NeuroImage: Clinical 32 (2021) 102814

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The utility of Magnetoencephalography in multiple sclerosis – A systematic review

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ARTICLE INFO

Keywords:
Multiple sclerosis
Magnetoencephalography
Cognition
Connectivity
Neuroinflammation
Biomarker

ABSTRACT

Introduction: Magnetoencephalography (MEG), allows for a high degree temporal and spatial accuracy in recording cortical oscillatory activity and evoked fields. To date, no review has been undertaken to synthesise all MEG studies in Multiple Sclerosis (MS). We undertook a Systematic Review of the utility of MEG in MS.
Methods: We identified MEG studies carried out in MS using EMBASE, Medline, Cochrane, TRIP and Psychinfo databases. We included original research articles with a cohort of minimum of five multiple sclerosis patients and quantifying of at least one MEG parameter. We used a modified version of the JBI (mJBI) for case-control studies to assess for risk of bias.
Results: We identified 30 studies from 13 centres involving at least 433 MS patients and 347 controls. We found evidence that MEG shows perturbed activity (most commonly reduced power modulations), reduced connectivity and association with altered clinical function in Multiple Sclerosis. Specific replicated findings were decreased motor induced responses in the beta band, diminished increase of gamma power after visual stimulation, increased latency and reduced connectivity for somatosensory evoked fields. There was an association between upper alpha connectivity and cognitive measures in people with MS. Overall studies were of moderate quality (mean mJBI score 6.7).
Discussion: We find evidence for the utility of MEG in Multiple Sclerosis. Event-related designs are of particular value and show replicability between centres. At this stage, it is not clear whether these changes are specific to Multiple Sclerosis or are also observable in other diseases. Further studies should look to explore cognitive control in more depth using in-task designs and undertake longitudinal studies to determine whether these changes have prognostic value.

1. Introduction

Multiple sclerosis (MS) is a chronic neuroinflammatory disorder affecting the central nervous system (CNS), causing demyelination and neurodegeneration with a prevalence of approximately 50–300 per 100,000 people (Mackenzie et al., 2014; Thompson et al., 2018). It is the most common non traumatic condition to cause disability in younger adults and has a rising incidence and prevalence with increasing geographical latitude (Dobson and Giovannoni, 2019). A combination of environmental and genetic risk factors predispose to MS, however the precise aetiological mechanisms are still unclear (Dobson and Giovannoni, 2019). The clinical course can manifest in the Relapsing Remitting Multiple Sclerosis (RRMS) form, which accounts for the majority of MS patients and tends to convert to Secondary Progressive MS (SPMS), approximately 10–15 years after initial presentation as incomplete resolution of attacks leads to accumulating disability. In contrast Primary Progressive MS (PPMS) accounts for 5–15% of MS cases and is clinically defined by accumulation of disability from the onset of diagnosis (Thompson et al., 2018; Dobson and Giovannoni, 2019).

MS is an acquired disorder with a variable disease course leading to physical and cognitive decline as a consequence of initially what was thought only to be a white matter disease seen on routine MRI studies (Barkhof, 2002). It is now being shown to also involve cortical and grey matter regions in forms of axonal damage and demyelination. Histopathological studies have identified cortical and grey matter lesions in

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https://doi.org/10.1016/j.nicl.2021.102814
Received 18 February 2021; Received in revised form 28 August 2021; Accepted 30 August 2021
Available online 9 September 2021

the context of early disease and limited white matter involvement (Geurts and Barkhof, 2008; Stys and Tsutsui, 2019).

A variety of structural neuroimaging modalities are conventionally used in MS, such as T1 weighted, T2 FLAIR, Susceptibility weighted and Gadolinium enhancement MRI. The use of structural MRI is the current gold standard and acts as a basis for routine assessment of whole brain lesion load and progression (Filippi et al., 2012). However, there are limitations in understanding the clinical picture and its association with radiologically identified lesions. This is known as the 'clinico-radiological paradox' highlighting the challenges faced in assessing both physical and cognitive impairments (Mollison et al., 2017; Uher et al., 2018). Structural MRI can both over-estimate and under-estimate clinical burden and is a poor indicator of symptomatology (Giorgio et al., 2008; Hemond and Bakshi, 2018). This is also evident in the context of the cognitive impairments with standard structural neuroimaging studies showing correlations with brain lesion load or atrophy and impairment in cognition. One *meta*-analysis has shown evidence of a weak to moderate correlation ($r = 0.3$) between white matter lesion load and cognitive function (Mollison et al., 2017). However, there is a great degree of variability in findings and inconsistencies are seen between current studies (Mollison et al., 2017; Uher et al., 2018). White matter lesions do not identify alterations in the grey matter, such as the cerebral cortex which is arguably the key biological substrate for cognitive impairment (Riccitelli et al., 2011).

Functional techniques such as EEG and fMRI have also been used in Multiple Sclerosis imaging. Evoked Potentials (EPs) such as Visual Evoked Potentials (VEPs), Auditory Evoked Potentials (AEPs), Motor Evoked Potentials (MEPs) and Somatosensory Evoked Potentials (SEPs) as measured by EEG have traditionally been used with evidence of prolonged latencies, as expected in demyelinating disease (Comi et al., 1999). Clinical use of EPs became less prominent in the MRI era however have more recently been proposed as a prognostic and response biomarker (Hardmeier, Leocani and Fuhr, 2017). EEG work has also proposed that cortical connectivity, as measured by interhemispheric coherence, has association with cognitive impairment (Leocani, 2000). Hence there is neurophysiological evidence of abnormalities in MS, although the poor spatial resolution of EEG provides limited anatomic specificity. Although both EEG and MEG measure ionic currents at the cellular level, there are differences in technique with MEG sensitive to tangential but not radial sources and less affected by scalp distortion (Lopes da Silva, 2013). MEG hence has an advantage in spatial resolution compared to EEG as it is not susceptible to distortion by intervening tissues (Hari and Puce, 2017). While the role of EEG in understanding MS is now well established and has been reviewed elsewhere (Leocani and Comi, 2000), this has not been previously undertaken for MEG. Hence, we focus on MEG in this review.

Conversely functional MRI has good spatial but poor temporal resolution with haemodynamic response in the order of seconds. fMRI has shown evidence for widely distributed connectivity abnormalities in MS with widespread evidence for perturbations of functional connectivity in resting state networks including the Default Mode Network and cortical connectivity with basal ganglia and thalamic loops (Stampanoni Bassi et al., 2017; Chard et al., 2021). However, no clear direction has been established likely due to heterogeneity in methodology and clinical sample. One possible reason for this is that initial increases in connectivity may diminish as disease status progresses (Chard et al., 2021). There is some evidence from the literature that diminished functional connectivity is associated with increased symptom severity (Tahedl et al., 2018). Taken together both EEG and fMRI demonstrate the utility of dynamic imaging in MS, whilst suffering from limitations in spatial and temporal resolution respectively.

Magnetoencephalography (MEG) allows for a high degree temporal and spatial accuracy in recording cortical oscillatory activity which can identify subtle oscillatory differences between neurological conditions and suggest patho-physiological differences. The cerebral cortex forms the top 3–4 mm of the brain surface which is an ideal depth for the highly sensitive sensors to record the magnetic fields generated by the cortex. However, the signal at any one channel can be confounded by the adjacent signal from neighbouring cortical regions and, therefore, cannot serve as an accurate proxy for the underlying cortical activity. Advanced source-space reconstruction techniques (Hari and Puce, 2017; Boon et al., 2019) and co-registration with structural MRI allows anatomical localisation to be attained. However, localising deeper subcortical signals is not always as accurate due to weak signals and low sensitivity of MEG to radial sources, as well as anatomical distance and complex cyto-architecture (Attal et al., 2013; Proudfoot et al., 2014). MEG studies, therefore, allow a better understanding of how cortical neuronal populations are affected. Although other dynamic functional techniques can also be used to quantify neuronal communication, there are specific advantages of MEG. Evoked Fields can be more precisely measured at source location from MEG, and this provides the opportunity to understand alterations in the Local Field Potentials in the main cortical generators of signal more directly than EEG. Furthermore, MEG has an improved temporal resolution to fMRI allowing for improved sampling frequency and response times, allowing for better characterisation of wave form. Finally, MEG like EEG but not fMRI can capture oscillatory activity across the brain, allowing for study of large scale neural activation and connectivity (Gross, 2019).

Several different outcome metrics can be quantified using MEG. In addition to conventional metrics such as amplitude, power and latencies, a number of connectivity metrics can be calculated which can help categorise differences between patients and controls in relation to oscillatory activity at distinct brain regions. MEG is well suited to such analysis due to millisecond temporal resolution. Forty two connectivity metrics have previously been identified (Wang et al., 2014) and a taxonomy of such measures has categorised these into directed and non-directed, model-based and model free and whether these were quantified in the time or frequency domains (Bastos and Schoffelen, 2016). Often used connectivity metrics are correlation (non-directed, model based in the time domain), coherence and phase locking value (non-directed, model based in the frequency domains) and Granger Causality (directed, model based in time or frequency domains) (Bastos and Schoffelen, 2016). Graph theoretical measures can also be quantified from MEG data.

Despite a number of studies in the area, to our knowledge there is no systematic review providing an overview of MEG studies in MS. Therefore, we set out to conduct a systematic review of all research literature available to understand whether MEG measures used can act as a useful biomarker of the disease process and provide evidence of altered connectivity in MS. In line with our understanding of the pathological process of multiple sclerosis outlined above we expected to see perturbations in both activity and connectivity in patients versus controls. We hypothesised that: (i) Multiple Sclerosis is associated with altered activity (we specifically expected reduced signal strength in terms of amplitude and power or delayed latency) compared to healthy controls (ii) Multiple Sclerosis is associated with perturbed connectivity between regions compared to healthy controls and further that (iii) markers of altered activity and connectivity are associated with impaired functioning and symptoms (as measured by EDSS scores and measures of cognitive function).

2. Methods

We undertook a systematic literature review to identify all MEG studies carried out in MS using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). The PRISMA reporting checklist can be found in the supplementary material. An initial review had been undertaken with the previous search in December 2019, reviewers to this manuscript advised repeating in line with systematic principles therefore a protocol was registered in line with PRISMA-Protocol guidance (https://osf.io/fj9sb) and the systematic review was repeated. Our search was undertaken on

12th April 2021 and included EMBASE, Medline, Cochrane, TRIP and Psychinfo databases. The key words were MEG and MS ("Multiple sclerosis" and (magnet*encephalogr* or "MEG"). We defined our PICO strategy as follows: Population: Individuals with Multiple Sclerosis; Intervention or Exposure: Magnetoencephalographic data acquisition; Comparators: Healthy Controls and individuals without Multiple Sclerosis; Outcomes: Any reported MEG outcome parameter including connectivity metrics, amplitude, power, latency and topographic metrics (such as Minimum Spanning Tree approaches).

Two researchers HK (Neurology Registrar) and MS (Psychiatry Consultant) working in mutual consultation went through all the article titles and abstracts using the following inclusion criteria. We included original research articles, published in English, with a cohort of minimum of five multiple sclerosis patients and quantification of at least one MEG parameter. We included all studies involving resting state analysis, evoked and event related analysis. There was no date restriction. We excluded conference abstracts and only included peer reviewed articles. We did not wish to include small case series which were not generalisable. Therefore, we used a threshold of five in line with a previous Systematic Review of MEG in Parkinson's Disease (Boon et al., 2019).

Both researchers reviewed each study and summarised the results in a table including the details of whether the study was sensor or source space based, whole brain or single region, resting or event related, as well as, the demographics of the cohort, the diagnostic criteria of MS and the various clinical and neuropsychological assessments undertaken. The findings were summarised along with the band and measure of interest. In addition to this, we extracted the specifics of the MEG equipment used. The above information allowed us to categorize and compare studies and their findings, for example the whole brain analyses and single region as two specific groups as well as the sensor and source space studies as separate categories. In cases where data was not reported (such as when MEG acquisition could not be obtained from the whole sample) we did not make any assumptions about missing data and reported acquired MEG data only. Outcomes extracted were for MEG activity: Power, Amplitude, Latency, Peak Frequency, and for

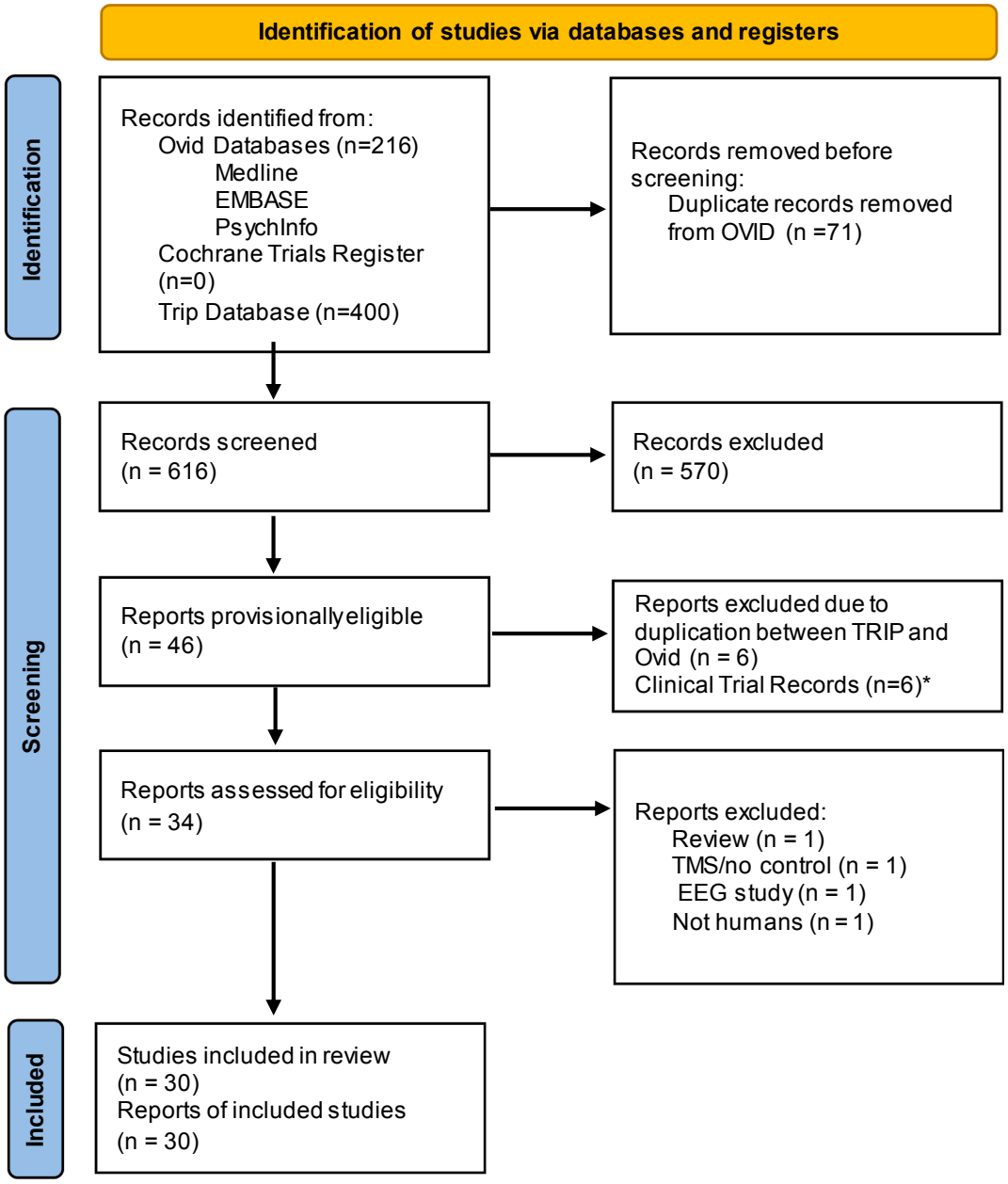

Fig. 1. PRISMA 2020 Flow Diagram for Systematic Review.

connectivity: Coherence, Correlation, Phase Lag Index, Synchronisation Likelihood, Phase Locking Value Topography: Minimum Spanning Tree metrics and Eigenvector centrality. Other MEG based parameters were also extracted if they had been tested between patients and controls. We also extracted outcomes on subgroups which were reported upon (such as MS with neuropathic pain, and without neuropathic pain). Since we expected heterogeneity of MEG measures and design we did not quantitatively synthesise the outcome measures. For the purpose of final presentation of the studies, data were tabulated to specify study, location, number of participants, main MEG measure, and main findings in three domains: (1) differences between patients and controls; (2) any relevant subgroup analysis and (3) correlation of MEG metrics with functional and symptom status. As sensitivity analysis, we also noted whether data was analysed in source or sensor space (to see if this affects outcome) and the centre where data were collected (to see if this affects outcome). Since we did not undertake quantitative synthesis there was no quantitative analysis of robustness for the results.

For quality assessment, both reviewers in consultation undertook the JBI Checklist for Case Control studies as modified with an item for MEG (Boon et al., 2019) which we refer to as the modified JBI (mJBI) checklist. We had originally planned to use the JBI checklist for Case Series as modified by Boon et al. (Boon et al., 2019), however on extraction it became clear that the JBI checklist for case control studies was more appropriate. The instrument used can be seen in the supplementary material. Because we did not expect a large number of studies and to summarise the extent of literature, we did not have a pre-set cut off for inclusion/exclusion into the Systematic Review (Fig. 1).

3. Results

We screened 616 records in total. Application of inclusion criteria led to 34 articles to be identified for further review. Four further papers were excluded because the first was a review article summarising the use of MEG in various diseases including MS and not primary research (Anninos, Adamopoulos and Kotini, 2015), while the other was an EEG based study (Keune et al., 2017). One of the studies focused on Transcranial Magnetic Stimulation (TMS) in MS patients with no control group (Anninos et al., 2016), with the final study focused on primary sensory processing using EEG and MEG in cats rather than humans (Schürmann, Başar-Eroglu and Başar, 1997). After discussion, we elected to included two studies which fell outside the formal criteria as they had no non-MS control group. One study reviewing the 5 year cognitive outcomes after MEG acquisition fell outside the formal inclusion/exclusion criteria as it had no control group (Nauta et al., 2020). This study was discussed between reviewers as it answered hypothesis 3 and was an important study in helping delineate whether MEG is a prognostic biomarker. Another study looked at a large sample of patients with MS characterised by whether or not there were different subgroups (Optic Neuritis) within the MS population (Tewarie et al., 2017). Given the importance of visual symptoms in Multiple Sclerosis, we considered it important to include this in a review of MEG in MS and elected to include this study.

After exclusion, we were left with 30 studies from 13 centers (Nottingham (1), Nebraska (3), Amsterdam (11), Rome (2), Minneapolis (1), Alexandropoulos (1), Erlangen-Nürnberg (1), Toronto (2), Fukuoka (1), Cardiff (1), Brussels (4), Philadelphia (1) and Helsinki (1)). Amongst these studies, there were at least 433 MS patients and 347 controls (when studies from the same centre were not double counted). Information regarding each study individually is presented in Table 1. A variety of outcome metrics were used as presented in Table 2.

We present the results based on the hypothesis below.

3.1. Is multiple sclerosis associated with altered MEG activity compared to healthy controls

Three studies looked at motor events (Arpin, Heinrichs-Graham, et al., 2017; Barratt et al., 2017; Waldman et al., 2020) whilst three studies looked at visual responses (Barratt et al., 2017; Stickland et al., 2019; Waldman et al., 2020). Since Barrett et al. and Waldman et al. undertook visuomotor tasks, these are presented together. Arpin et al (2017) and Waldman et al (2020) examined Event Related Beta Desynchronisation (ERBD) and Post Movement Beta Rebound (PMBR) (see Fig. 3). In Arpin et al. (2017) PMBR power was diminished in patients versus controls, while the visuo-motor task showed reduction in visual gamma and a reduction in PMBR amplitude associated with peak latency in patients vs controls (Waldman et al., 2020). Barrett et al (2017) demonstrated a reduction in visual gamma power on stimulation, and a lag in PMBR in patients vs controls. A single visual checkerboard task-based study analysing neurovascular coupling between fMRI and MEG also showed a reduction in peak visual gamma in patents vs controls (Stickland et al., 2019). Taken together, there is evidence of reduction in gamma power on visual stimulation in patients in three studies, and evidence of reduction in beta strength in two studies and evidence of delay in PMBR response in one study. This provides evidence that in simple paradigms there is evidence of altered induced responses in Multiple Sclerosis. The advantage of all four of these studies was superior source reconstruction techniques with localisation to motor and visual cortices respectively.

Three studies looked at Somatosensory Evoked Fields (Kassubek et al., 1999; Arpin, Gehringer, et al., 2017; Arpin et al., 2018). An early study looking at nerve stimulation demonstrated increased latencies in patients compared to controls (Karhu et al., 1992), whilst studies from the Nebraska group showed that patients had a reduction in attenuation of amplitude that is normally seen in healthy individuals after paired stimulations (Arpin, Gehringer, et al., 2017) i.e. loss of the usual gating response. This latter finding was replicated in 2018 by Arpin et al during stimulation of the tibial nerve paired with a dorsiflexion task. This study also demonstrated increased latency to the peak somatosensory response in the absence of dorsiflexion (Arpin et al., 2018). Both these studies were able to localise the signal to the primary somatosensory cortex using source-space reconstruction techniques.

Only one study undertook analysis within a cognitive task (2-back working task) looking at the maximum power change at the MEG measure. This demonstrated a reduction in the right hippocampus theta power (see Fig. 4) (Costers et al., 2021).

In the absence of evoked/event related designs results were more diffuse. Earlier resting state studies showed abnormal beta activity (Kassubek et al., 1999), while Kotini et al demonstrated in a small study ($n = 10$) using ISO spectral amplitude that healthy controls showed a higher amplitude at 6–7 Hz in the temporal regions bilaterally compared to patients. Later studies done by Van der Meer et al 2013a, showed abnormal activity in alpha1 and lower alpha2 in occipital and temporoparietal regions, while the study looking at pain pathways showed increase in alpha power, with decreased beta power in the ascending pain pathways in patients vs controls (Kim et al., 2019).

Taken together most studies suggest increased latencies of evoked fields in MS. There is also evidence of impaired gating suggesting impairment of the usual refractory period. Evidence of abnormal neuronal activity appears to be best demonstrated in simple paradigms (button press, visual stimulus and nerve stimulation). MEG appears to be particularly valuable for these designs because of the ability to localise specific cortical areas due to good spatial resolution.

3.2. Is multiple sclerosis associated with perturbed connectivity compared to healthy controls

Three studies showed evidence for reduction in connectivity in Somatosensory Evoked Fields (Tecchio et al., 2008; Dell'Acqua et al., 2010; Hagiwara et al., 2010). An early somatosensory evoked study demonstrated decreased intracortical connectivity in the right hemisphere for cortical regions, representing thumb and little finger in patients versus controls (Tecchio et al., 2008). A further study focusing on

Table 1
Summary of included studies.

First Authors	Centre	Patients vs controls	Type of MS cohort	mJBI score	MEG measure	Task	Patients vs Controls:	Subgroup Analysis	Clinical Correlations
(Arpin, Heinrichs-Graham, et al., 2017)	Nebraska	Patients: 15 Controls: 15	RRMS, SPMS	6	ERBD and PMBR power	Motor task	PMBR power significantly decreased in MS patients compared to controls		
(Barratt et al., 2017)	Nottingham	Patients: 18 Controls: 18	>80% RRMS	7	mean gamma % change from 0 to 2 secs (visual); Time to peak for beta (motor)	Visuo-motor task	Visual: increase in gamma power is significantly lower in patients vs healthy controls; Motor: lag in beta response time for MS patients vs controls; in MS patients compared to control there is a delay in time to peak of PMBR		Negative correlation between time-to peak of PMBR and SDMT cognitive assessment
(Waldman et al., 2020)	Philadelphia	Patients: 14 Controls: 15	Paediatric Onset MS	8	Visual gamma band power; Post Movement Beta Rebound amplitude and latency	Visuo-motor task	Visual Gamma power reduced in patients vs controls after visual stimuli; PMBR peak latency amplitude reduced in patients vs controls		
(Stickland et al., 2019)	Cardiff	Patients: 14 Controls: 10	MS	7	Neurovascular coupling - using BOLD and cerebral blood flow response	Visual checker-board stimulus	The usual increase in gamma power was seen to be decreased in the visual cortices on analysis in patients versus controls; decrease in cortical neuronal grey matter signalling in patients with MS but this is not associated with the integrity of the neurovascular unit		
(Karhu et al., 1992)	Helsinki	Patients: 10 Controls: 8	Recent diagnosis	7	Latency, Amplitude	Median & Ulnar nerve stimulation	Median nerve stimulation increased N20 and P30 latencies and ulnar nerve increased P20 latency in pts vs controls; increased P60 amplitudes vs controls	In subgroup analysis patients with periventricular MRI lesions showed increased N20 (ulnar), P30 (median) latencies and P60 amplitudes	
(Tecchio et al., 2005)	Rome	Patients: 21 Controls: 21	RRMS	6	Intracortical Connectivity in S1	Thumb & little finger stimulation	In Right Hemisphere ICC for thumb and little finger cortical representations reduced in patients vs controls, similar pattern seen for thumb in left hemisphere		
(Dell'Acqua et al., 2010)	Rome	Patients: 21 Controls: 21	RRMS	7	M20 waveform to index S1 EPSP; M30 waveform to index M1 EPSP; Similarity to previously characterised *Morf* S1M1 waveform	Median Nerve Stimulation	Altered S1M1 waveform in MS patients; M30 latency increased, and strength decreased in patients vs controls; Interhemispheric asymmetry in *Morf*S1M1 seen in MS patients but not controls		

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Table 1 (*continued*)

First Authors	Centre	Patients vs controls	Type of MS cohort	mJBI score	MEG measure	Task	Patients vs Controls:	Subgroup Analysis	Clinical Correlations
(Hagiwara et al., 2010)	Fukuoka	Patients: 23 Controls: 23	PPMS, RRMS, SPMS	7	PLV	Stimulation of median nerve left and right	PLVs between S1 and S2 - significant increase in gamma band activity. This began at an early post-stimulus phase in controls while was this increase was lessened in MS patients		
(Arpin, Gehringer, et al., 2017)	Nebraska	Patients: 11 Controls: 12	RRMS, SPMS	6	Amplitude of peak1 & peak2; Gating ratios = peak2/peak1; Latency to peak	Right posterior tibial nerve stimulation	MS patients do not attenuate amplitude of somatosensory response after paired stimulation vs healthy controls; patient with MS show impaired gating vs controls		There was moderate correlation between amplitude, gating ratio and walking measures
(Arpin et al., 2018)	Nebraska	Patients: 15 Controls: 15	RRMS, SPMS	6	Peak amplitude and latency	Right posterior tibial nerve stimulation in active and passive conditions	Reduced attenuation of amplitude of somatosensory cortices when posterior tibial nerve stimulated in active dorsiflexion task; Increased latency in patients vs controls on stimulation of posterior tibial nerve at rest		Positive correlation between ankle control measure and somatosensory response on dorsiflexion
(Kassubek et al., 1999)	Erlangen-Nurnberg	Patients: 8 Controls: 8	MS	4	Density dipole plotting	Resting State	The whole number dipoles of slow frequency and beta frequency showed lower values in MS patients compared to controls; in MS patients the abnormal beta activity was seen in the cortical areas		
(Cover et al., 2006)	Amsterdam	Patients: 10 Controls: 11	RRMS	3	IHCM	Resting State	Reduction in alpha Interhemispheric coherence measure in MS patients vs controls		
(Georgopoulos et al., 2007)	Minneapolis	Patients: 12 Controls: 89	MS	3	Pairwise Zero Lag Partial Correlation in Time Domain	Resting State	Specific clusters relating to different diseases identify distinct disorder including MS in 2 consecutive sub samples using CDF		
(Kotini, Anninos and Tamiolakis, 2007)	Alexandro-poulos	Patients: 10 Controls: 10	PPMS, RRMS, SPMS	6	ISO spectral amplitude	Resting State	Normal subjects showed a higher amplitude at 6–7 Hz compared to patients in temporal region bilaterally		
(Hardmeier et al., 2012)	Amsterdam	Patients: 34 Controls: 28	RRMS	8	Eigenvector centrality (nodal centrality) used to quantify each sensors connectivity and importance in the network	Resting State	In patients high biparietal centrality as measured by eigenvector centrality compared to controls; lower connectivity in temporal regions for patients vs controls.		These changes in patients correlate with cognitive scores
(Tewarie et al., 2013)	Amsterdam	Patients: 21	RRMS	7	PLI	Resting State	Lower global alpha2 band connectivity in pts vs controls;		Beta band connectivity in DMN correlates

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Table 1 (*continued*)

First Authors	Centre	Patients vs controls	Type of MS cohort	mJBI score	MEG measure	Task	Patients vs Controls:	Subgroup Analysis	Clinical Correlations
		Controls: 17					lower visual network and default mode network connectivity in alpha2 band pts vs controls; higher global beta band functional connectivity in pts vs controls; higher beta band functional connectivity in default mode and temporo-parietal networks		positively with EDSS and negatively with cognitive score
(Schoonheim et al., 2013)	Amsterdam	Patients: 34 Controls: 28	RRMS	7	Synchro-nisation Likelihood	Resting State	Interhemispheric showed increase in occipital and parietal regions in theta in pts vs controls; Interhemispheric temporal synchronisation is lowered in the upper alpha band; Intra-hemispheric increases are seen bilaterally in theta; increase is seen bilaterally in lower alpha; increases are seen bilaterally in beta band; in lower alpha band clustering coefficient and characteristic pathways were increased in patients vs controls		
(Van Der Meer et al., 2013)	Amsterdam	Patients: 34 Controls: 28	RRMS	7	Oscillatory activity; Global relative power; Regional relative power	Resting State	Abnormal brain activity in MS patients (higher alpha1 and lower alpha2) in occipital and temporo-parietal regions		A higher resting state alpha1 power was associated with lower cognitive performance and information processing speed in MS patients
(Prejaas Tewarie et al., 2014)	Amsterdam	Patients: 102 Controls: 42	PPMS, RRMS, SPMS	8	PLI, MST	Resting State	MS patients showed higher functional connectivity in bands delta and theta, with theta showing sparing of the frontal cortices; alpha2 had lower functional connectivity in temporal, occipital and parietal; there was a shift towards the path-like MST in MS patients with lower leaf fraction, lower degree, divergence and lower tree hierarchy; structurally and functionally regional similarities were higher in the		

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Table 1 (*continued*)

First Authors	Centre	Patients vs controls	Type of MS cohort	mJBI score	MEG measure	Task	Patients vs Controls:	Subgroup Analysis	Clinical Correlations
							temporo-posterior regions in patients in theta and alpha2 band, while in healthy controls this was found in the alpha2 band		
(P. Tewarie et al., 2014)	Amsterdam	Patients: 21 Controls: 17	RRMS	7	MST (several features): Distance, Betweenness Centrality, Degree, Diameter, Eccentricity, κ, Leaf Fraction, Tree Hierarchy	Resting State	Patients vs controls: Theta showed lower eccentricity, lower diameter and higher Leaf Fraction; Alpha 2 showed higher eccentricity in patients parietal and occipital regions, higher diameter and lower Leaf Fraction, κ and lower tree hierarchy; Beta showed higher eccentricity		Tree hierarchy in alpha 2 in patients was significantly correlated with overall cognition
(Tewarie et al., 2015)	Amsterdam	Patients: 86 Controls: 21	MS	8	PLI, MST	Resting State	The mean cortical functional connectivity showed higher theta band for MS patient; lower functional connectivity in gamma band was seen in MS patients; the cortical functional networks showed significantly lower normalized clustering (delta, theta, alpha1, alpha2, and gamma band) and lower normalized path length (theta band). Therefore, networks are possibly shifted towards random networks; The MST of MS patients showed a lower leaf fraction (delta, theta, and alpha2) with a lower degree divergence (delta, theta, alpha1, alpha2). This is suggestive of a shift towards more path life trees (reduced large scale integration)		MST leaf tree fraction was negatively correlated with BOLD thalamo-cortical functional connectivity and EDSS
(Tewarie et al., 2017)	Amsterdam	Patients: 102 Controls: 0	PPMS – MSON & MSNON RRMS – MSON & MSNON SPMS – MSON & MSNON	8	PLI	Resting State		Significant relationship between retinal layer thickness and average PLI in bilateral MSON cases, with outer retinal layer thickness being positively related to PLI in visual cortex of mainly alpha 2 and delta band	
(Schoonhoven et al., 2019)	Amsterdam	Patients: 83		8	Peak Frequency; Relative Power	Resting State		The regional cortical power	Increased whole brain relative

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Table 1 (*continued*)

First Authors	Centre	Patients vs controls	Type of MS cohort	mJBI score	MEG measure	Task	Patients vs Controls:	Subgroup Analysis	Clinical Correlations
		Controls: 34	PPMS, RRMS, SPMS		measurements of cortical and subcortical regions; Correlation of whole brain measurements and specific cognitive domains			differences between groups showed Cognitively Impaired (CI) patients with MS had significantly increased cortical theta and alpha1 power compared to controls and Cognitively Preserved patients; CI had significantly higher DGMV theta and lower alpha2 than CP. Differences in alpha 2 and theta were seen between Cognitively Impaired patients and controls in all subcortical areas, pronounced in bilateral thalami.	alpha1 power associated with impaired overall cognitive performance. Also increased whole brain theta was associated with worse overall cognition
(Van Schependom et al., 2019)	Brussels	Patients: 90 Controls: 46	RRMS, Progressive MS	8	Power at frequency bands; Transient State analysis of transient brain networks using Hidden Markov Models	Resting State		In subgroup analysis use of benzodiazepine medication had effect on power (increased beta, reduced theta in benzodiazepine patients) and difference in transient dynamics vs patients who had not used benzodiazepines	
(Kim et al., 2019)	Toronto	Patients: 27 Controls: 26	MS (NP) MS (NNP) RIS (NNP)	7	Spectral power	Resting State	Increase alpha power in MS compared to controls in nodes of ascending pain pathway; Beta power was decreased in the ascending pain pathway for MS compared to controls	When comparing subgroups beta at 13 Hz was found to be lower in NP vs controls; 'Slowing' of the alpha peak power in MS (NP) vs MS (NNP) and HC	
(Sjøgård et al., 2021)	Brussels	Patients: 99 Controls: 47	RRMS, PPMS	7	Resting State Functional Connectome based on power correlations at 32 nodes	Resting State	Reduced functional connectivity in Beta Band in Sensory Motor Network in patients vs controls; Reduced Default Mode Network connectivity in alpha band in patients vs controls		Lower beta connectivity in SMN associated with worse symptom scores (EDSS), DMN alpha integration associated with cognitive scores
(Nauta et al., 2020)	Amsterdam	Patients: 146 Controls: 0	RRMS, SPMS, PPMS	7	MST metrics - correlation with 5-year cognitive follow-up	Resting State			1. At baseline Tree Hierarchy predicts cognition independent of frequency band 2. At 5-year follow-up baseline MEG delta leaf fraction and beta band diameter predicts cognitive decline
	Toronto			7		Resting state			

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Table 1 (*continued*)

First Authors	Centre	Patients vs controls	Type of MS cohort	mJBI score	MEG measure	Task	Patients vs Controls:	Subgroup Analysis	Clinical Correlations
(Kim et al., 2020)		Patients: 33 Controls: 30	NP: RRMS, SPMS NNP: RRMS, RIS		Resting state static and dynamic functional coupling of pain connectome		Static functional coupling identified abnormal coupling in alpha and beta between DMN, SN and Descs.; low gamma coupling was abnormal between SN and Asc.; Within network coupling was particularly abnormal in Asc for all bands alpha, beta, theta and low gamma in both static and dynamic coupling; Dynamic functional coupling showed alterations in theta (SN and Asc) and alpha inter-network (SN, DMN, Asc) coupling	In NP MS patient subgroup alpha and low gamma coupling reduced with network analysis in Asc and SN, Asc, respectively compared to controls; in NP MS subgroup theta, alpha and beta had a lower coupling between networks compared to controls	Pain interference and intensity and a negative correlation with beta in whole group analysis, while on subgroup analysis negative correlations were seen in low gamma in NP MS patients
(Van Schependom et al., 2021)	Brussels	Patients: 67 Controls: 47	RRMS	8	Spectral Power; Post hoc correlations of Principle Component of brain atrophy	Resting State			Lower alpha band power in Temporo-Parietal Junction associated with pattern of brain atrophy and worse verbal and spatial memory
(Costers et al., 2021)	Brussels	Patient: 79 Controls: 38	>85% RRMS	7	Maximum power change	2-back Working Memory task	Decreased right hippocampus power increase in patient vs controls		Hippocampus theta power change correlated with task reaction time

Legend: MS: Multiple sclerosis; MEG: magnetoencephalography; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; ERBD: event related beta desynchronisation; PMBR: post motor beta rebound; SDMT: symbol digit modality test; BOLD: blood oxygen level dependent; N20: negative deflection at 20 s; P30: positive deflection at 30 s; P60: positive deflection at 60 s; S1: primary somatosensory cortex; ICC: intra-cortical connectivity; M20: somatosensory evoked field analysis on the 20-ms interval following the arrival of sensory input to the primary sensory cortex; M30: somatosensory evoked field analysis on the 30-ms interval following arrival of sensory input to the primary sensory cortex; EPSP: excitatory postsynaptic potential; MorfS1M1: morphology of somatosensory evoked field obtained at primary sensory and primary motor cortex; PLV: phase locking value; PPMS: primary progressive multiple sclerosis; S2: secondary sensory cortex; IHCM: interhemispheric coherence measure; CDF: canonical discriminate factor; ISO: iso contour lines; PLI: phase lag index; DMN: default mode network; EDSS - expanded disability status scale; MST: minimum spanning tree; MSON: multiple sclerosis with optic neuritis; MSNON: multiple sclerosis non-optic neuritis; DGWV: deep grey matter volume; CI: cognitively impaired; CP: cognitively preserved; NP: neuropathic pain; NNP: non-neuropathic pain; RIS: radiologically isolated syndrome; HC: healthy controls; SMN: sensorimotor network; SN: salience network; Asc: ascending nociceptive pathway.

the connectivity between motor and sensory cortices showed altered S1M1 waveforms and interhemispheric asymmetry in patients vs controls (Dell'Acqua et al., 2010), suggesting altered connectivity between the two regions. One study demonstrated increase in Phase Locking Value in the gamma band between S1 and S2 early post stimulation which was diminished in MS patients (Hagiwara et al., 2010).

Several studies from the Amsterdam group examined connectivity at rest. Cover et al, 2006, demonstrated a reduction in alpha interhemispheric coherence in patients vs controls. Various connectivity analyses showed evidence for reduction in upper alpha (10–13 Hz) connectivity in patients vs controls: Phase Lag Index (Tewarie et al., 2013), Synchronisation Likelihood (SL) (Schoonheim et al., 2013) and Eigenvector centrality (Hardmeier et al., 2012). This was noted both globally as well as in particular resting state networks (visual and default mode network). Beta was also noted to be globally increased and in particular default mode and temporo-parietal networks (Tewarie et al., 2013). Using SL, interhemispheric differences were noted in theta and alpha in various regions (Schoonheim et al., 2013) with biparietal and temporal region connectivity noted to be altered (Hardmeier et al., 2012). In the resting state analysis use of PLI as a measure of connectivity to construct the Minimum Spanning Tree using a graph theoretic approach showed patients had a higher functional connectivity in delta and theta bands, with lower alpha2 functional connectivity. A shift was noted towards a path-like MST in patients with MS along with a lower leaf fraction, lower degree, divergence and lower tree hierarchy rather than the more integrated star-like MST seen in controls (Prejaas Tewarie et al., 2014). Further work showed theta to have lower eccentricity, lower diameter and higher Leaf Fraction, with upper alpha showing higher eccentricity in patients parietal and occipital regions, higher diameter and lower Leaf Fraction, κ and lower tree hierarchy (P. Tewarie et al., 2014). In 2015 Tewarie et al., showed mean cortical functional connectivity to be higher in the theta band for patients with MS, with lower functional connectivity in gamma band. The cortical functional networks showed significantly lower normalized clustering (delta, theta, alpha1, alpha2, and gamma band) and lower normalized path length (theta band). Taken together networks in patients appear to be shifted towards more random connectivity structure. The minimum spanning tree of MS patients showed a lower leaf fraction (delta, theta, and alpha2) with a

Table 2
MEG metrics utilised.

Peak Amplitude	Maximum amplitude after stimuli presentation
Power	Calculated for different bandwidths and depending on task
Power Change	Change of power after task vs baseline power
Latency	Time taken to event of interest (e.g. peak)
ISO Spectral Amplitude	Map of isocontour lines for each spectral amplitude plotted for each frequency band (Kotini, Anninos and Tamiolakis, 2007)
Dipole Density Plotting	A dipole is fitted for each time point and then the density of these dipoles is quantified in 3D by convolving with a Gaussian (Vieth et al, 1996)
Gating Ratio	Peak power of second peak/Peak of first peak of paired stimuli
Interhemispheric Coherence Measure	Root-mean-square of all the complex coherences of all the left–right channel pairs (Cover et al., 2006). Coherence is a measure of phase consistency (Srinivasan et al., 2007)
Similarity Index *Morf* S1M1	Similarity to a previous *Morf* S1M1 waveform generated from healthy controls (Dell'Acqua et al., 2010)
Partial Correlation	Correlation for sensor pairs, adjusting for all other sensor pairs
Synchronisation Likelihood	Nondirected Nonlinear method for examining connectivity between regions (Stam and Van Dijk, 2002)
Minimum Spanning Tree	Distance, Betweeness Centrality, Degree, Diameter, Eccentricity, κ, Leaf Fraction, Tree Hierarchy (see Table 3)
Eigenvector centrality	Measure of centrality of a node in a network
Phase Locking Value	Model based non-directed measure. Mean phase consistence between two brain regions. Varies from 0 to 1 (Aydore, Pantazis and Leahy, 2013)
Phase Lag Index	Similar to PLV but not affected by synchronisation at zero lag. Varies from 0 to 1. (Aydore, Pantazis and Leahy, 2013)
Neurovascular coupling	Correlation between gamma power change and fMRI BOLD signa change or gamma power change and CBF change
Functional Coupling	Calculated across each pair of ROIs using the mathematical formula for amplitude envelope correlation (Liu et al., 2010) and weighted phase lag index (Vinck et al., 2011). Static Functional Coupling is the epoch average, Dynamic Functional Coupling is the standard deviation across epochs (Kim et al., 2020).
Intracortical Connectivity Index	Phase locking between two intra-cortical regions (Tecchio et al., 2005)
Transient state analysis	A measure of transient brain dynamics using the hidden Markov Model to determine instantaneous topographical networks (Van Schependom et al., 2019)

Table 3
Minimum Spanning Tree (MST) Metrics:

N	Nodes	Number of Nodes
M	Links	Number of Links
C	Clustering	The unweighted clustering coefficient describes the likelihood that neighbours are also connected, and it quantifies the tendency of network elements to form local clusters. Used to characterise local clustering
	Path length	Measure for integration; the path with the lowest sum of link weights between two nodes
k	Degree	The number of neighbours for any one node
L	Leaf fraction	Fraction of leaf nodes where a leaf fraction is defined as a node with a degree one
D	Diameter	Longest shortest path of an MST
Th	Tree hierarchy	A hierarchical metric that quantifies the trade-off between large scale integration in the MST and the overload of central nodes
κ	Degree divergence	Measure of the broadness of the degree of distribution

All MST Metric definitions taken from (Tewarie et al., 2015) as adapted from (Stam and van Straaten, 2012)

lower degree divergence (delta, theta, alpha1, alpha2). This is suggestive of a shift towards more path like trees with reduced large-scale integration.

More recent studies done in resting state used dynamic functional coupling of the pain connectome and the functional connectome based on power correlations. These showed abnormal coupling in alpha and beta between the default mode network, salience network and descending networks. Gamma coupling was abnormal between networks, while within network coupling was affected in all bands (Kim et al., 2020). Sjøgård et al. (2021) used similar metrics and showed a reduction in functional connectivity in the beta band in the sensorymotor networks in patients vs controls, and a reduction in DMN connectivity in the alpha band in patients vs controls.

Taken together there is good evidence for perturbed connectivity in relation to somatosensory evoked fields. Overall, most resting state studies also show some degree of altered connectivity and topology in patients versus controls. There are specific differences in bands and regions. Since a variety of metrics were used, it is difficult to make direct comparisons between studies.

3.3. Are markers of perturbed activity and connectivity associated with impaired functioning and symptoms (as measured by EDSS scores and measures of cognitive function)?

In different studies various clinical measures were used to search for correlations with MEG features. Within the visuo-motor study, the Symbol Digit Modality Test (SDMT) was shown to have a negative correlation with time-to-peak of PMBR in patients versus controls (Barratt et al., 2017). Other task-based studies looked at the Somatosensory Evoked Fields using nerve stimulation and paired nerve stimulations to look at differences in peak amplitude and latency between patients and controls. The first of these studies using paired stimulation showed a moderate correlation between the MEG measures of amplitude and gating ratio with walking measures attained using a spatiotemporal walking kinematic mat. The specific walking measures seen to correlate were velocity and stride length (Arpin, Heinrichs-Graham, et al., 2017). The second study undertaken also by Arpin et al (2018) looked further at the somatosensory regions using posterior tibial nerve stimulation during rest and a dorsiflexion task. They also saw a positive correlation between ankle control and somatosensory response during dorsiflexion. The only study that tried to elucidate cognitive difference using a cognitive task-based analysis in the form of the 2-back working memory task showed hippocampal theta power change correlated with task reaction time (Costers et al., 2021).

A number of resting state studies examined cognitive assessment using a single score to assess overall cognitive function. These studies demonstrated specific correlations with particular bands or networks. Studies undertaken by the Amsterdam group showed band specific correlations. Firstly, higher beta functional connectivity was associated with poorer cognitive function and disability (Tewarie et al., 2013). Secondly, using the MST theoretic approach a decrease in global integration and hierarchy particularly in the upper alpha band was associated with worse cognition (P. Tewarie et al., 2014). Such whole brain associations with overall cognition were also noted in more recent studies: increased lower alpha and theta power (Schoonhoven et al., 2019) and a reduction of DMN connectivity in the alpha band was associated with cognitive scores (Sjøgård et al., 2021). Taken together these studies demonstrated alpha power and connectivity to be associated with overall cognitive function, although this is of limited use due to the use of a single metric to assess overall cognitive function.

There were some studies that attempted to look at cognitive domain specific correlations which also involved the alpha band. Van Der Meer et al (2013a), showed that a higher alpha1 power was associated with lower performance scores in processing speed in patients versus controls. In the Brussels group, Van Schependem et al (2021) found that lower alpha power related to temporo-parietal junction atrophy was

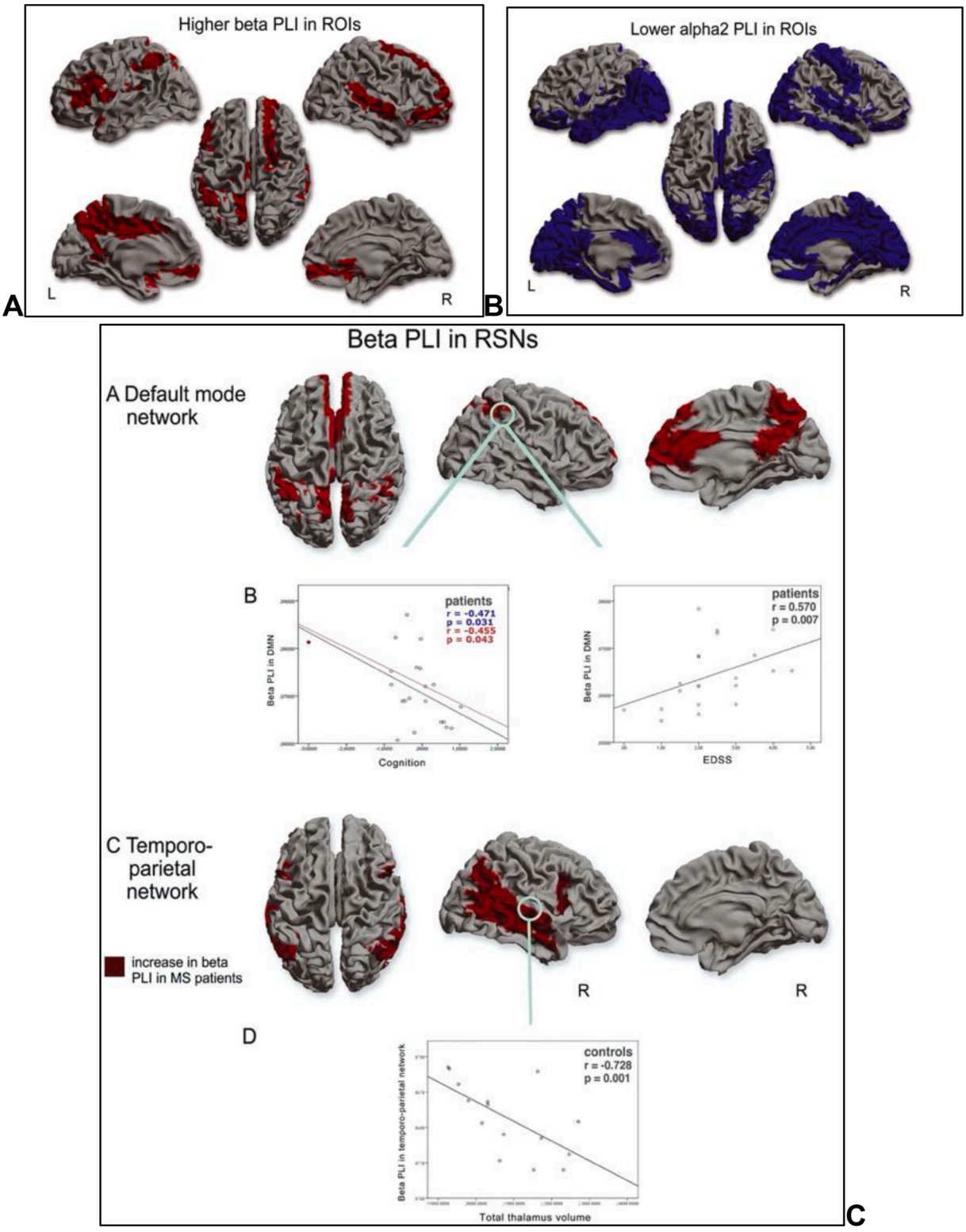

Fig. 2. Tewarie et al, 2013 examined resting state Phase Lag Index between patients and controls, A – whole brain analysis showed beta PLI was higher in ROIs (18/78) highlighted red in patients; B – In whole brain analysis PLI values were shown to be decreased in alpha2 bands in patients vs controls in regions (40/78) highlighted blue; C – Resting State Network (RSN) analysis showed in Default Mode Network (DMN) beta PLI had a negative correlation with cognition and positive correlation with the EDSS in patients, beta PLI correlating negatively with thalamic volume in the Temporo-parietal network; D – RSN analysis showed lower alpha2 PLI in the DMN and visual network, with a negative correlation with thalamic volume in the visual network (adapted from (Tewarie et al., 2013)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

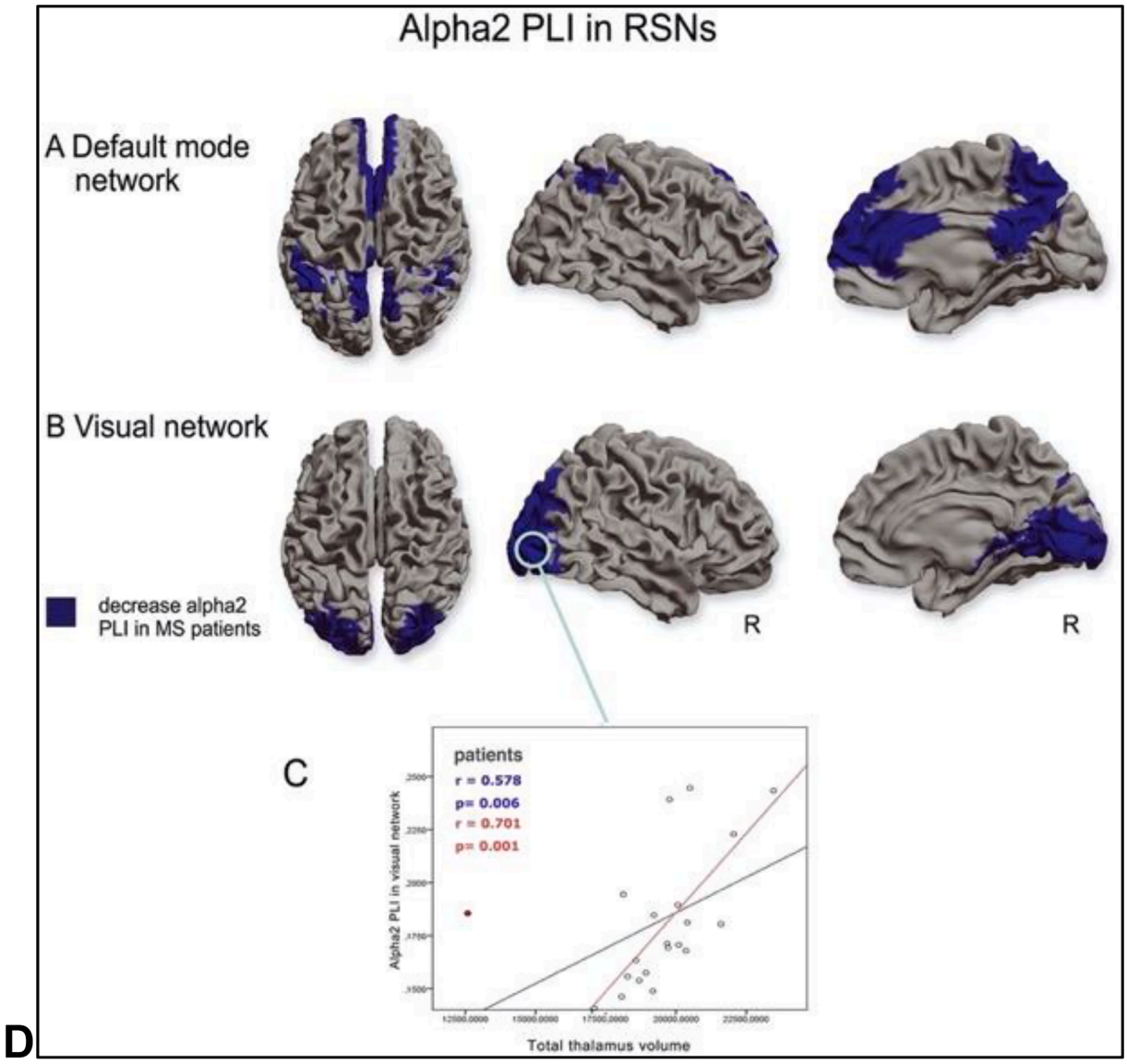

Fig. 2. (*continued*).

associated with worse verbal and spatial memory in patients.

While some studies showed no correlation with EDSS disability scores (Cover et al., 2006; Prejaas Tewarie et al., 2014), one study showed a positive correlation of EDSS with beta band PLI in the Default Mode Network (see Fig. 2) (Tewarie et al., 2013). From the same Amsterdam group further work using MST graph theoretic indices showed that MST leaf tree fraction was negatively correlated with both BOLD thalamo-cortical functional connectivity and EDSS suggesting that decrease in degree of nodes may be a sign of damage (Tewarie et al., 2015).

Almost all studies were cross-sectional in nature which precluded determining whether any MEG measures had prognostic value. There was only one longitudinal study which showed lower baseline delta leaf fraction (less integrated) and smaller beta band diameter (more integrated) to predict cognitive decline at five-year follow-up (Nauta et al., 2020).

Finally, Kim et al (2020) focused on use of functional coupling of the pain connectomes with validated pain scoring questionnaires to establish neuropathic pain in MS patients and controls. They reported a negative correlation of pain interference and intensity with beta functional coupling within inter-hemispheric nodes of the ascending nociceptive pathways, while state of pain showed a positive correlation with alpha band and negative correlation with low gamma in cross-network analysis. In the neuropathic pain group, low gamma showed negative correlation in inter-hemispheric analysis particularly in the ascending nociceptive pathway.

We also looked at several sensitivity analyses to see if these may have a bearing on results.

3.4. Subgroup analysis

There was some evidence for different measures as shown by MS-subgroups for Periventricular Lesions (Karhu et al., 1992), cognitive impairment (Schoonhoven et al., 2019), neuropathic pain (Kim et al., 2019, 2020), benzodiazepines (Van Schependom et al., 2019), optic neuritis (Tewarie et al., 2017) (see Table 1). Taken together there is some evidence that different disease features may be associated with different MEG parameters. In the absence of limited replicability between studies this cannot be confirmed at this stage. Surprisingly we did not find any papers which compared the known subgroups of MS (e.g. RRMS, SPMS, PPMS).

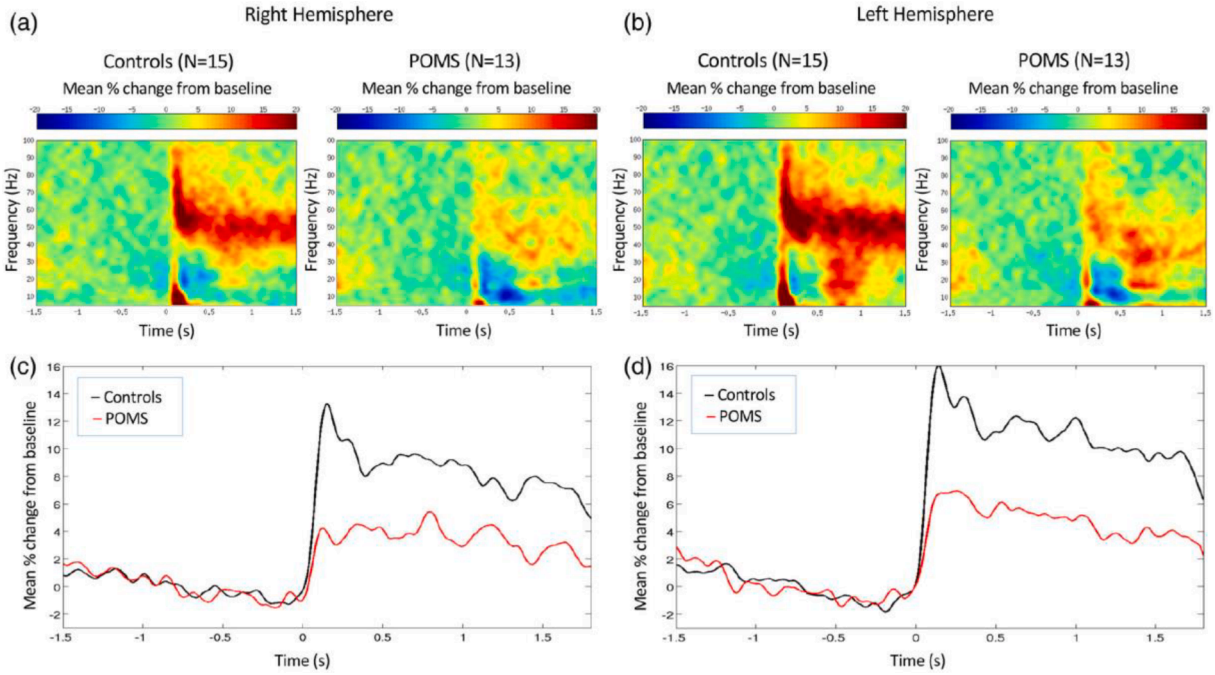

Fig. 3. Waldman et al, 2020 undertook a visuomotor task in patients with Paediatric Onset Multiple Sclerosis (POMS) vs controls: Visual Time Frequency Response and Visual amplitude plots are shown. a and b show group-averaged time–frequency for controls and paediatric onset multiple sclerosis (POMS) with reduction in visual gamma band in both hemispheres; c and d show the visual gamma power (30–80 Hz) compared between POMS (red) and controls (black) in right (c) and left (d) hemispheres (Adapted from (Waldman et al., 2020)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

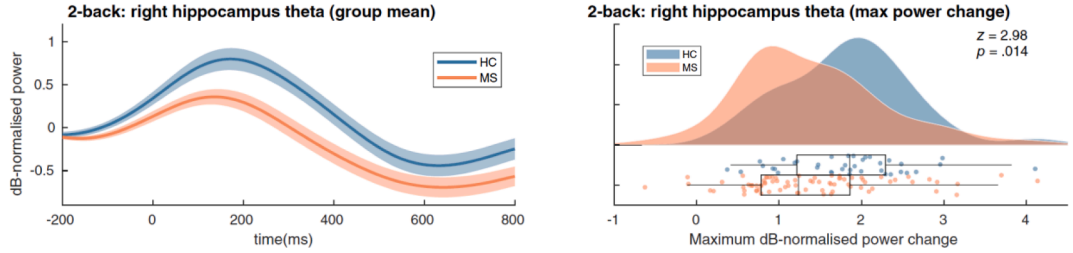

Fig. 4. Costers and colleagues (2020) examined adult patients with MS versus controls using a n-back task. Showing time–frequency max power change in right hippocampus. Left panel shows shaded error (using standard error) of group mean power changes in the right hippocampus. Right panel shows a raincloud plot of maximum power changes in hippocampus (Adapted from (Costers et al., 2021)).

3.5. *Source or sensor based analysis*

Seven studies looked at sensor-based analyses only (Karhu et al., 1992; Kassubek et al., 1999; Cover et al., 2006; Georgopoulos et al., 2007; Kotini, Anninos and Tamiolakis, 2007; Hagiwara et al., 2010; Hardmeier et al., 2012), whereas the others used source-based approaches. The sensor based analyses studies were earlier than the source-based analyses studies. As expected, source-based approaches allowed for superior anatomical localisation. There was otherwise no qualitative difference we could identify between source and sensor-based studies in relation to whether analyses showed positive results.

3.6. *Does the centre where data was collected affect the outcome*

Of the main results we identified above we considered whether these were only reported by a single centre as this would decrease confidence in the results, due to single cohort effects as well as analysis by a single team. We found that several findings were broadly repeatable: 1. Beta band changes between patients and controls on movement were shown in three different centres (Nottingham, Nebraska and Philadelphia); 2. Visual gamma changes between patients and controls were shown in three different centres (Nottingham, Cardiff and Philadelphia); 3. Increased latency of somatosensory evoked fields was shown in 2 different centres (Helsinki and Nebraska); 4. Decreased connectivity between somatosensory evoked fields was shown in two centres (Fukuoka, Rome); 5. Most cognitive findings in resting state analysis particularly those relating to the alpha band were shown in the Amsterdam cohort, although one study also reported this from the Brussels cohort (Van Schependom et al., 2019). Findings which were of interest, but which as yet have not be replicated beyond a single centre were: 1. Loss of the gating response to paired nerve stimulation which was only shown in one centre in two studies (Nebraska); 2. Alteration of theta hippocampal power in a 2-back memory task (Brussels); 3. Prognostic value of MEG findings in relation to cognition (Amsterdam); and 4. Changes in the pain connectome which was examined in two studies in a single centre (Toronto).

3.7. *Assessment of bias*

The lowest mJBI score was the 3 and the highest was 8, with the mean mJBI score being 6.7 indicating moderate quality of studies. The poorest scoring item were questions (i) were the same criteria used for

identification of cases and controls? and (ii) was exposure measured in the same way for cases and controls? This was because all studies recruited patients from clinic and controls from distinct populations and assessed them differently. There is a possible volunteer bias throughout the literature (https://catalogofbias.org/biases/volunteer-bias/) such that patients recruited from clinical settings may be systematically different from the volunteers acting as controls. Age and sex were matched in almost all studies. As a post-hoc analysis we noted that none of the studies made reference to pre-registered analysis plans.

4. Discussion

We set out to conduct a systematic review of primary research studies using MEG analysis that was done in multiple sclerosis. Our key questions were to identify (i) whether MEG could show that MS was associated with perturbed activity, (ii) whether MS was associated with perturbed connectivity and (iii) whether these markers were associated with clinically relevant findings. In brief, we found that there have been a range of measures utilised indexing power, latency and multiple connectivity metrics. In answer to our specific hypotheses: (i) there was evidence of perturbed activity in patients with MS vs controls. Furthermore (ii) there was evidence of alterations in connectivity. These metrics were (iii) associated with cognitive and other functional measures such as motor strength, gait impairment and cognitive function. Taken together the literature, therefore, does show utility in using MEG to study multiple sclerosis providing good evidence of both altered activity, and dysconnectivity processes in MS, which are associated with clinical impairment and evidence for cortical involvement in the disease. Findings, which were broadly replicable across centres were: 1. Alterations in movement-related beta band power changes in in the motor cortex; 2. Diminished visual gamma responses; 3. Increased latency of somatosensory evoked fields; and 4. decreased connectivity associated with somatosensory evoked fields; and further 5. evidence for upper alpha rhythm to be associated with impaired cognitive function in patients with MS.

As many different paradigms were used in the studies, it was difficult to compare the various studies directly. However, we do find that particular paradigms with differences that are replicable are simple motor, visual and somatosensory tasks. The studies were able to demonstrate in different paradigms a reduction in MEG power particularly in the task-based studies, such as pre and post motor stimulus (Arpin, Heinrichs-Graham, et al., 2017; Barratt et al., 2017; Waldman et al., 2020). In addition, we found evidence of diminished visual increase in gamma amongst the visuo-motor studies (Barratt et al., 2017; Stickland et al., 2019; Waldman et al., 2020). It should be noted, however, that the relation between MEG power and neural activity is not easily interpretable and particularly for the alpha and beta bands increased power might be a sign of inhibition or idling (Jensen and Mazaheri, 2010).

Studies that looked at the somatosensory evoked fields were able to demonstrate increased latencies post nerve stimulation (Karhu et al., 1992) that are suggestive of a demyelinating process. Further studies using paired stimulation also showed diminished gating response within the somatosensory cortices giving evidence of altered activity (Arpin, Gehringer, et al., 2017; Arpin et al., 2018). There was evidence of impaired connectivity relating to Somatosensory Evoked Fields: abnormal connectivity between motor and sensory cortices (Dell'Acqua et al., 2010), as well as primary and secondary sensory cortices (Hagiwara et al., 2010). Taken together MEG studies show good evidence of altered Evoked Fields, particularly when the cortical substrate for activity is well established. Whilst this is perhaps not surprising, given the robust evidence of altered EPs in MS (Walsh, Kane and Butler, 2005), MEG provides superior anatomical resolution. This allowed the cortical regions underlying the signal to be established.

This is of potential clinical interest as Evoked Potentials are being considered as a biomarker of disease activity (Hardmeier, Leocani and Fuhr, 2017). Established scoring systems for EPs provide qualitative methods on individual patients with cross sectional and longitudinal correlations for clinical outcomes and therefore can be used as a prognostication tool. Multimodal EP assessments have been suggested rather than single measurements to provide a broader prognostication tool. Traditionally, the lack of anatomical resolution that is provided by EEG limits its clinical use and MEG may potentially help to bridge this gap (Lascano et al., 2017). MEG Evoked Fields (EFs) may therefore putatively provide a superior biomarker to EEG Evoked Potentials, although a direct comparison between EEG and MEG is beyond the scope of this review. This review shows that studies are not yet at the stage where sensitivity and specificity can be calculated in large enough samples to allow us to determine whether MEG may have clinical utility. However, of all analyses conducted thus far, EFs appear to have the most promise as biological markers of the future.

A large body of work identified in this review considered resting state studies and the association with cognitive function. Overall cognition showed correlation with the alpha band connectivity in patients (Georgopoulos et al., 2007; Tewarie et al., 2014b; Schoonhoven et al., 2019), with some studies demonstrating association with specific domains of verbal and spatial memory (Van Schependom et al., 2021). Alpha band oscillations have been known to be associated with attention and retrieval of stored information and are underpinned by cortico-thalamic-cortical re-entrant loops (Klimesch, 2012) and hence the role of the alpha band changes related to cognition are of particular interest in implicating cortical-subcortical networks which may underpin the cognitive dysfunction seen in MS. Whilst of interest, we would urge caution since the high-dimensionality of the MEG data, including multiple methods for calculation of connectivity metrics, allows for multiple exploratory analyses and presentation of post-hoc findings. To date only one study has undertaken a cognitive task whilst simultaneously acquiring MEG data (Costers et al., 2021). Taken together MEG connectivity metrics show promise in assessing cognitive function but further work remains to determine whether these can be shown during specific cognitive tasks. One disease model which can be used to model future work on is Traumatic Brain Injury, with evidence from multiple studies that differences are shown in patients and controls across a variety of in-scanner paradigms: including working memory, set-shifting, visual attention and tracking, picture naming, and auditory information processing (Allen et al., 2021).

Of interest we found limited evidence that the EDSS correlated with MEG indices with some failing to find this (Cover et al., 2006; P. Tewarie *et al.*, 2014) and others showing an association (Tewarie et al., 2013, 2015)). EDSS is the main disability score used to stratify patients disease progression and monitor effectiveness of the disease modifying therapies used in multiple sclerosis (Meyer-Moock et al., 2014). The lack of association with MEG indices may not necessarily be surprising since EDSS is sensitive to all neuronal impairment including peripheral nervous system, autonomic and cerebellar functioning and the spinal cord. Conversely EDSS is less sensitive in picking up subtle disturbances in cognitive function focussed on ambulatory or physical disability (Uher et al., 2018). Hence MEG based brain metrics may be but of particular value in assessing cognition and less valuable in assessing overall physical disability, except when specific functional symptoms are mapped with specific regions (such as optic neuritis in the visual system, or sensorimotor disability in the sensory cortex). In relation to physical disability we suggest a role for spinal MEG when considering motor and sensory cortical assessment. MEG recordings from the spinal cord will potentially be afforded by novel MEG sensors based on Optically Pumped Magnetometers (OPMs). Given the increased mobility afforded by OPMs, this may also offer the opportunity for more clinically informed assessments of motor impairments that are currently key in diagnosing and evaluating multiple sclerosis (Boto et al., 2019).

After reviewing all studies, one key criticism would be the lack of detail on the clinical picture. Most studies provide EDSS scores for disability, duration of disease and a few studies report lesion load,

however this would not provide an overall clinical picture. Some of the missing features are, for example, types of relapses (visual, motor, sensory, brainstem, etc) experienced in the relapsing and remitting groups which would clearly impact the outcomes particularly in the task-based studies. There is limited information about the clinical picture of the functional system looked at per study. It would also be instructive to determine if MEG metrics are associated with other features known to be associated with MS such as depression, quality of life and fatigue (Ziemssen, 2009). In addition, there is little discussion of the therapeutics which patients may have been on or previously were on, all of which could be confounding factors in the results. This is a particular issue in these studies reporting on small samples. Therefore, future studies should look at the clinical background of patients in more detail to allow a better assessment of the generalisability of the results.

We found only one longitudinal study using MEG to understand how MEG may prospectively predict cognition (Nauta et al., 2020). However, there is some evidence to suggest that connectivity may change over time. Tewarie and colleagues found in a chronic cohort (mean duration of disease 18.11 year) higher functional connectivity in the delta band using PLI (Prejaas Tewarie et al., 2014) which had not been reported in previous cohorts (Cover et al., 2006; Schoonheim et al., 2013; P. Tewarie *et al.*, 2014). They considered that this may be a consequence of a longer disease duration than previous cohorts. This is consistent with findings seen in other neurodegenerative conditions like Alzheimer's and Parkinson's (De Haan et al., 2008; Bosboom et al., 2009) and may provide further evidence for prominence of slower waves in later stages of disease. A longitudinal study with MEG at multiple time points would be required to definitively confirm or refute this. Such studies may pave the way for MEG use as a prognostication tool, as well as providing understanding of clinical deficit beyond the structural lesions.

It would be of interest to consider how MEG advances on insights provided by fMRI and EEG. The literature demonstrates that MEG shows abnormalities in waveform in Evoked Fields in motor, sensory and visual primary cortices. Much fMRI work has related to specific networks with DMN nodes as key hubs (Group *et al.*, 2021). From the MEG literature there is evidence of altered connectivity in the Default Mode Network which is correlated with EDSS score (Tewarie et al., 2013) whereas alpha integration is associated with cognitive scores (Sjøgård et al., 2021). MEG literature also specifically demonstrates alterations of the ascending pain network, the salience network as well as the DMN (Kim et al., 2019, 2020). The literature is perhaps at too early a stage to compare these findings directly. To determine how these findings relate to fMRI findings would require ideally multimodal characterisation of fMRI and MEG in the same sample.

Our suggestions for future studies would be to utilise pre-defined or standardised parameters that may allow studies to be more comparable. Paradigms of particular use would be Motor Evoked Fields, Visual Evoked Fields and the Somatosensory Evoked Fields. There are several different connectivity metrics but widely used metrics should be used such as Phase Locking Value, Phase Lag Index and Synchronisation Likelihood, rather than being newly defined for each individual study. In order to ensure replicability of results we would also suggest that data from such studies are made open to allow for reanalysis. A further possibility for the future would be to determine whether MEG offers the possibility of aiding with treatment selection. This is currently not established by these studies as all studies are cross-sectional. If MEG is able to track clinical improvement, this could lead to new avenues for treatment stratification which is an ever-pressing requirement given the complexity of current therapeutic regimens. Such an approach is highly speculative at the moment but may have potential for exploration.

5. Limitations

The strength of this review is that this is the first systematic approach to compile the MEG studies in MS to date. This includes data from over 400 patients with MS and almost 350 controls, from 13 different centres. We do find limitations in our work identified in this review. Firstly, the use of a wide variety of parameters made direct comparison between studies difficult. Secondly, we note the possibility of publication bias in this review – six records showed preregistration of studies (see supplementary data) but none of these have as yet been published or were included in our review. Conversely none of the included studies included reference to pre-planned analyses. It is likely that there is a skew to publish positive findings in the papers included. Thirdly because of the heterogeneity of study designs and analyses we did not independently screen papers, rather reviewers screened and extracted data with mutual consultation. Finally, we are unable to assess whether these changes are specific to multiple sclerosis. One study using a data driven approach showed changes in connectivity (using correlations between all sensors) were specific to multiple sclerosis rather than other states after using a Canonical Discriminant Function (Georgopoulos et al., 2007). However no other study used disease controls other than healthy controls. We note some overlap in our findings with other conditions – attenuations in Post Movement Beta Rebound amplitude have been shown in schizophrenia (Robson et al., 2016) and schizotypal disorder (Hunt et al., 2019) whilst disruption in alpha connectivity is also shown in Alzheimer's Disease (Koelewijn et al., 2017). We are therefore unable to specifically determine whether these findings are specific to MS or evidence of a more general brain deficit. Studies which compared different clinical groups with different diagnoses would need to be undertaken to determine whether these findings are specific to multiple sclerosis.

6. Conclusion

In conclusion we find good evidence that MEG shows evidence of altered neural activity, perturbed connectivity, and association with clinical impairment in multiple sclerosis. Event-related designs are of particular value and show replicability between centres. Particular areas of interest are beta changes in the motor cortex, changes in visual gamma in the visual cortex and alterations in somatosensory processing in Somatosensory Evoked Fields. There is some evidence that diminished alpha connectivity is seen in patients and this is associated with altered cognitive functioning. At this stage it is not clear whether these changes are specific to multiple sclerosis or can be observed in other disease states. Further studies should look to explore cognitive control in more depth using in-task designs and undertake longitudinal studies to determine whether these changes have prognostic value.

Funding

There was no funding for this project. We are grateful to Emily Litvak for proofreading the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102814.

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