtenberger, 2005); HVLT-R=Hopkins Verbal Learning Test-revised (Benedict et al., 1998); JoLO=Judgement of Line Orientation (Benton et al., 1983b); Letter comparison and pattern comparison tasks (Salthouse, 1995); LLT=Location Learning Test (Bucks and Willison, 1997); LDST=letter digit substitution test (van der Elst et al., 2006b); MACFIMS=Minimal Assessment of Cognitive Function in Multiple Sclerosis (Benedict et al., 2002); Mattis Dementia Rating Scale (Hugonot-Diener et al., 2008); MCT=Memory Comparison Test; Mini Mental State Examination (Folstein et al., 1975); North American Reading Test (Blair and Spreen, 1989); PASAT=Paced Auditory Serial Additions Test (Fischer et al., 1999); Raven's Coloured Progressive Matrices (Basso et al., 1987); RCFT=Rey-Osterrieth Complex Figure Test (Caffarra et al., 2002); Regensburger Word Fluency Task (Aschenbrenner et al., 2000); Salthouse Perceptual Comparison Test (Salthouse et al., 1991); SDMT=symbol digit modalities test (Benedict et al., 2017);

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Semantic and Phonemic Fluency Tests (Lezak, 2004); SPART = 10/36 Spatial Recall Test (Rao, 1990); SRT=Selective Reminding Test (Rao, 1990); SST=Short Story Test; Stroop=Stroop Interference Test (Stroop, 1935); TAP=Test of Attentional Performance (Zimmermann and Fimm, 2002); Test of Premorbid Function (Wechsler, 2011); The computerised test of information processing (Tombaugh and Rees, 2008); The short test of mental status (Kokmen et al., 1991); TMT-trail making test (Tombaugh, 2004); Verbal Intelligence Test Mehrfachwortschatztest-B (Lehrl, 1991); VFT=Verbal Fluency Test (Patterson, 2011); Verbal Learning and Memory task (Helmstaedter and Durwen, 1990); WCST=Wisconsin card sorting test (Robinson et al., 1980); WAIS=Wechsler Adult Intelligence Scale (Kaufman and Lichtenberger, 2005); WMS=Wechsler Memory Scale (Wechsler, 1997); WLG=word list generation (Rao, 1990); WLT=word learning test; WTAR=Wechsler Test of Adult Reading (Holdnack, 2001)

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Figure legends

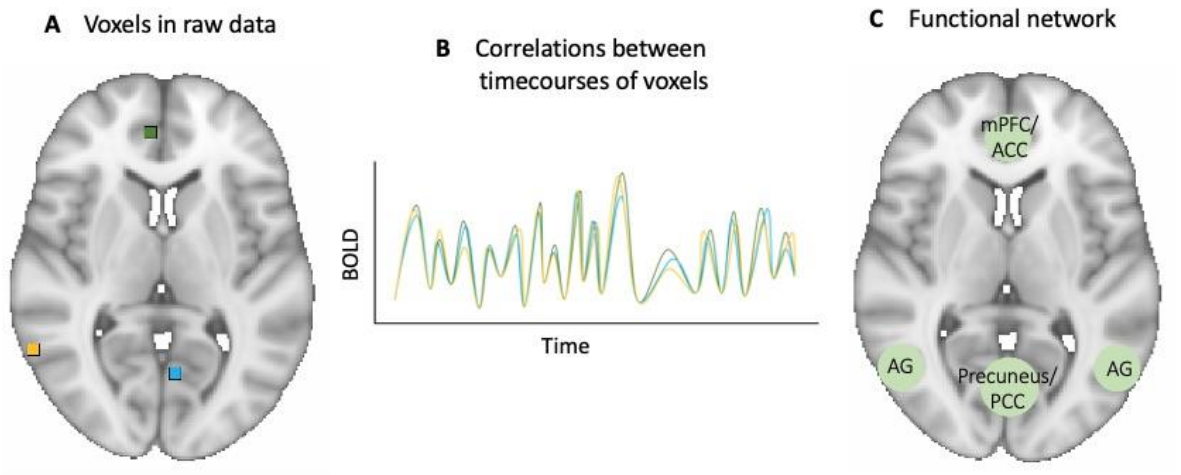

Figure 1. Schematic of functional connectivity and a functional network

Functional connectivity is a measure of the statistical correlation of blood-oxygenation-level-dependent signal timecourses (part **B**) between any selection of voxels (part **A**). Voxels or voxel clusters showing high correlations are considered functionally connected, and can be used to identify functional networks such as the default mode network (part **C**).

Abbreviations: ACC = anterior cingulate cortex; AG = angular gyrus; BOLD = Blood-oxygenation-level-dependent signal; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

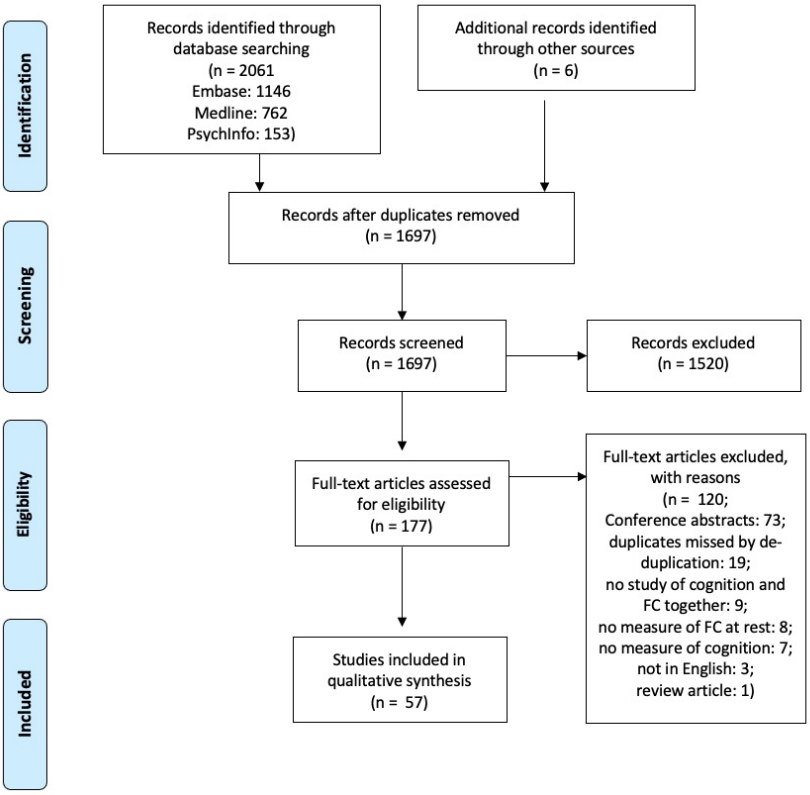

Figure 2. Flow diagram showing identification, screening and selection of records

Figure 2 outlines combined database searches conducted on the 31st October 2019 and on the 22nd October 2020 using the PRISMA protocol for studies of rs-fMRI and cognitive function in MS. Template from Moher *et al.* (2015)

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

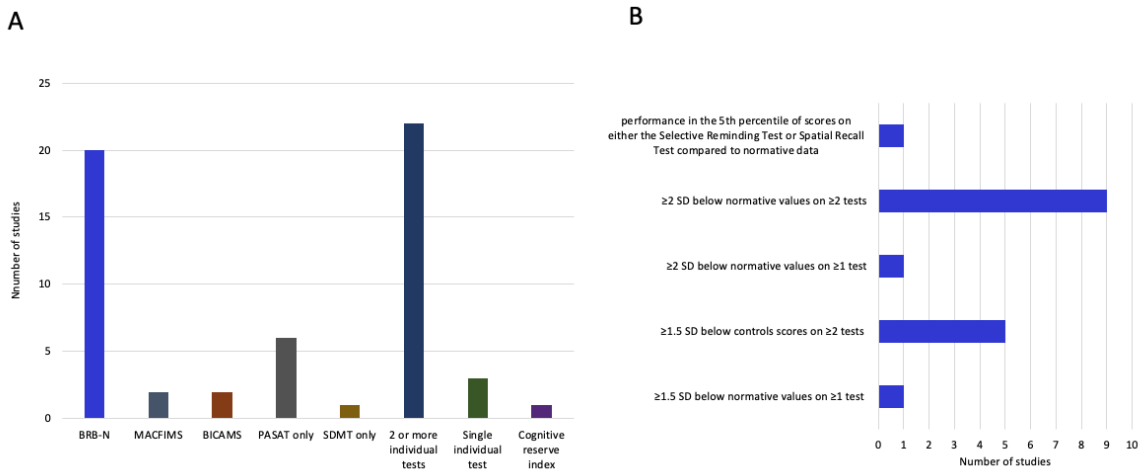

Figure 3. Neuropsychological tests used in the reviewed studies

Figure A shows the number of each neuropsychological test used in the 57 reviewed studies. The tally has been simplified for visualisation purposes. When the BRB-N, MACFIMS or BICAMS have been used in combination with other tests, only the battery has been counted in this figure. The PASAT and SDMT have only been counted when they have been used without other tests. Full details of tests used in each study are provided in Table 1. Figure B shows the definitions for cognitive impairment in the studies that used the BRB-N, and the number of studies that used that definition. Note that four of the five studies that used the definition of ≥1.5 SD below controls scores on ≥2 tests used it to define a mildly cognitively impaired group.

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

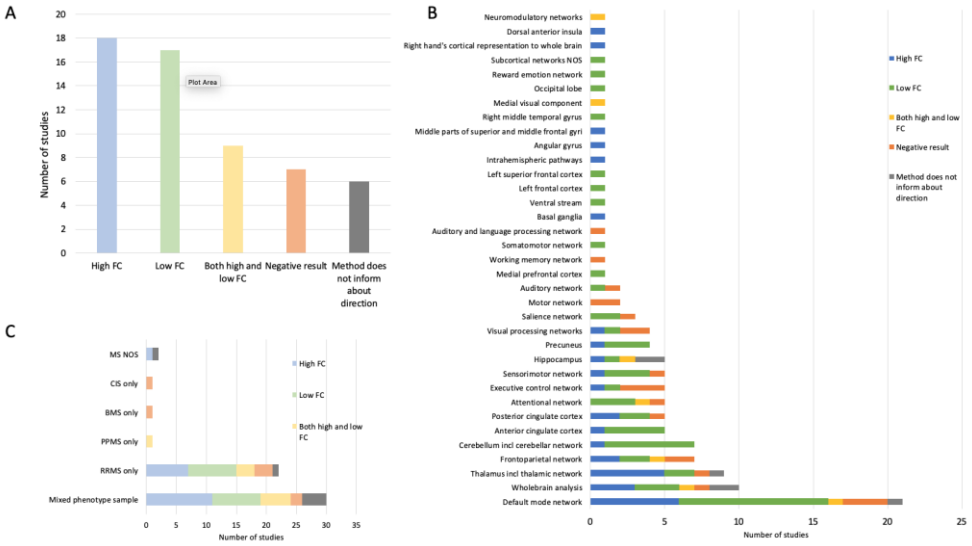

Figure 4. Number of studies reporting an association between poor cognitive test performance and high or low functional connectivity

A) Eighteen studies reported worse cognition to be associated with high functional connectivity (FC), seventeen with low FC and nine studies with both high and low FC. Seven studies did not find a link between FC abnormalities and cognitive function. Six studies used a method that does not provide information about directional changes in FC in relation to cognitive test performance. B) Number of studies showing directional FC findings associated with worse cognition, sorted by the brain region or network investigated. Studies which used different sub-networks of the same network have been grouped together, for example, the left, right, doral and ventral frontoparietal networks have been grouped into one 'Frontoparietal network' label. Otherwise labels have been kept as consistent with the wording used in original studies as possible. The label 'Neuromodulatory networks' refers to the serotonergic, noradrenergic, cholinergic and dopaminergic networks. The label 'Interhemispheric pathways' refers to right olfactory cortex to right amygdala, right middle temporal pole to right inferior frontal gyrus, and left parahippocampalgyrus to left inferior frontal gyrus. References are provided in Supplementary Table 2. C) Number of studies showing directional FC findings associated with worse cognition, sorted by the MS phenotype in the sample of each study.

Abbreviations: BMS = Benign Multiple Sclerosis, CIS = Clinically Isolated Syndrome, FC = functional connectivity, NOS = Not Otherwise Specified, PPMS = Primary Progressive Multiple Sclerosis, RRMS = Relapsing Remitting Multiple Sclerosis.

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

Brain Connectivity
A systematic review of resting state functional MRI connectivity changes and cognitive impairment in multiple sclerosis (DOI: 10.1089/brain.2021.0104)

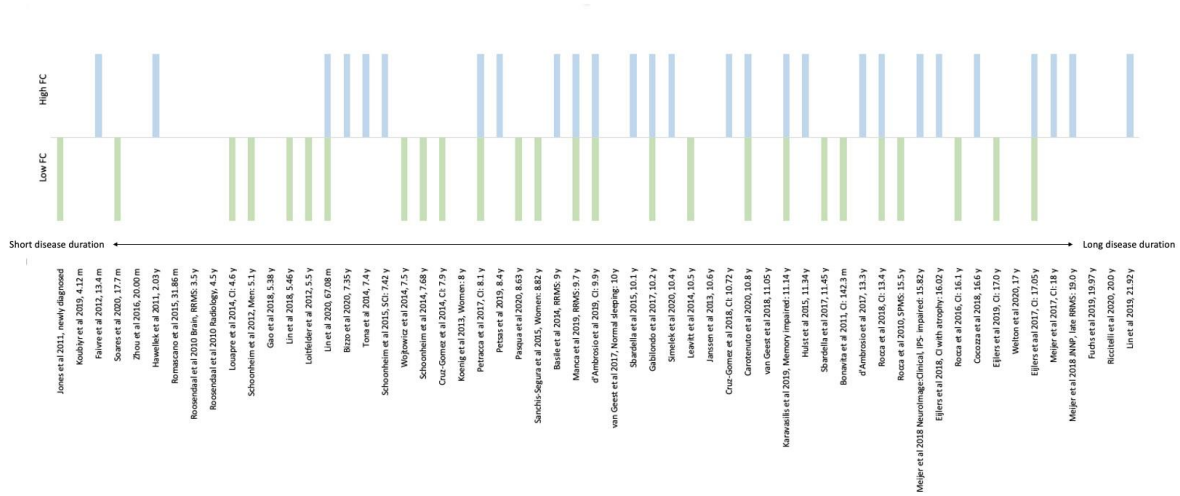

Figure 5. Direction of functional connectivity abnormalities sorted by average disease duration

Direction of functional connectivity abnormalities associated with worse cognition, sorted by average disease duration of the sample in each study. Disease durations reported in months in the original study have been converted to years by dividing by 12. Because several studies used samples of mixed phenotypes and different disease durations, the following decisions were taken when ordering studies by the disease duration: 1) studies were ordered by the overall disease duration of the sample, when given; 2) studies were ordered by the disease duration of the cognitively impaired group; 3) if there were two cognitively impaired groups, studies were ordered by the disease duration of the more impaired group, or the cognitively impaired group with atrophy, in one case; 4) when the disease duration was only reported for each MS phenotype, or sex, studies were ordered by the disease duration of the larger sample; 5) for a study which had equal numbers of males and females, the study was ordered by the sex with the longer disease duration; 6) for one study that used a subset of MS patients that were matched to HC, the study was ordered by the disease duration of the matched subset. References are provided in Supplementary Table 3.