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Novel EEG Biomarker Candidates of Cognitive Dysfunction in Multiple Sclerosis

differential diagnostics, novel re-phenotyping, and clinical trial design

Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

By

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Content resulting from input or data from related collaborative research is acknowledged in the text.

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Abstract

Multiple sclerosis (MS) is an autoimmune, inflammatory condition causing myelin damage and axonal degradation. Loss of myelin and axons causes impaired signal propagation throughout the body and impacts sensory and motor functions. Over recent decades, the presence of cognitive symptoms in MS has also been acknowledged. Cognitive impairment is also a frequently reported and distressing symptom of several other neurodegenerative conditions including amyotrophic lateral sclerosis (ALS). Impairments in cognition are now well recognized in these conditions, and an extensive body of research has characterized the extent and domains of this cognitive impairment in each condition.

However, measuring and tracking these changes clinically remains a challenge. Clinical measurement of cognitive impairment is generally accomplished through batteries of neuropsychological tests. These tests are extremely useful for diagnosing cognitive dysfunction and can provide information on the severity and the specific domain of the impairment. However, neuropsychological testing is time consuming, requires a trained experimenter, and can be impacted by practice. These factors make neuropsychological testing impractical for frequent or repeated use, such as in a clinical trial. Additionally, the tests do not provide information about underlying neural dysfunction.

Electroencephalography (EEG) is a safe, well-tolerated technique to directly measure fast neural activity. It has been proposed as an effective tool to measure biomarkers of cognitive impairment in neurodegenerative disease, and EEG alterations have been observed in MS and ALS. This project sought to use EEG to quantify cognitive changes in MS and to compare these changes with those observed in ALS.

83 people with MS, 74 people with ALS, and 130 healthy controls were included throughout this study. High-density EEG (128-channel) was recorded from each participant during a passive auditory frequency oddball paradigm, the sustained attention to response task (SART), and blocks of resting state with open eyes. Event-related potentials were extracted from the auditory oddball and SART data and compared among people with MS and healthy controls. ERPs were also compared among people with MS, people with ALS, and healthy controls to evaluate whether the similar cognitive

impairments observed in these conditions resulted from similar or divergent neural alterations. The test-retest reliability of these methods was also evaluated. Additionally, microstates were calculated from the resting state data, and their parameters were compared among subgroups of people with MS and controls.

The analyses revealed that P2, N2, and P3 ERPs produced during the SART have excellent reliability upon repeat testing, while the MMN produced during an auditory oddball should be used longitudinally with caution. No differences were found between any subgroup of MS and healthy controls on the MMN, in contrast to the altered MMN seen in ALS. In contrast to the MMN, the P2, N2, and P3 elicited from the SART were affected in MS, and several of these markers differed among MS subtypes. The pattern of these alterations differed in MS and ALS. Microstate parameters were largely unaffected in MS, but participants with secondary progressive MS (SPMS) differed from controls and participants with relapsing remitting MS (RRMS) in the duration of microstate B. This suggests that microstate Class B could be investigated further as a biomarker of the RRMS-to-SPMS transition.

In conclusion, EEG can quantify cognitively related neural dysfunction in MS and within MS subtypes. People with MS showed alterations in EEG microstates and in ERPs produced during the SART, but not on an MMN elicited during an auditory oddball. Furthermore, the SART method was shown to be a good tool for longitudinal studies due to its excellent test-retest reliability. These SART ERPs were also shown to be specific to MS, rather than reflective of general neurodegenerative processes. These results pave the way for future longitudinal EEG analysis of cognition in MS with the goal of developing robust biomarkers for the diagnosis, prognosis, and stratification of cognitive impairment in MS.

Lay abstract

What is MS?

Multiple sclerosis (MS) is a condition that causes damage to the protective coating on neurons, which are the cells that send and receive signals around your body.

Aims of the project

This project aimed to move away from pencil-and-paper tests or interviews and compare EEG (brain) signals between people with and without MS.

It also compared the EEG signals between people with MS and people with amyotrophic lateral sclerosis (ALS). ALS is another neurological condition that can affect thinking.

Results

We found that some EEG responses are different between people with MS and people without MS. Some responses are also different between people with different types of MS. This means that these signals may be able to tell us about thinking changes in these groups.

People with MS and people with ALS also show different EEG signals. This means that even though the thinking changes are similar in these conditions, they are not caused by the same brain changes.

Some of the EEG signals are stable when they are measured multiple times in people without MS. This means that these signals could be used to measure thinking repeatedly in MS, such as in a clinical trial.

Background

Many people with MS have changes to their thinking. These changes can impact learning, memory, attention, and other brain functions. Thinking problems are usually measured using pencil-and-paper tests or interviews. The tests show what parts of a person's thinking are impacted and how badly.

However, these tests have some problems that mean they are not normally used in clinical trials, which are research studies testing new medicines. The problems include:

- Trained psychologists must run the test, which costs money
- People can get better at the tests if they take them more than once
- The tests cannot tell us what brain changes cause these thinking problems

Why use EEG?

An electroencephalogram (EEG) is a sensor that safely and painlessly records your brain's electrical activity from on top of your scalp or hair. Unlike a thinking test, an EEG test can be repeated and can give information about the function of your neurons. Other scientists have linked thinking changes to changes in EEG signals.

Outputs

Poster presentations

Giglia, E., McMackin, R., Metzger, M., MacDomhnaill, É., Bista S., Mehra, P., Plaitano, S., Händel, L., Boyle, T., O'Sullivan, L., Strahan, O., Pinto-Grau, M., Heverin, M., Pender, N., Hardiman, O., Nasseroleslami, B. (2024). *Event related potentials enable discrimination of cognitive network impairment occurring in ALS and MS*. European Network to Cure ALS annual meeting. Stockholm, Sweden.

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Oral presentations

Giglia, R. *Using brain waves to study cognition in multiple sclerosis*. Pint of Science Dublin: Beautiful Minds. Dublin, Ireland, May 2024.

Giglia, R. *Quantifying cognitive dysfunction in MS with task-based EEG*. TCD Health Sciences Research Blitz. Dublin, Ireland, May 2024. **(Most Engaging Award)**

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Giglia, R. *Unravelling Cognitive Dysfunction: Crafting new tools for clinical trials in multiple sclerosis*. Trinity College Dublin 3-minute Thesis Competition. Dublin, Ireland, March 2024. **(First Place)**

Giglia, R. *Psychiatric and cognitive (dys)function in multiple sclerosis*. Lecture for 3rd year TCD Human Health and Disease: Biology of Neurological and Psychiatric Disease module. Dublin, Ireland, November 2023.

Giglia, R. *Tracking cognitive impairment in multiple sclerosis*. CÚRAM Teachers in Residence Programme. Online, November 2023.

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Giglia, E., McMackin, R., Dukic, S., Coffey, A., Bista, S., Mitchell, M., Fasano, A., Buxo, T., Heverin, M., Reilly, R., Pender, N., Hardiman, O., Nasseroleslami, B. (2021). *Test-Retest Reliability of EEG Markers of Cognition: Update*. [ENCALS Meeting 2021]. Virtual.

Peer-reviewed publications

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Coffey, A., Bista, S., Fasano, A., Buxo, T., Mitchell, M., **Giglia, E**., Dukic, S., Fenech, M., Barry, M., Wade, A., Heverin, M., Muthuraman, M., Carson, R., Lowery, M., Hardiman, O., Nasseroleslami, B. (2021). Altered supraspinal motor networks in survivors of poliomyelitis: A cortico-muscular coherence study. *Clinical Neurophysiology*, 132(1), 106-113. https://doi.org/10.1016/j.clinph.2020.10.011.

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Chapter 1

Introduction

Chapter summary

This chapter provides an overview of multiple sclerosis with a brief mention of ALS for comparative purposes. A discussion of biomarkers and their potential applications for cognition in neurodegenerative diseases follows.

Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory autoimmune disease that causes demyelination, leading to a range of sensory and motor symptoms. It is one of the leading causes of neurological disability in younger adults worldwide and affects over 2.8 million people (Walton et al. 2020). Recently, increased attention has been given to the cognitive and psychiatric symptoms of the condition, with the percentage of people with MS exhibiting cognitive and psychiatric symptoms estimated at between 45-70% and 20-50%, respectively (Chiaravalloti and DeLuca 2008; Patten et al. 2017).

Epidemiology

MS generally presents in adults between the ages of 20-40, with a global average age of onset of 32 years (Walton et al. 2020). However, approximately 10% of MS cases have a pediatric onset (Yeshokumar et al. 2017)[1]. It is approximately twice as prevalent in women than in men, though this ratio is closer to 3:1 in Ireland (Walton et al. 2020; O'Connell et al. 2017). Both the incidence and female:male sex ratio of MS have increased over time (Walton et al. 2020; Filippi et al. 2018). This increase in incidence may be partially attributable to improved methods for and access to MS diagnosis over time. The higher and increasing rate of MS in women could reflect hormonal mechanisms of MS development or environmental factors disproportionately affecting women. For example, obesity and oral contraceptive use are associated with higher rates of MS (Nova et al. 2024; Larsson and Burgess 2021).

[1] Pediatric MS is not addressed in this thesis. However, cognitive impairment is observed in children with MS and affects psychological and academic outcomes (Banwell and Anderson 2005; MacAllister et al. 2005; Amato et al. 2014; Weisbrot et al. 2014). Future work could apply the methods discussed in this thesis to identify reliable biomarkers of cognitive impairment progression and impact in this population.

The prevalence and incidence of MS varies widely among countries and ethnic groups. Generally, higher rates are seen in those with white European ancestry (including high rates in North Americans and Australians of European descent) and lower rates are seen in Africa and Asia and in those with African or Asian ancestry (Walton et al. 2020). Several environmental and genetic factors could contribute to these variations in global frequency.

Environmental risk factors

Several environmental risk factors for MS have been identified including latitude, Vitamin D exposure, smoking, and Epstein-Barr virus (EBV) infection. The rate of MS prevalence is higher at higher latitudes (Simpson et al. 2019). This may be due to a combination of both genetic effects and amount of sunlight exposure, which is lower at higher latitudes. Sunlight exposure (via ultraviolet radiation) is one mechanism of Vitamin D production in the body, along with nutritional Vitamin D. Lower serum Vitamin D levels and Vitamin D deficiency are associated with increased risks of developing MS (Vandebergh et al. 2022; Balasooriya et al. 2024; Gombash et al. 2022). Lower Vitamin D levels are also associated with increased disability and relapse risk (Oliveira et al. 2017; Ascherio et al. 2014). However, dietary supplementation of high-dose Vitamin D does not appear to have a substantial impact on disability or relapse in people with MS (Mahler et al. 2024). Seasonal variations are another piece of evidence supporting a role for Vitamin D in MS development and progression. MS risk varies by season of birth, with greater risk for people who were born in the spring (low sunlight winter gestation) than for people born in the autumn (high sunlight summer gestation)(Pantavou and Bagos 2020). In addition, relapse rates are lowest in the late summer and autumn and highest in the early spring (Nabizadeh et al. 2022). These observations suggest that decreased Vitamin D levels due to lower sun exposure during the winter months could contribute to this increased risk of developing MS or experiencing a relapse.

Along with sunlight and Vitamin D, smoking is one of the most established environmental risk factors for MS development and progression. Smoking increases the risk of developing MS (Olsson et al. 2017; McKay et al. 2017). The risk posed by smoking is cumulative over the lifespan and higher smoking levels are connected to faster disease progression and conversion from RRMS to SPMS (Filippi et al. 2018; Gouider et al. 2024). Environmental cigarette smoke exposure (“second-hand smoking”) is also associated with

an increased risk of developing MS (Schlindwein et al. 2024). In contrast, nicotine use may decrease MS progression (Hedström et al. 2013; Wu et al. 2023), suggesting that non-nicotine compounds in cigarette smoke may drive the increased risk reported by other studies.

Epstein-Barr virus (EBV) is another environmental risk factor for MS and shows the strongest evidence for potential causality of the known MS risk factors. A landmark study by Bjornevik et al. (2022) confirmed the effect of EBV on the development of MS hypothesized by previous associative studies. This study made use of longitudinally collected blood samples from over 10 million members of the US military. Samples from people who later developed MS were compared with samples from two randomly selected controls matched for age, sex, and other demographic features. The study showed that almost all individuals who developed MS are EBV-positive, and EBV infection led to a 32 times greater risk of developing MS. However, it must be noted that over 95% of adults have a history of EBV infection, and the majority of these will not go on to develop MS. Therefore, infection with EBV may trigger the development of MS in certain individuals. Research is ongoing to understand the mechanisms and susceptibility behind this effect (Ortega-Hernandez et al. 2023).

Other potential environmental risk factors include night-time shift work, excessive drug and alcohol exposure, obesity, oral contraceptive use, organic solvent exposure, comorbidities, stress, and air pollution (Gouider et al. 2024; McKay et al. 2017).

Genetic risk factors

Certain genetic factors are also associated with elevated MS risk, though familial MS accounts for less than 12% of total MS cases (Ehtesham et al. 2021). A slightly greater proportion (~15.5%) of pediatric MS cases are familial (Ehtesham et al. 2021). Genetic risk factors include HLA and interleukin variants, among others (Tempest et al. 2022; Baranzini and Oksenberg 2017).

The major histocompatibility complex (MHC), also termed human leukocyte antigens (HLA), are molecules responsible for presenting antigens to T cells and play a role in the body's adaptive- and auto- immune responses (Cruz-Tapias et al. 2013). Many variants of HLA class I and II genes are associated with increased risk of MS (Baranzini and Oksenberg 2017). Specifically, the gene HLA-DRB1 on chromosome 6p21 shows some of the

strongest associations with increased MS heritability (International Multiple Sclerosis Genetics Consortium et al. 2007; Oksenberg et al. 2008).

Interleukin receptors IL2RA and IL7R are two additional genes frequently associated with an elevated risk of MS (Tempest et al. 2022; Traboulsee et al. 2014). These receptors also regulate the activity of T cells and may be involved in T-cell mediated autoimmunity (Bielekova et al. 1999; International Multiple Sclerosis Genetics Consortium et al. 2007).

However, these genetic polymorphisms also increase the risk of other immune conditions, so they do not specifically indicate MS risk (Candore et al. 2002). Additionally, each identified MS genetic risk factor accounts for a small amount of increased MS risk. Therefore, these factors and their interactions may increase susceptibility to MS, rather than causing MS.

Pathophysiology

In MS, autoimmune and inflammatory processes cause damage to myelin, which is the fatty protective coating surrounding sections of axons of all neurons in the central nervous system (CNS) and of some neurons in the peripheral nervous system (PNS). Myelin is made up of glial cells of two types: oligodendrocytes in the CNS and Schwann cells in the PNS. Myelin serves as an insulator, allowing electrochemical signals to travel more quickly down an axon. Signal travels down an axon via an action potential, or unidirectional cascade of voltage-gated ion channel openings. In a myelinated neuron, only portions of the axon wall containing these voltage-gated channels are exposed. Therefore, signal “jumps” between these exposed sections, or nodes of Ranvier, in a process called saltatory conduction. Damaged myelin slows down the speed of action potential propagation and can leave the axon vulnerable to degeneration. Myelin loss and axonal degeneration lead to a wide range of motor, sensory, and cognitive symptoms. MS is generally considered to be an upper motor neuron (UMN) disorder, though some people with MS show damage in lower motor neurons (LMN) and other peripheral nerves (Oudejans et al. 2021).

Several mechanisms of myelin damage have been proposed in MS, which can be broadly grouped into autoimmune and inflammatory responses. In each case, particular immune cells gain access to the central nervous system through dysfunction of the blood-brain barrier (BBB) (Ortiz et al. 2014). The BBB is a combination of structural and glial

adaptations at the wall of CNS capillaries that prevents large molecules, including many immune cells, from entering the CNS. When the integrity of the BBB is impaired, these cells and molecules are allowed access to the CNS environment. Infiltration of activated leukocytes causes myelin and axon damage through direct attack or the effects of inflammation (Filippi et al. 2018). Regions of inflammation, called plaques or lesions, can be observed in the white and grey matter using T1 and T2-weighted magnetic resonance imaging (MRI). Contrast-enhanced MRI can also show the presence of actively demyelinating lesions. The presence and extent of these lesions show only slight associations with clinical disability, a phenomenon known as the "clinical-radiological paradox" (Barkhof 1999). However, recent studies indicate that more sensitive measures of lesion location and function may help to elucidate this relationship (Chard and Trip 2017).

Clinical presentation

MS is a condition characterized by heterogeneity of presentations. Damage to myelin and axons can impair signal transfer throughout the body, causing impairments in a wide range of body systems. Common symptoms include muscular weakness, spasticity, pain, numbness and tingling, unsteady gait, optic neuritis, visual disturbances, speech impairment, bladder and bowel dysfunctions, fatigue, anxiety, depression, and cognitive impairment (Filippi et al. 2018).

MS severity is classified according to the Expanded Disability Status Scale (EDSS), a half-point 1-10 rating scale reflecting walking ability with consideration for symptom severity across eight functional domains (pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral, and other) (Kurtzke 1983). This tool provides a useful standardized framework to compare disability level across individuals or over time for research and clinical trials. However, its focus on walking ability and clinician-observed signs may fail to reflect changes in impactful patient-experienced symptoms like sensory disturbances, cognitive impairment, and fine motor control. Additionally, it has somewhat limited inter- and intra-rater reliability (Meyer-Moock et al. 2014).

The multiple sclerosis functional composite (MSFC) is one alternative classification tool that was proposed to address some of the limitations of the EDSS (Fischer et al., n.d.). It includes three equally weighted subscales for walking and lower limb function, hand and

arm function, and cognitive function. The tool shows good inter-rater reliability, but is affected by practice (Fischer et al., n.d.; Meyer-Moock et al. 2014). While the measure is frequently used in research and clinical trials, it is less commonly used than the EDSS (Meyer-Moock et al. 2014).

Subtypes and progression

Around 85% of MS cases begin with a solitary episode of neurological impairment known as clinically isolated syndrome (CIS), which has approximately a 70% chance of converting to clinically definite MS within 2-5 years (Kolčava et al. 2020; Kuhle et al. 2015). A radiologically isolated syndrome (RIS) with MRI changes indicative of MS but no corresponding neurological indications of MS may also occur (Granberg et al. 2013). One third of people with RIS develop clinical symptoms within five years, and two thirds develop further MRI lesions (Granberg et al. 2013).

According to the 2017 revision of the McDonald diagnostic criteria, diagnosis of clinically definite MS can be made based on evidence of lesions or disability that are disseminated in space and time (Thompson et al. 2018). Dissemination in space refers to observations of multiple MRI lesions or clinical signs indicative of damage to multiple CNS regions. Dissemination in time refers to evidence of new MRI lesions, multiple clinical episodes, or steady accumulation of disability over time.

MS is classified into subtypes based on clinical observations of the disease course. These subtypes differ in regard to the presence of relapses, which are periods of days to weeks of sudden symptom increase. Around 85% of MS cases follow a relapsing-remitting disease course (RRMS) characterized by relapses interspersed with periods of complete or incomplete symptom recovery. If untreated, most people with RRMS will convert within 20 years to a secondary progressive (SPMS) disease course indicated by progressive disability accumulation with or without relapses (Cree et al. 2021; Rovaris et al. 2006; Lublin et al. 2014). However, improved treatment options for RRMS may be increasing this time to conversion (Tedeholm et al. 2022). Diagnosis of SPMS is made retrospectively based on clinical observation of symptom progression. In addition to RRMS and SPMS, some patients with MS show a progressive accumulation of disability from disease outset (PPMS) (Lublin et al. 2014).

Neurophysiological diagnostic tools

Structural MRI is the most used neurophysiological tool in the diagnosis of MS. MRI provides excellent spatial resolution and can distinguish active and historical lesions, allowing for demonstration of dissemination in space and time even at initial recording (Rocca et al. 2024). New markers like the central vein sign and paramagnetic rim lesions may improve the diagnostic specificity of MRI, though they provide limited additional utility in late-onset MS (Tena-Cucala et al. 2025).

Visual evoked potentials are electroencephalogram (EEG) [2] responses elicited through repetitive presentation of a time-locked visual stimulus, often a black and white checkerboard pattern or flash of light. The height and timing of the peak of these potentials are used as indices of visual system functioning, with slowed peaks representing demyelination. Amplitude reductions are more difficult to interpret but likely represent smaller or weaker cortical generators, through either normal inter-individual differences or damage (Barton et al. 2019). The optic nerve is often one of the earliest sites of MS pathology, so the VEP may be able to capture early or subclinical neurophysiological changes. However, like many event-related potentials, VEPs are highly variable based on the eliciting paradigm, recording environment and equipment, and inter-subject differences. This makes the application of clinical standards for VEP interpretation difficult and disfavours their use relative to MRI as a primary tool for diagnosis and monitoring, though they are still used and may provide complimentary information.

Motor evoked potentials (MEP) are another evoked potential that can support the diagnosis of MS, though these are less commonly used. MEPs are recorded in a target muscle in response to the stimulation of the motor cortex, usually through application of a transcranial magnetic stimulation (TMS) pulse. They can be used to monitor cortical excitability and activity along the corticospinal tract, and correlate with some measures of clinical disability (Šoda et al. 2023). However, they are generally considered less clinically practical than because they can be technically challenging and time consuming to collect,

[2] See the following chapter for a more thorough discussion of EEG and evoked/event-related potentials.

are less reproducible, and provide information that can be obtained from existing MRI measures (McGuigan 2013; Šoda et al. 2023).

MRI and simple cortical EEG event-related potentials are routinely used in the diagnosis or monitoring or MS. Therefore, these tools are already available in clinics and could be repurposed to measure novel MRI or EEG biomarkers.

Treatments

Many disease-modifying therapies (DMT) are now available for RRMS that decrease the rate of relapses and may delay EDSS progression. While these treatments were previously prescribed in a stepwise fashion of increasing efficacy (and correspondingly increasing risk), current evidence suggests that early initiation of high efficacy treatment is the best method to prevent long-term disability accumulation (Freeman et al. 2022; Buron et al. 2020; Selmaj et al. 2024).

Misdiagnosis

Given the high degree of variability in presentations of MS, it is perhaps not surprising that many people are both misdiagnosed with MS or misdiagnosed with other conditions before receiving a correct diagnosis of MS ("underdiagnosis"). A recent meta-analysis estimates the frequency of MS misdiagnosis and underdiagnosis at 15% and 36%, respectively (Zürrer et al. 2024). This contributes to diagnostic delays for people with MS and exposure to ineffective or potentially harmful treatments for people misdiagnosed with MS. The identification of reliable indicators of disease presence could help to alleviate this issue.

Cognitive impairment in MS

Cognitive impairment is a frequently reported and distressing symptom of multiple sclerosis, whose prevalence is generally estimated at around 40-70%, depending on study populations, clinical characteristics, and test batteries (Benedict et al. 2020). Recent meta-analyses suggest lower pooled prevalences of 41% overall (Askari et al. 2024) and 32% in relapsing-remitting MS (Wu et al. 2024). However, the neuropsychological test batteries used in the studies included in these meta-analyses vary widely. Therefore, given the heterogeneity of multiple sclerosis, it is possible that very focused batteries could miss the presence of cognitive impairment in participants who show impairments in atypical domains. This is supported by the finding that studies using a greater number of

tests identified a greater proportion of cognitive impairment (Wu et al. 2024). While exact estimates of prevalence may be flawed, it is clear that cognitive impairment impacts a substantial proportion of people with MS.

These impairments are also known to have important impacts on daily life for people with MS. For example, cognitive impairment is associated with lower scores on quality-of-life (QoL) measures (Marafioti et al. 2024; Gómez-Melero et al. 2024; Bergmann et al. 2023) and impacts QoL more strongly than does disease severity (Ciubotaru et al. 2024). Cognitive performance is also associated with increased anxiety and depression (Altieri et al. 2024; Freedman et al. 2024; Lester et al. 2007), increased fatigue (Candiri et al. 2024), reduced safe driving ability (Lincoln and Radford 2008; Kotterba et al. 2003), decreased employment (Espiritu et al. 2024; van Wegen et al. 2022; Srpova et al. 2022; Renner et al. 2020; Rao et al. 1991), and increased economic burden (Maltby et al. 2022), all of which could impact independence and well-being. Cognitive impairment can also impact burden and quality of life in caregivers (Sarhan et al. 2022; Figved et al. 2007).

Clinical presentation and progression

Cognitive impairment is seen across all subtypes of MS (Lugosi et al. 2024) and may be observable from the earliest stages of the disease (Reuter et al. 2011; Amato et al. 2012). However, the frequency and severity of impairment varies across types, with people with secondary-progressive MS generally displaying the most severely impacted cognition (Denney et al. 2005; Bergendal et al. 2007). Evidence suggests that cognitive impairment is increased in both progressive forms compared to RRMS (Gaudino et al. 2001; Huijbregts et al. 2004), though other studies suggest cognition is less impaired in PPMS than in RRMS or SPMS (Denney et al. 2005; Comi et al. 1995). Some of the variability in these results may be attributed to differences in which domains are more likely to be impaired in each subtype. The severity of cognitive impairment may also be impacted by age of disease onset, possibly due to an age-related decline in cortical plasticity (Oliveira et al. 2024). Conversations about cognitive dysfunction in MS generally assume a low prevalence of severe impairments at the level of a dementia. This may reflect a view that the term "dementia" indicates a severe and global impairment, rather than the domain-specific impairments generally seen in MS (Rao 1990)[3]. However, there is a lack of direct research

[3] Quoted in "Dementia in Multiple Sclerosis: Why Is It Rarely Discussed" (Westervelt 2015)

on dementia prevalence in addition to the lack of consensus around what constitutes dementia in this population. Surprisingly, one of the few direct studies on the topic in MS found that 22% of patients had dementia (Benedict and Bobholz 2007), which does not support the assertion that the prevalence of dementia is low in MS. Other studies have reported increased risk for Alzheimer's disease and vascular dementia in people with MS compared to age-matched peers (Cho et al. 2023; Mahmoudi et al. 2022). This highlights the need for additional focus and consensus diagnostic criteria for cases of dementia or severe cognitive impairment in multiple sclerosis.

The most affected cognitive domains across participants with MS are information processing speed, learning, and long-term memory (Benedict et al. 2020). However, deficits in executive function (Migliore et al. 2018; Abrahams et al. 2000; Mistri et al. 2024), attention (van Dam et al. 2024; Mistri et al. 2024), inhibition (van Dam et al. 2024; Ternes et al. 2019), verbal fluency (França et al. 2024; Delgado-Álvarez et al. 2020), verbal, visuospatial, and working memory (Vacchi et al. 2017; Hammer et al. 2011; van Dam et al. 2024; Leavitt et al. 2018), and social cognition (Bora 2017; Bora et al. 2016) are also seen.

Some longitudinal studies of cognitive impairment in MS suggest that the level of impairment remains relatively stable or even improves (Barbu et al. 2018; Piras et al. 2003; Nyári et al. 2024). However, other studies report an increased prevalence of cognitive impairment over time (Amato et al. 2001; Zivadinov et al. 2001). It is possible that this discrepancy reflects a disconnect between cognitive impairment presence and severity; perhaps cognitive impairment emerges at variable points within the disease course but remains stable once present. However, this explanation does not account for the increased severity of cognitive problems seen in secondary progressive MS. Like physical disability, cognitive impairment may also show progression independent of relapse activity (PIRA) (Fuchs et al. 2024).

Neuropathological correlates

No definitive causal mechanism for cognitive impairment in MS has been identified. Potential mechanisms could include decreased oxygen and nutrient availability in the CNS, decreased firing efficiency of neurons, and disconnection of neural networks. These proposed mechanisms are supported by the observation of correlations between neuropathological features and cognitive impairment presence or severity.

Features affecting CNS oxygen and nutrient availability that are associated with cognitive impairment in MS include lower cerebral blood flow (D'haeseleer et al. 2015), lower cerebral vasoreactivity (Metzger et al. 2018), and inflammation-mediated increases in local energy consumption by leukocytes or mitochondria (Yang and Dunn 2019). Cognitive processes could also be altered by decreases in transmission efficiency due to synaptic dysfunction in addition to MS's characteristic demyelination. Dysfunction of the synapse due to inflammation and excitotoxicity have been documented in MS and are correlated with cognitive outcomes prior to and independently of white matter lesions (Schwarz and Schmitz 2023).

Finally, network pathway disconnection or rearrangement could be caused by physical loss of connections due to axonal damage or reduction in pathway efficiency below a threshold needed to maintain a functional connection. Neuroimaging results supporting a network disconnection theory of cognitive impairment are presented in the subsequent chapter.

The lack of a clear link between cognitive impairment and specific neuropathological changes is a key challenge in predicting, identifying, and treating cognitive impairment in MS. Greater understanding of this biological link could provide more sensitive biomarkers or targets for treatment.

Neuropsychological screening and assessment

Cognitive impairment is identified clinically by health care providers (HCP) using screening tools, assessment batteries, or reports from the patient, their family, or the wider healthcare team. Once identified, HCP can offer mitigation strategies or refer the patient for further assessment or rehabilitation, though the availability of such referral options may be limited for many providers.

Screening tools

Screening tools should be short, repeatable tasks or surveys that show changes when cognitive changes are present in MS (sensitivity) but do not show changes when cognition is unaffected (specificity). These short tests generally measure one or a small number of cognitively relevant domains, in contrast to more comprehensive tests.

The paced auditory serial addition task[4] (PASAT) and symbol digit modalities test[5] (SDMT) are commonly used individual measures generally taken to reflect processing speed and attention. The measures are brief (10-15 minutes for the PASAT and around 5 for the SDMT) and can be administered with minimal equipment. However, the PASAT is heavily impacted by practice, sociodemographic confounds, dysarthria or other language impairment, and participant anxiety (Tombaugh 2006). Additionally, the 10–15-minute time requirement, while brief in a research setting, is likely to be unacceptably long in a clinical one. In contrast, the administration of the SDMT takes 90 seconds after explanation. However, both tests suffer from a lack of domain specificity, so they may need to be used in conjunction with other tests to determine the nature of cognitive impairment. Additionally, both tests require the presence of an examiner and therefore cannot be completed independently by patients during waiting time in a clinic visit. The ability to be completed independently and even asynchronously is a benefit of self-report measures like surveys.

The multiple sclerosis neuropsychological questionnaire (MSNQ) is a brief (5 min.) self-report survey tool developed for use in multiple sclerosis with both patient report (MSNQ-P) and informant report (MSNQ-I) versions (Benedict et al. 2003). The test shows good validity and reliability (Benedict and Zivadinov 2007), and may be more reflective of composite cognitive status rather than performance on individual objective cognitive tests. Like many self-reported measures of cognitive status, it is associated with depression scores (Benedict et al. 2003; Lester et al. 2007; Akbar et al. 2011; Carone et al. 2005). This is not necessarily a disqualifying drawback for clinical use, as high levels of cognitive impairment and depression should both warrant referral, and follow-up assessment can determine whether the appropriate support will be cognitive or psychological. However, research studies should be aware of the potential for confounding effects. When direct agreement with neuropsychiatric scores is important, the MSNQ-I may be a more reliable choice (Benedict et al. 2003; O'Brien et al. 2007).

[4] A series of spoken (recorded) digits at a set inter-stimulus interval that varies between trials are presented. Participants must respond orally with the sum of the number just presented and the number preceding it.

[5] Participants are presented with a page of unfamiliar symbols and a symbol-digit reference key and must "decode" as many symbols as they can within a 90 second time limit.

Commonly used screening tools in an Irish context include the Addenbrooke's Cognitive Examination-Revised (ACE-R) and Montreal Cognitive Assessment (MoCA) (Hynes et al. 2022), though neither battery was developed specifically to identify cognitive dysfunction in MS. The ACE-R has been used (though infrequently) to measure cognition in MS research (Connick et al. 2013), and was developed to identify and differentiate mild cognitive impairment (MCI) and dementia (Mioshi et al. 2006). The MoCA is more commonly used and appears to show good utility as a screening tool in MS, though cutoff scores may need to be adjusted for this population (Dagenais et al. 2013; Charest et al. 2020; Rosca and Simu 2020). However, this tool was also developed to detect MCI rather than MS-specific cognitive impairment (Nasreddine et al. 2005).

Screening and assessment batteries

Shorter tests measuring functions on individual domains can be combined into series of tests known as batteries. In multiple sclerosis, these include the brief repeatable battery of neuropsychological tests (BRB-N), the minimal assessment of cognitive function in MS (MACFIMS), and the brief international cognitive assessment for MS (BICAMS). These tests can be used to screen for the presence of cognitive impairment or to assess which domains are impaired and may need support.

The BRB-N includes the selective reminding test (SRT, verbal learning/memory), the 10/36 spatial recall test (visuospatial memory), the SDMT, the PASAT, and the word list generation test (verbal fluency) (Bever et al. 1995). The MACFIMS also contains the SDMT and PASAT along with the California verbal learning test (CVLT, verbal learning/memory), brief visuospatial memory test (BVMT, visuospatial memory), Delis-Kaplan Executive Function System (D-KEFS) card sorting task (executive function), the judgement of line orientation test (JLOT, visuospatial processing), and the controlled oral word association test (COWAT, verbal fluency) (Benedict et al. 2002). The BICAMS includes the SDMT, with the CVLT and BVMT included if time allows (Langdon et al. 2012). These test batteries all aim to assess the main domains that are likely to be impaired in multiple sclerosis. However, the construction of a test battery will always represent a trade-off between comprehensiveness and length. For example, cognitive impairment in a person who struggles with language impairments in her daily life is unlikely to be identified by the comparatively short (15 minutes) BICAMS and is even less likely to be identified with the minimal BICAMS (SDMT only). This highlights the utility of soliciting self-reports of

subjective cognitive functioning within the clinic. Though these self-reports cannot provide as much specificity as an in-depth battery, their high sensitivity and practicality make them optimal screening tools. This suggests that one manner of dealing with cognitive evaluation within a busy clinic could be to present a self-report tool like the MSNQ during waiting periods and to conduct a follow-up conversation or brief assessment only for those patients scoring abnormally to determine the need for further referral. This "two-tiered" screening system could help to integrate conversations about cognitive dysfunction into the clinic without placing the burden of in-depth cognitive evaluation on a non-cognitive specialist.

Clinical challenges

Despite the importance and availability of MS-specific cognitive screening tools, a survey of 94 Irish MS health care providers found that only 34% routinely screened for cognition within the clinic and only 60% referred suspected cases of cognitive dysfunction for specialist assessment or intervention (Hynes et al. 2022). The 94 respondents seem to represent a relatively small proportion of individuals involved in MS care, given that 213 hospital or primary locations assumed to treat patients with MS were approached, in addition to online recruitment. If these respondents decided to complete the survey due to prior interest or knowledge about cognitive dysfunction in MS, then assessment and referral percentages may be even lower in the wider population of providers treating MS without this prior interest.

Even among clinicians who would like to test for cognitive impairment, time constraints often make this impossible within the clinical setting. Additionally, some clinicians may feel underprepared to carry out such assessments (Hynes et al. 2022; Klein et al. 2019). These factors further support the use of self-report screening tools discussed above.

Cognitive rehabilitation

If a patient is referred for further assessment and cognitive impairment is identified, then cognitive rehabilitation may be recommended. Cognitive rehabilitation is a goal-directed process seeking both to retrain cognitive functions and to embed supports within the patient's thought processes, actions, and environment (Wilson 2008). Cognitive rehabilitation approaches are common after traumatic brain injury (TBI) and stroke, and have more recently been applied to chronic conditions like MS. Several meta-analyses and systematic reviews have aimed to summarize the research in this area. These reviews

support the effectiveness of cognitive interventions, though the effects may be small (Redero et al. 2023; Taylor et al. 2021; Rosti-Otajärvi and Hämäläinen 2014). Effective interventions can also be delivered through virtual reality environments (Zhang et al. 2024).

Interestingly, some cognitive interventions may have greater impact on self-report measures rather than objective cognitive functioning (Nauta et al. 2024; Mäntynen et al. 2014). On the other hand, some interventions affecting objective cognition are also associated with changes on functional MRI measures (Parisi et al. 2014; Filippi et al. 2012).

ALS

Amyotrophic lateral sclerosis (ALS) is rapidly progressive, fatal neurodegenerative condition affecting the upper and lower motor neurons. It is the most common of the motor neuron diseases (MND) and affects movement, behavior, and cognition (Hardiman, Al-Chalabi, Chio, et al. 2017).

Epidemiology

ALS is a rare disease, with reported prevalences between 0.26 and 23.46 per 100,000 person-years (Wolfson et al. 2023). European incidence is approximately 2 per 100,000 person-years (Logroscino et al. 2010; Chiò et al. 2013). ALS is approximately two times more common in males than in females, though this ratio may begin to decrease with increasing age (Manjaly et al. 2010). The higher frequency in men could be due to biological risk factors or gender differences in exposure to environmental risk factors. Some evidence suggests that the incidence of ALS is increasing, though this may relate to the aging global population (Mata et al. 2023; Xu et al. 2020; Arthur et al. 2016). Additionally, these estimates could be affected by expanded diagnostic criteria, improved awareness driving referral to specialists, and improvements to data capture procedures in population based registers over time (Hardiman, Al-Chalabi, Brayne, et al. 2017).

Approximately 10% of ALS cases are familial, or related to gene variants such as SOD1 and C9ORF72 (Boylan 2015). These genes are not completely penetrant, meaning that not every carrier will develop ALS or a related condition (Hardiman, Al-Chalabi, Chio, et al. 2017). The variants may also occur in sporadic ALS, or cases in a person with no family history of the disease. In addition to causative genes like SOD1 and C9ORF72, other

genetic variants associated with ALS have been identified, but work is ongoing to determine the degree of susceptibility or causation contributed by these factors (Boylan 2015).

Environmental, occupational, and lifestyle factors conferring increased and decreased ALS risk have also been identified. Environmental factors increasing ALS risk include exposure to heavy metals, organic solvents, pesticides, and magnetic fields (Gunnarsson and Bodin 2018; Wang et al. 2017; Zhang et al. 2023). Living in an urban environment is associated with decreased risk of ALS (Duan et al. 2023). Military service is associated with increased risk, possibly due to associations with environmental and lifestyle factors associated with ALS (McKay et al. 2017). Medical and lifestyle factors like trauma (especially head trauma) (Gu et al. 2021; Wang et al. 2017), physical activity (Gunnarsson and Bodin 2018; Zhu et al. 2023), and contact sports (Blecher et al. 2019) are associated with increased risk, while factors like high BMI (O'Reilly et al. 2013; Wang et al. 2017) and type 2 diabetes (Wannarong and Ungprasert 2020; Zhu et al. 2023) are associated with decreased risk.

Pathophysiology

ALS pathology is characterized by the progressive loss of upper and motor neurons, leading to muscle weakness and eventual death from respiratory failure. Several mechanisms of ALS cell death have been posited, many related to the observation that people with ALS develop pathological accumulations of proteins in the motor neurons. Such protein inclusions are well-known features of the pathophysiology of other neurodegenerative conditions like Alzheimer's disease or Parkinson's disease. In ALS, the protein TAR DNA-binding protein 43 (TDP-43) is the most common component of these inclusions (Hardiman, Al-Chalabi, Chio, et al. 2017). TDP-43 proteinopathy is present in almost all patients with both familial and sporadic forms of the condition (Mackenzie et al. 2010).

Other pathological mechanisms include mitochondrial dysfunction, metabolic dysfunction, inflammation, dysfunctional protein and RNA metabolism, excitotoxicity, and structural and functional defects of the cytoskeleton (Feldman et al. 2022; Hardiman, Al-Chalabi, Chio, et al. 2017).

Clinical presentation

ALS risk increases with age from around 40 years until a peak between 60 and 80 years (Marin et al. 2018). Once diagnosed, the condition generally progresses rapidly, with death due to respiratory failure occurring within 2-4 years, though around 5-10% of people with ALS live for over 10 years after diagnosis (Hardiman, Al-Chalabi, Chio, et al. 2017; Chiò et al. 2009). ALS is currently incurable, but two disease modifying therapies have been identified: riluzole and edaravone. Only riluzole is approved by the European Medicines Agency (EMA), and provides a modest (3 month) increase in mean survival (Hardiman, Al-Chalabi, Chio, et al. 2017; Miller et al. 2012). Other medications may be prescribed to manage common symptoms like pain, spasticity, sleep disturbances, psychiatric symptoms, and excessive salivation.

The majority of ALS cases (~60%) present with a spinal, or limb, onset involving weakness, fasciculations, or muscle wasting. Another substantial portion of cases (~30%) present with bulbar onset, which causes speaking and swallowing difficulties and emotional lability. Different sets of diagnostic criteria have been used to diagnose ALS over time, adding difficulty to the comparison of population parameters longitudinally. The most recent set of criteria (Gold Coast criteria) was formed from consensus recommendations in 2019 (Shefner et al. 2020) and has been found to have increased sensitivity and preserved specificity compared to previous criteria (Vucic, Ferguson, et al. 2021). While cognitive and behavioral impairment are now widely acknowledged to present in many cases of ALS, they are not currently incorporated into the Gold Coast criteria. However, a separate set of diagnostic criteria, the Strong criteria, are used to diagnose concomitant ALS and FTD, referred to as ALS-FTD spectrum disorder (Strong et al. 2017).

Cognitive impairment in ALS

The topic of cognitive impairment in amyotrophic lateral sclerosis (ALS) is briefly addressed here to provide background for a comparison of EEG data between participants with MS and ALS later in this thesis. An in-depth study of the cognitive impairments seen in ALS and their EEG correlates was made in the PhD thesis *Human Neurodegeneration: A Spectral EEG and TMS based Approach in Amyotrophic Lateral Sclerosis* (McMackin 2021).

Clinical presentation and progression

Approximately 50% of people with ALS show some level of cognitive impairment (Phukan et al. 2012; Montuschi et al. 2015; Oh et al. 2014). Behavioral impairments like apathy and disinhibition (Gibbons et al. 2008) may also be seen in over 40% of people with ALS (Burke et al. 2017). Cognitive and behavioral impairment are sometimes collectively termed “extra-motor impairments” to distinguish these features from the classic motor symptoms of ALS. This review will focus on cognitive impairment seen in ALS to facilitate comparisons with MS later in the thesis.

The most commonly reported impairments in ALS are in executive impairment and language, though learning and memory impairments are also commonly seen (Jellinger 2023; Abrahams 2023; Pender et al. 2020). Deficits in social cognition (Bora 2017; Bora et al. 2016) and increases in emotional lability may also occur (Finegan et al. 2019). The presence of these impairments at diagnosis may have prognostic value in ALS. Some evidence suggests that those who show preserved cognition at baseline tend to remain relatively cognitively intact over the course of the disease (Öijerstedt et al. 2024). In contrast, cognition tends to worsen over time in people who show early cognitive changes (Öijerstedt et al. 2024). However, other studies find progression over time even in patients showing no cognitive impairment at baseline (Bersano et al. 2020).

Cognition is severely impacted in approximately 5-15% of people with ALS, leading to a diagnosis of FTD. ALS and FTD are now thought to exist along a clinical spectrum of relative degrees of motor and cognitive involvements known as fronto-temporal spectrum disorder (ALS-FTSD) (Pender et al. 2020; Strong et al. 2017).

Screening tools

The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) is a tool designed to screen for impairments in executive function, social cognition, verbal fluency, language (naming, comprehension, and spelling), memory, and visuospatial function (Abrahams et al. 2014). (It also includes a carer interview section to assess behavioral impairment).

Other ALS-specific cognitive screening tools sometimes employed for this population include the ALS Cognitive Behavioral Screen (ALS-CBS), ALS Brief Cognitive Assessment (ALS-BCA), ALS-FTD Questionnaire (ALS-FTD-Q), Penn State screening examination of frontal and temporal dysfunction syndromes (PSSFTS), and the University of California San

Francisco screening battery (UCSF-SB). Non-ALS specific screening tools include the Montreal Cognitive Assessment (MoCA), the Addenbrooke's Cognitive Examination (ACE), the mini mental state exam (MMSE), and the frontal assessment battery (FAB).

While these other tools have been used in clinics and research, the ECAS shows the strongest evidence of reliability and validity (Didcote et al. 2024; Gosselt et al. 2020; Simon and Goldstein 2019). The ECAS (and other screening tools) are designed to alert the clinical team to the presence of cognitive impairments and to trigger further investigation, rather than to comprehensively determine the presence or nature of cognitive impairment.

Biomarkers of cognitive impairment

As mentioned above and discussed more thoroughly in the next chapter, both MS and ALS are associated with cognitive impairment. The presence and progression of these impairments can be difficult to predict. The development of better tools to identify, track, and predict cognitive impairment in neurodegenerative conditions could improve cognitive outcomes for patients. Such tools are known as *biomarkers*.

Types of biomarkers

"Biomarker" (biological marker) is a broad term to indicate any observable sign that corresponds to another characteristic of interest, for example, the presence of a disease (Strimbu and Tavel 2010). Biomarkers encompass a wide range of observable signs such as levels of certain proteins in the blood, signal intensity on an MRI, or force output in a motor task. A biomarker should show high sensitivity (few false negatives) and high specificity (few false positives) for the characteristic of interest. Ideal biomarkers are inexpensive, non-invasive, quickly and easily measured, and responsive to change.

Some broad categories of biomarker include diagnostic, prognostic, stratifying, or response markers. The distinctions between these categories are not absolute, as many biomarkers may be used in multiple applications. Diagnostic biomarkers identify the presence of a condition or help to distinguish between conditions. A diagnostic biomarker of cognition would be an objectively measurable sign indicating that cognition is impaired, or that cognition within a specified domain is impaired. Prognostic or predictive biomarkers are signs measured at a baseline and used to infer future status. An ideal prognostic measure of cognition for ALS or MS would be measurable at diagnosis and

accurately reflect the presence, domain, or degree of cognitive impairment later in the disease course. Stratifying biomarkers are used to classify people into clinically relevant groups. A stratifying biomarker for cognition could classify individuals based on the domain or extent of cognitive impairment. These groups may not correspond to current clinical distinctions and could therefore help to account for some sources of disease heterogeneity. Stratifying biomarkers are also useful in clinical trials to select groups of people who may be more likely to show a response to a treatment. Clinical trials also use response markers, which reflect the degree of improvement or deterioration due to treatment.

Differential diagnosis *with* and *of* cognitive impairment

While cognitive impairment is detectable early in the disease course in both ALS and MS, it is not routinely considered as part of the diagnostic criteria for either condition[6]. If improvements in the quantification or classification of cognitive impairment progressed to the point of identifying reliable cognitive phenotypes distinctive to a particular neurodegenerative disease, then cognition could potentially be used as part of the differential diagnosis for these conditions (differential diagnosis *with* cognitive impairment). However, the state of the field is not yet such to permit this level of specificity owing to the large overlaps in cognitive impairment seen between conditions.

At present, we lack reliable biomarkers to effectively measure or predict cognition within a condition, much less to distinguish among different conditions. Therefore, our current challenge lies in identifying diagnostic, stratifying, and prognostic biomarkers for cognitive impairment in ALS and MS individually (differential diagnosis *of* cognitive impairment). It is possible that future developments in knowledge and technology will allow us to apply this knowledge toward the development of biomarkers for differential diagnosis.

[6] The Strong criteria for ALS-FTD spectrum disorder are separate to the Gold Coast criteria for the diagnosis of ALS.

Chapter 2

Literature Review

Chapter summary

This review provides an overview of currently available biomarkers of the cognitive changes seen in MS and ALS. Particular attention is paid to electrophysiological markers of network dysfunction in multiple sclerosis.

Biomarkers of cognitive impairment in MS

The following sections provide an overview of the use of fluid, radiological, and electrophysiological biomarkers of cognition in MS.

Fluid biomarkers

Several CSF and serum fluid biomarkers for cognitive impairment have been observed in multiple sclerosis. A selection of these is discussed below. Some fluid biomarkers can be measured in the blood, making these preferable in safety and tolerability to other markers of neural dysfunction that can only be measured within the CSF. Overall, fluid markers provide indirect information about neural and cognitive processes, so overinterpretation of associations with specific cognitive functions should be avoided. However, CSF and serum biomarker candidates do appear to show good diagnostic and predictive potential of global cognitive impairment in MS.

Oligoclonal bands

The presence of immunoglobulin G (IgG) oligoclonal bands (OCB) in the cerebrospinal fluid (CSF) is used clinically as a diagnostic marker for MS. While most people with MS display the bands, some do not, and the bands may likewise be found in people with other inflammatory conditions (Deisenhammer et al. 2019). Patients who are positive for OCB appear to show worse cognitive performance than those without the bands (Anagnostouli et al. 2015). Evidence also suggests that OCBs may be associated with increased cognitive decline over 5-10 years (Giedraitiene et al. 2021; Farina et al. 2017).

CSF parvalbumin

Parvalbumin is a protein contained in some GABAergic (inhibitory) neurons within the CNS (Rupert and Shea 2022). If these neurons are destroyed, the level of parvalbumin

measurable in the CSF may increase. Two studies have reported increases in CSF parvalbumin associated with increased cognitive decline in MS: Magliozzi et al. (2021) reported higher parvalbumin levels in severely cognitively impaired people with MS compared to those with milder impairments and controls. This suggests that different degrees of cognitive impairment could be caused by different mechanisms. A follow-up study by Ziccardi et al. (2024) replicated the finding of higher CSF parvalbumin in patients with severe cognitive impairment compared to controls. They also found correlations between parvalbumin levels at diagnosis and cognitive performance four years later. These results provide preliminary evidence that CSF parvalbumin could be used as a prognostic biomarker of global cognitive functioning.

Neurofilament light chain

Neurofilament light chain (NfL) is a protein component of the neuron cytoskeleton that can be released into the extracellular fluid and blood when axons are damaged. Because NfL can be measured in the blood, it could be a more clinically acceptable biomarker than markers found only in the CSF, which require a lumbar puncture to obtain. Elevated levels of NfL have been reported across a range of neurological and psychiatric conditions (Khalil et al. 2024; Bavato et al. 2024) and are associated with increased relapse rates, disability progression, and MRI activity in MS (Kuhle et al. 2019). This has prompted investigation of the relationships between NfL levels and cognitive impairment in MS. Some evidence suggests that increased CSF or serum NfL levels correspond to worse cognitive outcomes (van Dam et al. 2023; Barro et al. 2023; Tiu et al. 2022; Cruz-Gomez et al. 2021; Gaetani et al. 2019; Kalatha et al. 2019; Quintana et al. 2018; Tortorella et al. 2015; Jakimovski et al. 2020; Mattioli et al. 2020). However, other studies find no relationship between NfL and cognitive status (Oset et al. 2023; Virgilio et al. 2022; Friedova et al. 2020; Ziccardi et al. 2024). Given the heterogeneity of physical and cognitive presentations in MS, it is possible that the relationship between NfL and cognitive status varies among disease subtypes or other clinical distinctions. Thus, while NfL seems to be a promising peripheral biomarker of cognitive impairment, additional research is needed to fine-tune our understanding of this relationship.

Serum vitamin D

Vitamin D has been implicated in various pathways of MS development and progression (Gombash et al. 2022). Vitamin D levels are easily measurable within the blood, making

them a convenient biomarker choice. Lower vitamin D levels have been associated with cognitive impairment, particularly decreased processing speed, in MS (Spiezia et al. 2023; Virgilio et al. 2021; Darwish et al. 2020; Cortese et al. 2020). Strikingly, Virgilio et al. (2021) noted that only 10 out of 81 studied patients showed sufficient vitamin D levels, and no cognitively impaired patient showed normal vitamin D levels. Promisingly, preliminary evidence suggests that these associations may be modifiable with vitamin D supplementation (Darwish et al. 2017; Maghbooli et al. 2024; Essa et al. 2023), though vitamin D supplementation appears to have no effect on other clinical outcomes (Mahler et al. 2024).

Other markers

Additional markers of cognitive status or progression have been proposed, including chitinases, homocysteine, apolipoprotein, neurotrophins, amyloid β, and τ protein (Rademacher et al. 2023).

Neurophysiological biomarkers

Neurophysiological techniques like EEG, MEG, and TMS have been used to investigate brain network function in MS. Evidence from these studies points to impairment in network oscillations, connectivity, and excitability. Measures that reliably identify MS presence, subtypes, or progression could be further developed as biomarkers for use in clinical trials for MS. The following sections focus specifically on neurophysiological measures that have been associated with cognitive or cortical dysfunction in MS.

MRI

Magnetic resonance imaging (MRI) is a commonly used tool in the clinical monitoring of MS. Structural MRI uses magnetic pulses and radio waves to construct a map of tissues based on water content. The identification of MRI biomarkers for cognitive impairment in MS has been hampered by the clinical-radiological paradox, or the observation that the level of radiological lesions generally do not correlate precisely with the level of clinically observed disability (Barkhof 1999). However, recent evidence indicates that accounting for the location or connectivity of these lesions improves associations with disability, including cognitive disability (Hartmann et al. 2023; Chard and Trip 2017; Benedict et al. 2005). Among structural MRI measures, reductions in thalamic volume appear to be the best predictor of cognitive impairment (Mirmosayyeb et al. 2024). Corpus callosum

volume, grey and white matter volumes, whole-brain volume, and T2 lesion volumes have also been proposed to reflect cognitive impairment (Lomer et al. 2024).

In comparison to structural measurements, functional electrical and magnetic techniques have the advantage of better characterizing the role of the damaged tissue. This could potentially provide better predictors of cognitive status compared to structural predictors. Functional MRI (fMRI) measures blood flow (via oxygen levels) to approximate activity at specific brain locations. This technique takes advantage of the excellent spatial resolution of MRI. However, MRI has a limited temporal resolution of approximately 5 seconds[7] (Glover 2011), which may be insufficient to capture the fast dynamics of neurons. Nonetheless, a variety of fMRI alterations related to cognitive impairment have been shown in MS. Reviews show that these alterations tend to reflect compensatory increases in activity and connectivity, especially in cognitively preserved patients (Rocca et al. 2016).

Optical coherence tomography

Optical coherence tomography (OCT) is an imaging modality using the scatter of near-infrared light to create an image of the retina's layers with micrometer resolution (Gordon-Lipkin and Calabresi 2017). Compared to other imaging modalities like MRI, OCT has advantages in cost, test duration, and ability to directly image axonal health, which is considered to be a major contributor to long-term disability in MS (Gordon-Lipkin and Calabresi 2017). The thickness of the retinal nerve fiber layer (RNFL) is the most common OCT measure studied in relation to cognitive impairment in MS. Several studies show that the RNFL's thickness is associated with cognitive scores in MS (Stellmann et al. 2017; Ko et al. 2018; Davion et al. 2023; Toledo et al. 2008; Covey et al. 2024; Baetge et al. 2021; Bsteh et al. 2019; Birkeldh et al. 2019; El Ayoubi et al. 2016; Esmael et al. 2020; Abdel Naseer et al. 2019; Coric et al. 2018; Dreyer-Alster et al. 2022; Cerdá-Fuertes et al. 2023), though this effect is not universally observed or observed in other layers (Anhoque et al. 2013; Frau et al. 2018; Petracca et al. 2018; Jakimovski et al. 2021). Evidence also

[7] Recent innovations in experimental design and analysis can produce decisecond (0.1s) temporal resolutions (Ogawa et al. 2000). These techniques are not yet standard, and superior temporal resolution (0.001s) can be obtained through other techniques like EEG.

suggests that the changes in RFNL thickness are associated with cognitive decline over time (Giedraitiene et al. 2021; Alba-Arbalat et al. 2024; Ko et al. 2018; Silva et al. 2022).

A 2023 meta-analysis concluded that RNFL thickness is associated with SDMT performance, PASAT score, and word-list generation scores (Mirmosayyeb et al. 2023). These results suggest that OCT measurements of RNFL could be useful diagnostic indicator of cognitive impairment. However, further study is needed to understand whether these measures can serve as reliable prognostic indicators of future cognitive decline. However, while a prognostic RNFL thickness biomarker for cognitive decline does appear possible, a single low-to-high scale seems unlikely to be able to accurately predict the *nature* of the expected impairment. To accomplish this, multi-factor measurements that account for several retinal layers or retinal locations may prove more informative. OCT could also be combined with other neuroimaging modalities to add information on relevant cortical structures or processes.

TMS

Network dysfunction caused by MS is not limited to changes in structure, activity, or connectivity; overall network excitability may be altered as well. Transcranial magnetic stimulation (TMS) is an effective tool for assessing cortical network excitability, especially when used in conjunction with electromyography (EMG) to interrogate motor networks. TMS involves the application of focal magnetic pulses to the cortex via a coil placed on the scalp which induce an electric field in the underlying cortex. This electrical field can elicit cortical activity by altering the charge across neural membranes. TMS pulses applied to motor regions of the cortex can experimentally elicit motor responses, which can be measured using surface EMG. Additionally, repetitive stimulation of cortical areas with TMS (RTMS) may be used to experimentally alter cortical excitability. Alterations in cortical excitability, either due to disease processes or TMS interventions, may be observable as altered motor responses in relation to controls.

Resting motor threshold (RMT) is the lowest intensity of TMS stimulation capable of eliciting a minimal motor evoked potential (MEP), which is typically defined as an MEP of at least 50 μV evoked 50% of the time. It is measured by delivering single TMS pulses of varying intensities to specific motor areas while recording responses in the associated muscle using EMG. RMT is increased in patients with MS (Zipser et al. 2018; Vucic et al. 2012; Conte et al. 2009; Liepert et al. 2005; Caramia et al. 2004; Perretti et al. 2004). RMT

may indicate disease progression and symptom severity, as increases in RMT have been reported in patients with SPMS (Vucic et al. 2012; Conte et al. 2009), higher EDSS (Conte et al. 2009), and active relapse status (Caramia et al. 2004). Increases in RMT suggest a decrease in excitability at some point between the motor cortex and lower motor neurons. However, RMT measures cannot identify what structures along this pathway are responsible for changes in excitability.

Single-pulse paradigms are also used to quantify the EMG motor evoked potential itself. MEP measures have a similar drawback to RMT for the assessment of cortical networks in that the MEP may be affected by changes at any point along the cortico-muscular pathway. In MS, smaller amplitudes and longer latencies of MEP peaks reflect slowed nerve conduction along demyelinated axons. Decreased MEP amplitude has been reported in patients (Perretti et al. 2004) and specifically in patients with SPMS (Conte et al. 2009; Vucic et al. 2012), perhaps due to loss of axons at a more advanced disease stage.

MEPs have also been utilized as relative measures to describe within-individual motor changes as a result of exercise or TMS pulses. In healthy subjects, the MEP amplitude increases relative to the individual's baseline after a non-fatiguing voluntary movement (post-exercise facilitation) and decreases after a fatiguing exercise (post-exercise depression) (Brasil-Neto et al. 1993). TMS evidence may indicate an impairment of inhibitory networks in MS patients, specifically in those with fatigue. PED after a non-fatiguing movement, rather than the PEF expected from healthy controls, has been reported in MS patients with fatigue (Russo et al. 2015). However, the same study also found PEF in other non-fatigued patients. In contrast, Perretti et al. (2004) found PEF in both patients and controls, with no differences between patients with and without fatigue. Interestingly, the study also found PED after muscle fatigue in controls but not in patients, suggesting an inhibitory failure in MS.

MEP changes are also good markers for TMS-induced cortical facilitation or inhibition through paired-pulse paradigms. In paired-pulse experiments, a "conditioning" pulse is administered at a specified length of time before a "test" pulse. The length of time between the conditioning and test pulses determines whether the stimulus is inhibitory or facilitatory. Paired-pulse TMS paradigms point to a cortical network disinhibition in certain groups with MS. Decreased intercortical inhibition (ICI) has been shown in

patients with SPMS, fatigue, or active relapses (Vucic et al. 2012; Conte et al. 2009; Liepert et al. 2005; Caramia et al. 2004). Furthermore, increased intercortical facilitation (ICF) has been reported in patients with SPMS (Vucic et al. 2012).

Other TMS-based measures in MS include cortical silent period (cSP) and TMS evoked potentials (TEP). The cSP refers to the break in voluntary muscle contraction after TMS stimulation to the muscle's associated motor area. Caramia et al. (2004) report a shortened cSP during RRMS relapse and lengthened cSP during RRMS remission, suggesting disinhibition during MS relapse. TEP are the EEG potentials evoked by TMS stimulation. Zipser et al. (2018) found a higher amplitude in one peak of the TEP (N280) in MS patients in comparison to controls and did not observe differences in TEP latencies or interhemispheric signal processing.

Repetitive TMS (RTMS) may be used to alter cortical excitability with therapeutic benefit, as in treatments for depression (McClintock et al. 2018). If cortical excitability dysfunction underlies certain symptoms of MS, then modulating cortical excitability with TMS could potentially alleviate these symptoms. RTMS treatment was associated with several improved measures of gait in a case study of RRMS (Burhan et al. 2015). TMS has also been reported to improve spasticity using intermittent theta burst stimulation (iTBS) (Mori et al. 2010; 2011). Additional work is needed to determine whether RTMS could be used to improve cognitive outcomes in MS.

EEG and MEG

Electroencephalography (EEG) and magnetoencephalography (MEG) are neuroimaging techniques measuring the electrical or magnetic currents produced by mainly cortical pyramidal neurons. Unlike MRI, they are direct measures of this neural activity. These methods also have the advantage of excellent temporal resolution (on the order of milliseconds) when compared to blood flow dependent MRI measures. Additionally, mathematical source analysis methods provide good spatial resolution and the ability to correlate specific structures and networks with brain electrical activity, which is not possible using traditional MRI scans. EEG, in particular, is an attractive option for longitudinal studies and clinical trials given its lower cost and ability to be used in ambulatory paradigms compared to MEG. Additionally, EEG can be used with participants who cannot remain still or supine for long periods of time, as would be required for an MRI. EEG's adaptability and cost make it a good choice for repetitive measurements, such

as in a clinical trial. Many EEG and MEG markers of MS presence, symptom status, or cognitive impairment have been proposed and are summarized below.

Oscillatory band power

Raw EEG and MEG signals exist in the time domain. Transformation into the time-frequency domain allows for investigation of the power of the EEG or MEG signal within frequency bands at specific time points. Multiple sclerosis may result in changes in power within frequency bands.

Increased delta band power has been reported in patients with cognitive impairment compared to both non-impaired patients and controls (Leocani 2000). A lower frequency of peak gamma power was also found in patients with cognitive impairment relative to cognitively preserved patients and controls (Arrondo et al. 2009).

Event-related synchronization and desynchronization

Event related synchronization and desynchronization (ERS and ERD) are other potential targets for biomarker development. Decreased ERS was reported in both fatigued and non-fatigued patients in the beta band (Leocani et al. 2001). Increased ERD was reported in the alpha and beta bands in patients with MS fatigue (Leocani et al. 2001). As ERS and ERD are typically seen as markers of network deactivation and activation, respectively, these results seem to indicate an overall increase in network activation in MS fatigue.

Functional connectivity

Oscillatory changes may also be tracked through measures of functional connectivity. Functional connectivity is assessed by computing measures like coherence, synchronization likelihood (SL), phase-locking value (PLV), or phase lag index (PLI) between pairs of signals from different sensors or sources.

In the theta band, Leocani et al. (2000) reported decreased coherence between interhemispheric pairs and antero-posterior neighbors in patients with cognitive impairment. In the alpha band, increased functional connectivity (coherence) has been reported in patients with MS (Buyukturkoglu et al. 2017; Cogliati Dezza et al. 2015). Interhemispheric coherence was also higher when recruiting the left hemisphere than when recruiting the right, and this effect was correlated with fatigue (Cogliati Dezza et al. 2015). However, other studies report decreased alpha band functional connectivity in cognitively impaired participants with MS (Leocani 2000).

Functional connectivity may also be altered in the beta band. Increases in PLI have been found in the DMN and temporo-parietal regions, and these increases correlated with increased disability scores and more highly impaired cognition

Like results from studies on band power, results from functional connectivity (FC) measures provide an ambiguous picture of changes in MS. While decreases in functional connectivity would align with the view of MS as a disconnection syndrome, evidence for both increased and decreased functional connectivity has been found in most frequency bands. It is possible that these differences can be explained by differences in choice of parameter used to define functional connectivity. However, conflicting results can be seen using the same parameter; for example, the observations of both increased EEG coherence across all frequency bands (Buyukturkoglu et al. 2017) and no change in EEG coherence in any band (Lenne et al. 2013). The relatively small number of studies on non-MRI functional connectivity precludes subdivision of studies by factors like neurophysiological method, parameter, or patient group, so additional research is needed to establish the effect of these factors.

Network graphs

Graph theory has been applied to the study of human brain networks with the proposal of a "connectome", or connectivity matrix for the human brain, as a conceptual framework for the study of healthy and diseased human brain networks (Sporns et al. 2005). Similar approaches have been used to identify network changes in neurodegenerative diseases such as MS. A graph is a mathematical structure representing the relationships among groups of points. In relation to EEG data, sensors or sources may be thought of as the points, or nodes, of the graph, and properties that can be calculated between pairs of nodes (e.g. coherence or phase-lag) give weight to the edges connecting these nodes. Edges may be non-directed or directed, as in the case of causal relationships. Graphs may also be binarized (a connection is either present or absent) by selecting a cut off value for the edge weights to create a graph representation of the organization of the network.

Overall network organizations are often described as being regular or random based on network features like average path length and clustering. Path length refers to the "distance" between two points in the graph, measured as the smallest number of edges between the points. Several measures are used to describe clustering, a measure

reflecting the relative presence of hub nodes, or nodes with a high number of connections to other nodes ("high degree"). Regular networks are characterized by a longer path length and more clustering, while random networks have shorter path lengths and less clustering.

Human brain networks (and indeed many biological systems) tend to display a small-world network structure characterized by high clustering and low average path length. The prevalence of this configuration in healthy systems suggests that it may represent an optimally efficient balance between regular and random network configurations. Loss of network nodes or edges through MS lesions may therefore result in disrupted network efficiency. It is currently unclear whether this loss of efficiency comes in the form of a shift in network organization toward regularity or randomness. However, it is possible that the specific location of lesions in the network impacts the nature of the network disruption.

Some of the variability in these results may be caused by the bias introduced using experimenter-defined cut-offs to define edge presence or absence. One potential solution to this methodological bias may come from the use of minimum spanning trees (MST). An MST is a spanning subgraph of the original network graph created starting with the minimum weight edge of the original graph. Subsequent lowest weight edges (that do not produce loops) are added in order until all nodes have been connected to produce a "backbone" of the original graph. MSTs may be a better network representation than conventional graphs when comparing networks that vary in size, density, or other characteristics while remaining as sensitive to changes in network topology as conventional graphs (Tewarie et al. 2014). At one extreme, an MST may be a star: a central node surrounded by dead-end "leaf" nodes with a minimal diameter (the highest number of edges between any two points normalized for the total number of edges). At the other extreme, an MST could be a straight path with no leaves and maximal diameter. The high clustering of regular network graphs is likely to produce more star-like MSTs with many leaves and low diameter, and the low clustering in a random network is likely to produce a more path-like MST with few leaves and high diameter. Network reorganization in MS is not uniform across frequency bands, with some bands showing increased regularity and others showing increased randomness. Also, studies claim

conflicting directions of changes within some frequency bands. Additional research will be needed to resolve these discrepancies.

In addition to identifying increases or decreases in the presence of hubs through measures of clustering, network analysis may be used to locate these hubs. Hardmeier et al. (2012) plotted the spatial distribution of a measure of node centrality to visualize the location of network hubs in patients with MS and healthy controls. In relation to the healthy controls, patients had increased node centrality in parietal regions and decreased node centrality in temporal regions in the delta, theta, alpha and beta bands. The level of decrease in temporal centrality was positively correlated with impaired cognition. Gamma band results showed decreased centrality for network nodes in the right parietal lobe. Localization of network results in this way could be a useful way of relating cognitive outcomes to underlying brain dysfunction.

Changes in network organization may be associated with symptoms like cognition and fatigue. Cognitive impairment has been associated with both random (Tewarie et al. 2015; 2014), and regular (Schoonheim et al. 2013) network reorganizations. A shift toward a random network organization was also correlated with worse clinical status and atrophy (Tewarie et al. 2015). In contrast, Vecchio et al. (2017) reported a positive correlation between fatigue severity and small-world index. This observation seems to contradict the hypothesis that regularization and randomization represent a shift away from the optimal-efficiency of a small-world network. Future work should aim to clarify whether the loss of small-world organization could be a compensatory change in patients with lower fatigue, cognitive impairment, or physical disability severity.

Additionally, the complexity of graph measures may make them especially suitable for use in classification approaches. MRI structural connectivity data has been used to train a classifier to successfully distinguish controls and patients with clinically isolated syndrome (CIS), RRMS, SPMS, and PPMS (Marzullo et al. 2019). Likewise, k-nearest neighbour classification (kNN) performed on MEG graph data was able to identify patients from controls (Hadriche et al. 2019). The success of these methods suggests that graph analysis has the potential to provide meaningful markers of cognitive impairment.

Microstate

Microstates are brief, quasi-stable topographies of EEG activity that are altered in several neurological and psychiatric conditions, including MS (Michel and Koenig 2018). A review of the relevant literature is presented in Chapter 8.

ERP

Event-related potentials (ERPs) are time-locked EEG responses to repetitive stimuli. These responses are generally too small to be observed over the background of random EEG fluctuations ("noise") during any one stimulus presentation. However, averaging the responses to many stimulus presentations increases the signal to noise ratio, revealing the time-locked brain response, or ERP. The number of stimulus presentations, or "trials", needed to obtain an ERP will depend on the size and stability of the ERP. Stimuli that produce higher-amplitude or more consistent ERPs will need to be repeated fewer times than stimuli that produce lower-amplitude or more variable ERPs do. A wide variety of stimuli are used to produce such ERPs, and particular peaks ("components") of these response waveforms are well-documented to reflect distinct neural processes. Changes in the height or speed of these peaks are taken to reflect changes in these neural processes, for example, due to a disease or intervention.

MMN

One common ERP in cognitive research is the mismatch negativity (MMN): a negative waveform produced when responses to a novel stimulus are subtracted from responses to a habituated stimulus (Näätänen and Michie 1979). It has been used as an index of the functioning of early change detection processes across a number of neurodegenerative conditions (Raggi et al. 2008; Brønnick et al. 2010; Papadaniil et al. 2016; Beste et al. 2008). Limited research has been conducted on the MMN in MS. Only one study has reported alterations in the MMN in MS compared to controls (Jung et al. 2006). However, the MMN may show associations with clinical scores even when it does not distinguish people with MS from controls (Santos et al. 2006; Bissonnette et al. 2023). Additional information about the MMN can be found in Chapter 7.

P2 and N2

The P2 and N2 are other common early cognitive ERP components that may reflect change detection and target monitoring (Luck and Hillyard 1994; Freunberger et al. 2007). In MS, studies generally show longer latencies (Whelan, Lonergan, Kiiski, Nolan, Kinsella,

Bramham, et al. 2010; Collins et al. 1978) and smaller amplitudes (Vázquez-Marrufo et al. 2008; Jung et al. 2006) of the P2 and N2 peaks. These components may also be responsive to cognitive training, with increased amplitudes and faster latencies seen after a 20-session cognitive training program (Covey et al. 2018; Turtola and Covey 2021). This suggests that these markers could be used to track treatment response to cognitive rehabilitation or other interventions.

P3

The P3 (or P300) is one of the most studied ERP components and reflects attention and decision processes. The latency and amplitude of P3 components may therefore be a useful way of indexing impairment in attentional networks in patients with MS. The waveform is typically evoked using visual or auditory "oddball" paradigms and can be divided into P3a and P3b components representing responses to novel and expected non-target stimuli, respectively (Polich 2007).

Findings differ regarding the presence and nature of P3 changes in people with multiple sclerosis. In general, P3 latency appears to be higher in patients compared to controls (Gonzalez-Rosa et al. 2006; Vázquez-Marrufo et al. 2008; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al. 2010; Sundgren, VV, et al. 2015; Gonzalez-Rosa et al. 2011). However, this result may vary with choice of paradigm and subcomponent. For example, Whelan et al. (2010) elicited the P3 using auditory frequency and visual size oddball tasks and reported a slower patient latency for the auditory task only. However, in a later study of P3 subcomponents, the same group saw an increase in P3a latency in patients for both auditory and visual conditions (Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al. 2010). The P3a latency in the visual condition differed between patients with RRMS and SPMS, with longer latencies for RRMS patients frontally and for SPMS patients parietally. In contrast to these studies using auditory frequency oddball tasks, a study using auditory duration oddball stimuli observed a shorter P3a latency in patients (Jung et al. 2006), suggesting that attentional networks in patients may respond differently to different stimulus features.

Changes in the amplitude of the P3 in patients with MS are less well-characterized than are changes in latency. Evidence has been found for both increases and decreases in P3 amplitude in patients with MS. Other studies have found no differences between patients and controls. Like P3 latency, P3 amplitude results may be affected by the stimulus type.

For instance, Migliore et al. (2018) found a higher amplitude P3 in patients in response to affective images and no difference between patient and controls in response to neutral images. Likewise, Sundgren et al. (2015) and Whelan et al. (2010) found no difference in P3 amplitude between patients and controls in an auditory condition and did find differences in a visual condition. However, these studies disagree on the direction of the differences. A decreased P3 amplitude may also be apparent over time, with patients displaying more of a decrease in visual task P3 than controls over 12 months (Kiiski, Reilly, et al. 2011).

These conflicting P3 amplitude findings may be underpinned by differing effects of P3a and P3b subcomponents. Amplitude changes in these subcomponents are incompletely documented in patients. Some evidence suggests that there is no difference between patients with MS and controls in P3a (Sailer et al. 2001; López-Góngora et al. 2015) or P3b amplitude (Azcárraga-Guirola et al. 2017; Sailer et al. 2001; López-Góngora et al. 2015). Other studies suggest decreases in these amplitudes, for example, in P3a as approximated by a decrease in the "area" of the component (Jung et al. 2006) and in P3b as measured over a year (Kiiski, Reilly, et al. 2011). A decrease in P3b activity in patients with MS is also evidenced by the finding of smaller event-related theta power increases in patients (Kiiski et al. 2012).

In addition to showing differences between patients and controls, the P3 and its components may also differentiate subgroups of patients. For example, the latency of a visual P3a was found to be slowed over different regions in RRMS and SPMS (Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al. 2010). RRMS and SPMS patients could also be distinguished by a combined ERP-MRI model developed by Kimiskidis et al. (2016). Additionally, the amplitude of an auditory P3b was found to differ between PPMS and SPMS patients (Kiiski, Whelan, et al. 2011). Further research is needed to confirm these findings. If identified, consistent differences in ERP measures between groups of patients could allow for the development of tools to aid the diagnosis and subgrouping of these patients.

The P3 also appears to correlate with cognition in MS. Several studies have found correlations between P3 component characteristics and PASAT score or other measures of cognition in patients with MS. For example, auditory P3 latency was found to correlate with scores on the PASAT and a test of verbal memory (Whelan, Lonergan, Kiiski, Nolan,

Kinsella, Bramham, et al. 2010; Kimiskidis et al. 2016). Visual P3 amplitude was found to correlate with a global composite cognition score across patients and controls (Sundgren, Wahlin, et al. 2015). Furthermore, the change in PASAT score over 12 months was found to correlate with the change in visual and auditory P3a amplitude on an individual level, despite no significant changes in group-level PASAT scores over that time (Kiiski, Reilly, et al. 2011). This finding, taken together with the finding that P3 measures were more correlated with cognitive scores in patients than in controls (Sundgren, Nikulin, et al. 2015), suggests that the P3 may be a more useful indicator of cognitive function among patients than between patients and controls.

Biomarkers of cognitive impairment in ALS

A brief overview of fluid and imaging biomarkers for cognitive impairment in ALS is presented here. This is not intended to be a comprehensive review of the literature, but rather a summary of some key points to facilitate discussion in the context of multiple sclerosis. Like in MS, fluid, radiological, and electrophysiological biomarkers of cognitive impairment presence and prognosis have been proposed.

Fluid

As in MS, fluid biomarkers such as neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) have been studied in the blood and CSF of people with ALS. A recent meta-analysis shows that levels of NfL in the CSF are elevated in people with ALS (Verde et al. 2024; Escal et al. 2022). NfL levels are also elevated in people with ALS compared to healthy controls (Verde, Milone, Colombo, et al. 2023; Falzone et al. 2022; Escal et al. 2022). However, reports differ as to whether CSF and serum NfL levels are associated with cognitive function (Verde, Milone, Colombo, et al. 2023; Olsson et al. 2019; Illán-Gala et al. 2018). In contrast, increased levels of GFAP, a protein expressed by active astrocytes, appears to reflect decreased cognitive function (Falzone et al. 2022; Verde, Milone, Maranzano, et al. 2023).

Radiological

Structural and functional biomarkers of cognitive dysfunction have also been identified in ALS. However, MRI is not used for routine clinical monitoring for ALS as it is for MS. This means that the drawbacks of MRI use (cost, comfort, temporal resolution) are not

mitigated by the potential for integration into routine practices as would be the case for MS.

Structural and functional changes have been shown in people with ALS cognitive impairment. For example, memory impairment was associated with reduced hypothalamus volume (Michielsen et al. 2024). Systematic reviews support effects of hippocampal and thalamic atrophy and altered connectivity on memory impairment (Mohammadi, Ghaderi, and Fatehi 2024; Mohammadi, Ghaderi, Mohammadi, et al. 2024). Total grey matter volume may also be related to cognitive status (Lehto et al. 2024). However, other studies find no associations between structure or connectivity and cognition (Spinelli et al. 2024).

Positron emission tomography (PET) is an imaging modality used to show metabolism in specific brain regions. Evidence of altered metabolism has been shown in ALS, with decreased metabolism in frontal and temporal regions and increased metabolism in occipital and cerebellar regions accompanying reduced cognitive function (Lehto et al. 2024; Foucher et al. 2024; Canosa et al. 2020).

Electrophysiological

Electrophysiological correlates of ALS-related cognitive decline have also been identified. Much of the electroencephalographic literature in ALS focuses on the P300 and its use in brain-computer interfaces for communication or mobility. However, resting state and task-based EEG measures have also identified markers of domain-specific cognitive dysfunction. EEG results also support the PET observations of hyperactivity in frontal and temporal regions as the disease progresses (McMackin, Dukic, Costello, Pinto-Grau, McManus, et al. 2021).

Decreased performance on composite measures of cognitive status are associated with decreased β-band ERS (McMackin, Dukic, Costello, Pinto-Grau, Keenan, et al. 2021), decreased N2 amplitude (McMackin et al. 2020), and decreased microstate transition probabilities from A → D, C→B, and C→D (Metzger et al. 2024). Impaired language functions have been associated with increased θ-band frontotemporal connectivity (Dukic et al. 2019). Impaired executive function is associated with decreases in error-related negativity amplitude (Seer et al. 2017), P3a amplitude (Lange et al. 2016), and P3 right precuneus power (McMackin et al. 2020), and increases in θ-band frontotemporal

connectivity (Dukic et al. 2019), left primary motor cortex and posterior parietal cortex power (McMackin et al. 2019), and MMN latency (Iyer et al. 2017).

Conclusions

As in ALS, neurophysiological biomarkers of MS presence, subtypes, and progression can be identified using methods such as EEG, MEG, and TMS. Composite measures and network representations of the brain may be especially suited to representing complex and subtle dysfunctions in the brain networks of MS patients. However, non-MRI network studies of MS remain relatively scarce and report variable results. MS network neurophysiology, and in particular network electrophysiology, is an underexplored field with the potential to identify meaningful markers of disease presence and progression. Identification of such markers would substantially benefit clinical practice and trials due to EEG's practicality.

Chapter 3

Aims and Objectives

Chapter summary

This chapter presents the aims and objectives of the research program. The overarching goals of the project are listed in “Aims”. Then, specific steps to achieve these aims are listed in “Objectives” along with brief methodological details and hypotheses.

Aims

Cognitive impairment is a common symptom of both multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). However, routine investigation of cognitive function is generally not conducted in MS due to clinical constraints. Electroencephalography (EEG) has shown promise for quantifying, classifying, and tracking cognitive dysfunction in other neurodegenerative conditions like ALS. Alterations in EEG event-related potentials (ERP) and resting state microstates have been found in ALS, and these changes are associated with cognitive and clinical outcomes. The cognitive impairments seen in ALS show some similarities to the impairments seen in MS. Therefore, this thesis aimed to apply methods used previously in ALS to quantify cognitive impairment in multiple sclerosis, and to compare these impairments to those seen in ALS to understand the degree of disease specificity of the alterations. This overall goal can be divided into four specific aims that are listed below.

Aim 1

Quantify brain activity related to specific cognitive tasks and whole-cortex network activity in MS.

Aim 2

Understand relationships among age, gender, disease severity, EEG measurements, and neuropsychological screening tools in MS.

Aim 3

Determine whether cognitive EEG changes are specific to individual conditions (MS, ALS) and sub-conditions (RRMS, SPMS, PPMS) or are reflective of processes common to multiple neurodegenerative conditions.

Objectives

In service of these aims, a research program with four objectives was constructed. These objectives are described below.

Objective 1

Measure task-based ERP responses in people with MS and evaluate their relationships to demographic and clinical variables

People with ALS and people with MS both show evidence of impaired executive function, which includes processes like attention, working memory, task switching, and response inhibition. These processes have been evaluated in ALS using task-based event-related potential (ERP) EEG measurements like oddball paradigms and the sustained attention to response task (SART) (Iyer et al. 2017; McMackin et al. 2020). Impaired ERPs relative to controls on these tasks are associated with cognitive outcomes in ALS. Therefore, these tasks and ERPs may also capture cortical activity relevant to cognitive function in people with MS.

Approach: Collect data from people with MS and healthy controls during a passive auditory frequency oddball task and the sustained attention to response task (SART). Measure ERP responses to these tasks in MS and compare them among MS subtypes and to healthy controls. Compare features of the ERP response to demographic and neuropsychological screening measures.

Hypothesis: People with MS will show altered ERP responses to the passive auditory frequency oddball and SART paradigms. These alterations will differ between subtypes and correlate meaningfully with demographic characteristics and scores on neuropsychological screening tools.

Objective 2

Measure whole-brain EEG network activity in people with MS and evaluate relationships to demographic and clinical variables

Presentations of cognitive dysfunction, like other symptoms of MS, are highly heterogeneous. Therefore, the specificity of measuring task-based activity at individual electrodes may fail to capture cognitively related cortical changes in people who are affected in atypical processes or locations. Additionally, task-based paradigms can be time

consuming and often require an active cognitive or motor response from participants. Therefore, they can be influenced by levels of cognitive or physical disability, fatigue, and participant motivation. In contrast, resting state EEG (rsEEG) can be recorded in minimal time from participants with high levels of physical or cognitive disability.

Resting state EEG microstates are one method to quantify the activity of brain networks at rest. Network-level analysis may be able to more broadly characterize cognitively related cortical alterations in MS. Alterations to rsEEG microstate parameters have been described in ALS and MS (Metzger et al. 2023; Gschwind et al. 2016; Baldini et al. 2023). However, no studies have evaluated these microstates in people with progressive forms of MS.

Approach: Collect resting state data from people with MS and healthy controls and quantify the activity of microstates during these recordings. Compare microstate properties between people with and without MS as a replication of the literature. Compare microstate properties among subtypes of MS. Correlate these properties with demographic and neuropsychological variables.

Hypothesis: Resting state EEG microstate properties will be altered in MS and among MS subtypes. These alterations will reflect clinically meaningful demographic or neuropsychological features.

Objective 3

Directly compare ERP alterations in MS and ALS using identical methodologies

The cognitive impairments seen in MS and ALS overlap, yet it remains unclear whether these shared changes are caused by shared neurodegenerative processes. Comparing alterations reported in the literature between studies is difficult due to the high degree of paradigm-specificity of these measures. Slight differences in stimulus type, recording equipment, or analysis methods could produce ERP variations, so direct comparison between studies remains difficult.

ERP responses to the passive auditory frequency oddball and SART have been previously studied in ALS by members of the Academic Unit of Neurology (Iyer et al. 2017; McMackin et al. 2020). These analyses were conducted in the same location using the same recording equipment and analysis methods as the MS participant recordings used in this

thesis. Therefore, these datasets represent a unique opportunity to directly compare ERP alterations between neurodegenerative conditions.

Approach: Assemble a joint MS-ALS dataset of ERP responses to the passive auditory frequency oddball and SART implementations used by the Academic Unit of Neurology. Compare ERP measurements between participants with MS, ALS, and healthy controls to understand whether ERP alterations are standard or disease specific.

Hypothesis: ERP alterations will differ between MS and ALS, indicating that cognitive dysfunction in these conditions is related to disease-specific cortical changes, rather than solely the presence of neurodegeneration.

Objective 4

Enable future longitudinal analysis of cognition across MS subtypes

The presence of cognitive impairment in MS is now widely acknowledged, but methods to reliably track or predict dysfunction are still lacking. EEG may be a better tool for longitudinal tracking and prediction of cognitive impairment than MRI than due to its cost, flexibility, and participant comfort. Additionally, EEG may show advantages over neuropsychological testing in biological relevance and reduced practice effects. However, the identification of EEG biomarkers for prediction or progression tracking of cognitive impairment in MS will require repetitive measurement of these signals over time. The variables of interest used in such an analysis should remain stable over time in the absence of cognitive change, so that any changes observed reflect changes to cognition or MS progression rather than variability in the measure. Therefore, this thesis aims to assemble the primary “Time 1” basis of a longitudinal dataset and to evaluate the potential of the EEG methods used here for longitudinal use.

Approach: Collect cognitively related EEG data from a large, representative sample of people with MS who may be willing to complete additional follow-up recordings. Assess the test-retest reliability of ERP measurements to determine which ones will be suitable for use in these follow-up recordings.

Hypothesis: EEG measurements will vary in their test-retest reliability. A selection of measures will show satisfactory reliability for longitudinal use.

Chapter 4

Materials and Methods

Chapter summary

This chapter contains a general discussion of the participants, protocols, and analyses used in this project. Specific information pertaining to individual studies are included in each results chapter.

Experimental design and research plan

The studies included in this thesis center around the individual research questions posed in the previous chapter. In short, the studies aim to identify cognitively relevant EEG changes in multiple sclerosis (MS) and place these in the context of cognitive EEG alterations found in ALS.

Three cross-sectional studies (Chapter 6-Chapter 8) were planned to understand ERP and EEG microstate alterations in MS. A comparative study of ERPs in MS and ALS was planned to understand commonalities and differences in EEG-captured cognitive impairment in these conditions (Chapter 9).

The original proposal for this thesis included a longitudinal assessment of ERP measures in MS. However, this part of the project became practically infeasible due to facility restrictions during the COVID-19 pandemic. Instead, the test-retest reliability of these ERP measures was assessed to prepare for future longitudinal study (Chapter 5).

Recruitment and participants

Ethical approval

All studies were carried out with prior ethical approval from the relevant bodies[8] and in accordance with the Declaration of Helsinki. Information leaflets (Appendix D) and procedural information were provided to all study participants before the study visit.

[8] Beaumont Hospital Ethics (Medical Research) Committee –reference: 18/63
St. Vincent's University Hospital Research Ethics Committee –reference: RS19-054
St. James's Hospital/Tallaght University Hospital Joint Research Ethics Committee –reference: 2017-02, Chairman's Action 18

Informed, voluntary consent was obtained from all study participants prior to data collection.

Recruitment process and sources

Participants were recruited to the study through a combination of in-person interactions in neurology clinics and outreach events, online advertisements, and word-of-mouth. The recruitment of a large sample of vulnerable participants (age and/or disability) during a pandemic was a major obstacle to the project and required adaptation of typical recruitment procedures, so a detailed protocol is provided in Appendix B as a resource for researchers facing similar challenges.

MS participant recruitment

Potential participants with MS were approached by study team members, research nurses, or consultants during routine visits to general neurology or MS specialist clinics at Beaumont Hospital, St. Vincent's Hospital, and St. James' Hospital. Interested and eligible participants were contacted by phone or email to confirm eligibility, provide study materials, and schedule EEG visits.

Additional participants were recruited through online advertisements.

ALS participant recruitment

Some ALS datasets were recorded prior to the start of this project and were made available in a pseudo-anonymized format. Additional participants were recruited during this project. All participants were recruited in a similar manner to the process described above: prospective participants with diagnosed ALS were approached during multi-disciplinary ALS clinics at Beaumont Hospital to ascertain interest in research and consent for future contact. Those interested, willing, and able to participate were given more information in a follow-up phone call and were scheduled for an EEG visit if suitable.

Control recruitment

Neurologically healthy control participants were recruited directly through this thesis project and via existing databanks within the Academic Unit of Neurology. Datasets from prior projects were shared in pseudo anonymized form. Control data collected prior to this project was intended to be age-matched to participants with ALS (which generally has an older age of onset than does MS) and therefore was not appropriately age-matched to

our participants with MS. Therefore, an effort was made to recruit younger controls through word-of-mouth and online advertisements.

Inclusion and exclusion criteria

Complete eligibility criteria are provided in Appendix A. All participants were subject to standard EEG exclusion criteria. Controls were excluded for neurological and muscular conditions or first-degree relatives with ALS or MND. Participants with ALS or MS were excluded for any diagnosis of neurological or muscular conditions other than ALS or MS. No participants with both ALS and MS were recruited. Participants with MS were excluded for changes to disease-modifying therapies (DMT) or relapses within the previous 3 months.

In contradiction to typical EEG exclusion criteria, people with MS taking SSRIs and SNRIs were eligible for recruitment, though severe active psychiatric disease remained an exclusion criterion for this group. This was allowed due to the expected high rate of participants with MS taking these medications. An unpublished undergraduate thesis found no effect of SSRI or SNRI medications on the ERP measures used in this thesis (O'Meara 2024).

Demographics

In total, data from 87 people with MS, 74 people with ALS, and 130 healthy controls were included in this thesis. Relevant demographic data about the samples for each study are included in the respective Results chapters. The collection and assembly of a novel MS dataset represents a key output of this thesis project. Therefore, a summary of the demographic features of this dataset is included here (**Table 1**). This sample is generally reflective of the wider MS population in Ireland (O'Connell et al. 2017). Our sample has a slightly higher female to male ratio (approximately 3:1 rather than 2.7:1) and lower depression rates as measured by the HADS-D (approximately 22% compared to 34%). The average age of onset reported here (37 years) is the same as the average age of RRMS onset in Ireland (O'Connell et al. 2017). Anxiety and cognitive impairment screenings were not reported in the reference study.

Table 1. Demographic features of the newly collected Multiple Sclerosis Cognitive EEG dataset.

		n (%)		
n	*overall*	87		
gender	*female*	66 (76%)		
	male	21 (24%)		
subtype	*RRMS*	67 (77%)		
	SPMS	10 (11%)		
	PPMS	9 (10%)		
	missing	1 (1%)		
handedness	*right-handed*	76 (87%)		
	left-handed	8 (9%)		
	ambidextrous	3 (3%)		
medication use	*DMD*	63 (72%)		
	SSRI or SNRI	13 (15%)		
		mean ± st. dev.	**range**	
age and duration	*age*	48.6 ± 12.1	21-72	
	age at onset	36.5 ± 11.1	15-58	
	disease duration	10.68 ± 9.78	0-51	
		mean ± st. dev.	**range**	**# abnormal**
screening scores	*MSNQ (≥ 27 abnormal)*	27.9 ± 13.1	0-58	48
	HADS-A (≥ 8 abnormal)	7.1 ± 4.0	0-18	37
	HADS-D (8 abnormal)	4.9 ± 2.8	0-11	19

Experimental design

Data for this thesis were collected as part of a three-arm study of cognition in multiple sclerosis consisting of 1) questionnaires, 2) a full-battery neuropsychological visit, and 3) the EEG visit. All participants completed phase one (questionnaires) and could choose whether to then complete only phase two, only phase three, or both phase two and phase three. The thesis focuses on the EEG arm of the study, with inclusion of some data from the questionnaire phase.

Questionnaire collection and neuropsychological visit

Participants with MS completed the multiple sclerosis neuropsychological questionnaire (MSNQ) (Benedict et al. 2003) and hospital anxiety and depression scale (HADS) during in-

person recruitment, online Qualtrics recruitment, or during the EEG visit if recruited directly.

The neuropsychological visit phase consisted of a 2-3hr in-person or video call visit with a trained neuropsychologist researcher[9] at Beaumont Hospital. Participants completed a full battery of clinical neuropsychological tests. The tests included in this visit are listed in Appendix F.

Equipment and set-up

All EEG recordings were carried out in the Wellcome-HRB Clinical Research Facility at St. James's Hospital[10]. Recording procedures were the same for each participant group. Experimenters were not blinded due to overlap between the recruitment, consenting, and study visit personnel.

Participants sat on a comfortable, high-backed chair or their own wheelchair in an electrically shielded room approximately 1m in front of a standard computer monitor. Flat Ag-Ag/Cl active EMG electrodes (BioSemi) with a small amount of conductive gel (Signagel, Parker Labs) were attached to cleaned right and left earlobes, right and left mastoids, right and left outer canthi, and above and below the left eye as alternate references and to aid in the detection of blink artefacts.

Participants wore an EASYCAP (GmbH) mesh cap fitted with 128 active pin Ag-Ag/Cl wet electrodes. EEG signals were recorded at 512Hz using a BioSemi ActiveTwo EEG system in Actiview software. Signal offsets (electrode voltage-CMS reference voltage) were kept between ± 25mV throughout.

Experimental blocks

All EEG tasks were recorded in short blocks (2-7min) to minimize movement and monitor participant comfort and safety.

Auditory oddball

Three blocks (~7min each) of a passive auditory frequency oddball task (Iyer et al. 2017) were recorded. Participants watched a silent movie (*The Artist* (Hazanavicius 2011)) in a

[9] Dr. Marta Pinto-Grau; Dr. Orla Strahan; Tara Boyle, Lorna O'Sullivan, Letícia Händel
[10] https://www.sjhcrf.ie/

darkened room while unattended auditory stimuli played through Sennheiser HD650 headphones (Wedemark, Germany). Auditory stimuli were 150ms pure tones of standard (720Hz) or deviant (800Hz) frequencies with 833ms inter-stimulus intervals. Deviant tones were presented at random and accounted for around 10% of the total stimuli.

SART

Four, five-minute blocks of the sustained attention to response task (SART) (Robertson et al. 1997) were delivered as described in McMackin et al. (McMackin et al. 2020). Participants were presented with a series of random single digits and asked to click a standard computer mouse in response to each digit except the digit "3". Digits were presented in light grey (RGB: 250,250,250) on a black background with randomly varied font sizes of 100, 120, 140, 160, or 180pt and randomly varied inter-stimulus intervals of 1120-1220ms.

Participants completed an unrecorded practice block of up to 45 trials with experimenter feedback on the nature of task performance (e.g. "remember to keep the rest of your body still", "click every time you see a number except for the number three"). No feedback was given on the quality of task performance (e.g. "go faster", "you got all of those right"). After the practice block, participants completed four blocks of 252 trials each.

Resting state

Six two-minute blocks of resting state EEG were recorded: three with eyes open (lights on, 6x8cm^2 "X" gaze target) and three with eyes closed (lights off). Participants were instructed to relax their body and let their mind wander. The EEG signal was monitored for wakefulness and movement throughout.

Data storage and protection

Participant data collected as a part of this project is subject to the protections laid out in the General Data Protection Regulations (GDPR). All participants were informed of their rights under GDPR during the informed consent process. All data collection, handling, and storage procedures were carried out in compliance with GDPR. A data protection impact assessment was performed for all research in the Academic Unit of Neurology and was approved by the Data Protection Officer of TCD. Data storage and protection details are provided in Appendix C.

CHAPTER 4

Data processing

These sections provide details on signal pre- and post-processing for the major types of analyses used in this project. Deviations from these methods and information about choices related to statistical analysis are given in the relevant chapters.

Code acknowledgements

Data processing was completed in MATLAB R2016a-R2020a (2020) with additional toolboxes: EEGLAB (v14_1_2) (Delorme and Makeig 2004), ADJUST (v1.1.1) (Mognon et al. 2010), EyeBallGUI (1.0) (Mohr et al. 2017), erplab (7.0.0) (Lopez-Calderon and Luck 2014), Biosig (3.3.0) (Schloegl 2017), and FieldTrip (fieldtrip-20190419) (Oostenveld et al. 2011). Analysis codes were adapted from those written by previous group members.

MMN analysis codes were authored by Michael Broderick[11] with updates from Roisin McMackin[12]. SART ERP codes were created by Roisin McMackin based on MMN analyses written by Michael Broderick. Some ERP plotting steps were written by Etain O'Meara[13], and these are referenced in figure legends when used. Resting state preprocessing was written by Stefan Đukić[14]. Microstate analysis was written by Marjorie Metzger[15].

ERP analysis

Data from the auditory oddball and SART paradigms were analyzed to obtain event-related potentials (ERP), or averaged, time-locked responses to stimuli. A general overview of the data processing steps is given here. Details specific to each analysis are mentioned within the relevant chapters.

Data cleaning

A 0.3Hz dual-pass 5th-order Butterworth high-pass filter was applied bidirectionally (zero-phase) to remove slow drifts due to sweat or electrical drift. A 30Hz (MMN) or 35Hz (SART) dual-pass (zero-phase) 117th order equiripple finite impulse response (FIR) low-pass filter was applied to remove high-frequency artefacts like EMG signals while maintaining a sharp cutoff to avoid distortion of EEG signals in the upper part of the

[11] ORCID: 0000-0001-9765-5537
[12] ORCID: 0000-0002-9223-2241
[13] ORCID: 0009-0007-5581-5011
[14] ORCID: 0000-0001-7867-2876
[15] ORCID: 0009-0007-5463-1931

passband. A slightly higher cutoff frequency had previously been chosen for low-pass filtering data in the SART study to preserve the integrity of higher frequency signals in the passband for spectral or source analyses. This choice was maintained here to ensure compatibility with linked datasets.

Continuous data were manually scanned to mark sections of time points corresponding to muscle tension, cable movement, or other non-stereotyped artefacts using the ERPLAB v7.0.0 (Lopez-Calderon and Luck 2014) and EEGLAB v14.1.2 (Delorme and Makeig 2004) toolboxes. These sections were removed, and data were epoched from 200ms before the stimulus to 600ms (MMN) or 900ms (SART) after the stimulus. Epoched data were submitted to independent component analysis using the ADJUST toolbox v1.1.1 (Mognon et al. 2010). Components corresponding to stereotyped artefacts (eye blinks, horizontal eye movement, line noise, faulty channels) were identified through manual inspection and removed from the data.

Signals were baseline subtracted and referenced to the common average. A common average reference (CAR) was chosen for all electrodes to reduce bias from location-specific variations that could affect single reference electrodes, whether “inert” or active. CAR was deemed appropriate due to the high density and full head coverage of our experimental setup.

ERP feature calculation

ERP waveforms were created for each participant at each electrode by averaging signals across all trials. Signals were referenced to the common average and the average baseline was subtracted from the post-stimulus ERP. For each ERP component of interest, a search window was determined based on prior literature or manual inspection of the plotted waveform. Amplitude values were averaged across this time window to obtain the component’s **mean amplitude**. If the component of interest was positive (e.g. P2), the positive data points within this window were defined as the component. Negative data within the window was selected for negative components (e.g. N2).

If a peak of the correct direction was found within the window, four additional characteristics were calculated based on its size and timing. The **maximal amplitude**, or peak amplitude, of the component was the amplitude value with the largest magnitude measured within the component. The **latency**, or standard latency, of the component was

the time point corresponding to the maximal amplitude. The **area** of the component was the sum of the amplitude values across the window. The timepoint corresponding to the centroid of this area was labelled the **amplitude-weighted latency**.

If no positive data was found within the search window (or negative data for a negative component), then only the mean amplitude was calculated. The remaining component characteristics were set as "NaN" (not a number) to exclude the participant's data from further calculations.

Channel selection

Four electrodes along the central midline (Fz, FCz, Cz, Pz) were chosen for analysis in the ERP studies included here. These electrodes were selected because they are the locations at which the ERPs of interest (MMN, P2, N2, P3) are maximal and typically recorded. The ERP responses at these electrodes represent summed activity throughout the brain and are generated by multiple regions (including the temporal sources expected to show maximal pathology in MS), but are best recorded from the central chain. Additionally, the selection of a common and minimal set of electrodes capable of recording these electrodes was intended to facilitate future translation of this battery to clinical or mobile applications.

Microstate analysis

Resting state data were analyzed to obtain EEG microstates using methods described in Dukic et al. (2019) and Metzger et al. (2023). Detailed explanations of the preprocessing and microstate computation steps are given within Chapter 8.

For each participant, the length of individual instances (**duration**), number of instances (**occurrence**), proportion of the full signal spent in the class (**coverage**), global explained variance (**GEV**), and global field power (**GFP**) were calculated for each microstate class. Additionally, the probability of transition between each pair of microstate classes was calculated for each participant.

Statistical analysis

Pairwise comparisons

Comparisons between two sample data (e.g. microstate properties between participants with MS and healthy controls) were completed using the non-parametric Mann-Whitney

U test (Mann and Whitney 1947a). A non-parametric test was chosen because it does not require the variable being compared to be normally distributed.

ANOVA

Between-group comparisons with covariates were carried out using multi-way analyses of variance (ANOVA). To satisfy the assumptions of this parametric test, the data were subjected to an inverse normal transformation (across all groups) to enforce a normal distribution. First, data were ranked and converted to quantiles. The cumulative distribution function (CDF) of the standard normal distribution was then applied to obtain normalized scores corresponding to the cumulative probabilities represented by the quantiles.

The ANOVA test compares group means by assessing the ratio of variance between groups to variance within a group. The test reveals the presence of an effect but not its location, so it must be followed by pair-wise post-hoc tests between groups or factors to locate the significant effect.

In anticipation of subsequent multiple comparisons, post-hoc testing was conducted using Fisher's Least Significant Difference (LSD) test to avoid "over-correcting" the data and committing Type II errors, or incorrect acceptance of the null hypothesis (false negative). This test is similar to a series of t-tests but uses a pooled standard deviation from all groups instead of from just the two groups being compared (Williams and Abdi 2010).

Correlation measures

Relationships between EEG measures and clinical or demographic features were assessed using Spearman's rank correlation coefficients, a non-parametric test of the strength and direction of the relationship between two monotonically related variables (Spearman 1904). This test was chosen over Pearson's correlation coefficient because it does not assume a linear relationship between the two variables being tested.

The correlation between inverse normal transformed repeated measurements (test-retest reliability, Chapter 5) was assessed using intraclass correlation coefficients. Details of the model used are provided in Chapter 5. Model selection was made according to recommendations in McGraw and Wong (1996) and Koo et al. (2016).

Corrections for multiple comparisons

When conducting a large number of hypothesis tests, the likelihood of rejecting a true null hypothesis (Type I error) increases with increasing numbers of tests. To counteract this phenomenon, the output of groups of hypothesis tests should be subjected to corrective measures to control the level of error. A false-discovery rate (FDR) correction is a method often used when the number of comparisons is high, as is often the case with electrophysiology data. In such cases, methods that control the family-wise error rate (FWER), like the Bonferroni correction (1936), may be too stringent. The FDR was introduced by Benjamini and Hochberg (1995) to control the rate of expected false discoveries at a set level. An update to this method based on the distributions of the p values provides more power (Benjamini et al. 2006). An implementation of this updated "adaptive" approach was used to correct for multiple comparisons throughout this thesis (Nasseroleslami 2018).

Presentation of values

Measured and calculated data values are shown rounded to the appropriate level of precision. For example, EEG measures on a millisecond scale, so values with the unit "second" are rounded to the nearest thousandth place and values with the unit "millisecond" are rounded to the nearest integer.

Statistical values such as correlation coefficients and F-statistics are shown to two decimal points. P-values are rounded to three decimal points in the text unless they are below 0.0005 (rounding to 0.000), in which case they are shown as "$p<0.0005$". Due to the nature of FDR correction, p-values are shown in their uncorrected form, unless otherwise indicated.

Chapter 5

Results: Test-Retest Reliability

The sustained attention to response task elicits highly reliable ERPs

Chapter summary

This chapter presents a test-retest reliability analysis of the ERP measurements used in the thesis. This is the first reported analysis of the reliability of EEG components during the sustained attention to response task (SART). ERPs elicited during the SART are shown to be highly reliable upon repeat testing, while ERPs elicited during a passive auditory oddball are shown to be less stable over time. The implications of these results for future longitudinal applications are discussed.

Introduction

Electroencephalography (EEG) is a safe, well-tolerated method for investigating fast cortical activity. The cost, portability, and flexibility of EEG recording make EEG a good choice for longitudinal research, including the measurement of cognition as part of clinical trials. ERPs that change over time in accordance with changes to cognitive impairment could be used as biomarkers of cognitive impairment progression. However, it is important to establish whether longitudinal changes to these ERPs reflect changes in cognitive neural activity or random variation in the measure. If an ERP is highly variable when measured repeatedly, then changes in the ERP due to changes in cognitive processes may be hidden. Therefore, it is important to use ERP biomarkers that produce markers that are stable over repeat testing in the absence of cognitive change. If a measurement shows a high degree of stability upon repeat testing (high test-retest reliability), then observed changes in these markers can be interpreted as indicative of cognitive or neurological change because of disease progression or treatment response.

This study aims to evaluate the reliability of the ERP markers of cognition described in the methodology section. This thesis project does not include longitudinal analyses. However, metrics with good test-retest reliability will allow this work to be extended longitudinally and supports the work of others using these methods and analyses longitudinally.

The reliability of ERPs elicited by the sustained attention to response task (SART) (Robertson et al. 1997) has not previously been studied. However, components like the

P2, N2, and P3 produced by other tasks have been reported to have good reliability in related tasks (Hämmerer et al. 2013; Brunner et al. 2013).

In contrast, the reliability of the mismatch negativity (MMN) has been the subject of extensive cognitive and sensory research. Reports of the MMN's reliability vary, which may be partially attributable to the wide variety of tasks used to produce it. In this study, we used a two-stimulus passive auditory frequency oddball task in which participants watched a silent movie while unattended auditory stimuli of two different pitches (one frequent and the other infrequent) played through headphones.

A similarly passive task using frequency deviations in complex tones was studied by Tervaniemi et al. (1999), who found poor to moderate Pearson test-retest correlations of 0.41 for the MMN's latency and 0.53 for its amplitude over inter-test intervals of 1-27 days. Escera et al. (1996) found slightly higher Pearson coefficients for the passive frequency deviation MMN's latency at Fz (r=0.582) and amplitude at F4 and C3 (r=0.598, r=0.657) over a shorter inter-test interval of 2 hours.

However, the use of Pearson's correlations to assess test-retest reliability may be insufficient to assess reliability where the goal is to assess changes on an individual, rather than group, level. The Pearson test assesses the direction and strength of the relationship between sets of paired data. This means that a high Pearson's r in an MMN amplitude test-retest experiment would indicate that participants with higher amplitudes at the first test tended to have higher amplitudes at the second test, and vice versa. This correlation would be unchanged even if the amplitudes on the second day were each 10μV higher than on the first day; high amplitude producers remain high amplitude producers, and low amplitude producers remain low amplitude producers. (This property of the method is what allows it to be used to compare paired data of different modalities, for example, patients' age and blood pressure).

This way of looking at reliability may be sufficient if we aim to compare groups of participants at multiple time points. If, for example, we are aiming to compare MMN amplitudes between people with RRMS and SPMS at multiple time points, we would observe an effect if one group's MMN amplitudes are consistently higher than the other, regardless of the specific values of these amplitudes.

However, if we would like to assess change in an individual over time or compare experimental groups to a control group that is only recorded once at baseline, the values themselves of these measurements become important. In this case, the intraclass correlation coefficient (ICC) (Fisher 1915) can be used to assess the "absolute agreement" of values over time.

Using this method to evaluate test-retest reliability, Wang et al. (2021) observed good reliability (ICC= 0.722) for a frequency oddball across 3-4 time points. Localizing the dipole sources of a passive frequency deviation MMN obtained in the background during a distractor task also produced good ICC reliabilities (0.78) (Frodl-Bauch et al. 1997).

This study aims to determine the ICC test-retest reliability of the ERPs obtained by the methods used in this thesis to assess whether these markers are suitable for future longitudinal research.

Methods

Ethical approval

This study was covered by approvals from the Beaumont Hospital Ethics (Medical Research) Committee (REC reference: 18/63), the St. Vincent's University Hospital Research Ethics Committee (REC reference: RS19-054), and the St. James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (REC reference: 2017-02 Chairman's Action 18). Informed, voluntary consent was obtained from all study participants.

Participants

Recruitment

Neurologically healthy young adults (n=11) were recruited via email circulation and word of mouth within the Academic Unit of Neurology and associated teams. Potential participants were not approached directly to help ensure that the decision to participate was voluntary and minimally influenced by interpersonal dynamics. The indirect approach also allowed potential participants to self-assess their eligibility against our criteria before expressing their interest. This minimized the risk of unnecessary disclosure of medical, psychiatric, or medicinal information in the case of ineligibility.

Exclusion criteria

The study used the standard healthy control exclusion criteria in use by the lab to maximize applicability to our experimental data. These criteria include any diagnosis of neurological, psychological, or muscular conditions, use of CNS-acting medications, history of seizures, history of head trauma causing a diagnosed concussion or loss of consciousness, metallic implants in the head, and current pregnancy or breastfeeding (Appendix A).

Participants not meeting these exclusion criteria and able and willing to attend the Clinical Research Facility at St. James' Hospital, Dublin on two consecutive days were invited to participate.

Demographics

Eleven participants were recruited, and one participant was excluded following the Day 1 recording due to an illness preventing attendance on Day 2. The remaining participants (n=10) had an average age of 25.9 ± 2.5 years and were evenly balanced male and female (n=5 each). Half of the participants attended during the morning on both days and the other half attended during the afternoon on both days.

Characteristics of the final sample are presented in **Table 2**.

Table 2. Demographics of the sample

n	10
mean age (years) [SD]	25.9 [2.5]
age range (years)	23-31
Gender (f/m)	5/5
Handedness (R/L)	9/1
Appointment time (AM/PM)	5/5

Data acquisition

Participants were seated in a comfortable, high-backed chair placed approximately 1m in front of a standard computer monitor in an electrically shielded room. 128-channel EEG (BioSemi ActiveTwo) with 8 facial EMG electrodes was recorded during four different experimental blocks (discussed in detail in the Materials and Methods chapter): 1) a

passive auditory-oddball paradigm (Iyer et al. 2017), 2) the sustained attention to response task (Robertson et al. 1997; McMackin et al. 2020), 3) resting blocks with eyes open and closed, and 4) the MotorMarker paradigm[16]. The auditory oddball and sustained attention to response tasks were selected for the analysis described in this chapter. Three participants did not complete the MotorMarker block due to the unavailability of a trained experimenter for that paradigm. As this block came at the end of the four tasks, omission of the task would not cause differences in performance in the prior blocks. The MotorMarker recording block lasted generally between 30-60min and represents a negligible exertion for the young, healthy participants included in this study, so we furthermore would not expect inclusion or omission of this block on Day 1 to influence physical or mental performance during the other blocks on Day 2.

After completing these four recording blocks, participants were offered the use of a shower within the facility to wash their hair or given the option to wash their hair at home. In both cases, participants were instructed to return the following day with clean and dry hair to avoid introducing a new source of noise or bridging on the second day.

The start time for both days was kept consistent within a single participant to limit the potential effects of circadian variability in these measures. Participants were evenly divided across morning and afternoon sessions. The experimenters were also kept consistent between days.

Data pre-processing

Data were pre-processed according to the general steps described in the Materials and Methods chapter. Specifics of the implementations used here are provided below. Where a step or setting is not specified, this step is as described in the Materials and Methods chapter. Untrimmed means were used during averaging steps for this analysis.

ERP calculation

Auditory oddball recordings were epoched between 200ms pre-stimulus and 600ms post-stimulus. Average responses to standard and deviant trials were obtained for each

[16] The MotorMarker experimental paradigm is a series of pincer grip tasks requiring sustained, intermittent, or modulated force. The paradigm and its analysis are described in detail in Bista, S. (2024) *Network Analysis in Amyotrophic Lateral Sclerosis during Voluntary Motor Task: Neurophysiological Biomarkers of Disrupted Cortical Connections*. PhD thesis. Trinity College Dublin.

participant at each day and channel and subtracted to obtain the mismatch negativity (MMN). Visual inspection of the plotted difference waveforms suggested 200-400ms post-stimulus as the appropriate MMN time window for this cohort (**Figure 1**). The maximal negative deflection during this window was taken to be the MMN peak.

SART recordings were epoched between 200ms and 900ms post-stimulus. Responses to "Go" and "NoGo" trials were averaged separately within each participant at each channel. For each trial type, the P2, N2, and P3 components were selected from windows 100-300ms, 150-350ms and 350-550ms post-stimulus, respectively.

Waveform feature calculation

The amplitude and latency of the peak, mean amplitude across the component, amplitude-weighted latency, and area under the component were calculated for each ERP component (auditory oddball: MMN; SART: P2, N2, P3) at four channels of interest along the central midline: Fz, FCz, Cz, and Pz. An inverse normal transformation was applied to the data for each feature across days to ensure a normal distribution prior to statistical analysis with parametric tests.

Statistical analysis

Intraclass correlation coefficients (ICC) between Day 1 and Day 2 measurements were calculated for each waveform feature and channel pair using the MATLAB implementation by Arash Salarian (2021) based on the work of McGraw et al. (1996). A two-way mixed-effects absolute agreement model[17] was selected based on the recommendations of Koo et al. (2016).

ICC values are generally interpreted in the context of ranges, with ICCs less than 0.50 indicating poor reliability, between 0.50 and 0.75 indicating moderate reliability, between 0.75 and 0.90 indicating good reliability, and greater than 0.90 indicating excellent reliability (Koo and Li 2016).

Hypothesis tests were conducted for each ICC value with the null hypothesis that the true test-retest reliability of the measure does not differ from zero, or in other words, that the

[17] $\frac{MSR-MSE}{MSR+\frac{MSC-MSE}{n}}$

measure has no reliability (H_0: ICC=0). P-values for these tests were corrected separately for auditory oddball and SART analyses using a 5% adaptive false discovery rate correction (Benjamini et al. 2006). Uncorrected p-values and their significance after adaptive FDR correction are reported here. The values of (1-ICC) are also provided, representing the proportion of the variance due to all sources of measurement error. ERP features with lower levels of measurement error can be interpreted to have higher retest reliability.

Results

MMN amplitude shows good test-retest reliability at Cz

MMN responses were observed at electrodes Fz, FCz, and Cz on Day 1 and Day 2 (**Figure 1**). No MMN was visible at Pz on either day. ICCs for each component feature and channel are shown in **Table 3**. After adaptive FDR correction, only the amplitude of the peak at Cz showed statistically significant reliability (p=0.002) (**Table 3**). The observed ICC of 0.87 for this measurement indicates good reliability according to conventional guidelines (Koo and Li 2016).

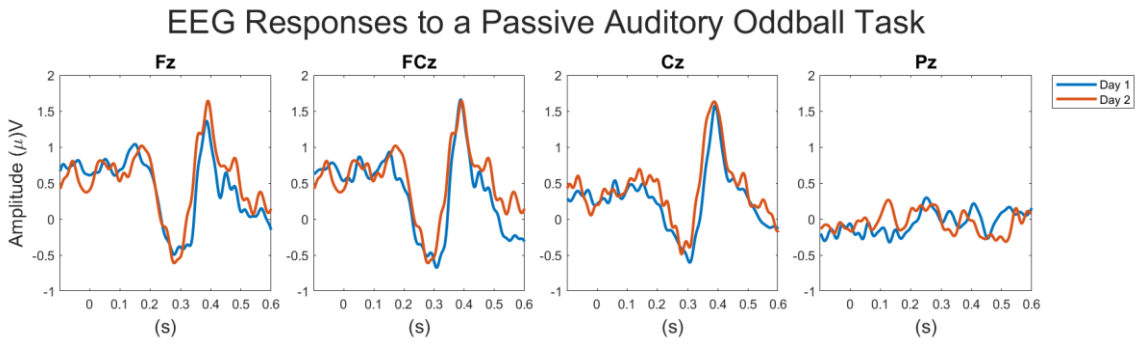


***Figure 1. Mismatch negativity event-related responses**. The waveform is the subtraction of the responses to the deviant stimuli from the responses to the standard stimuli. Day 1 subtracted responses are shown in blue, and Day 2 subtracted responses are shown in red. The peak of the mismatch negativity (MMN) component can be observed between 0.2 and 0.4s (200-400ms) post-stimulus. No clear evoked responses are observed at Pz.*

Table 3. ICCs for MMN components along central midline. *Intraclass correlation coefficient (ICC) and measurement error (1-ICC) values are shown for five waveform features at four channels of interest. The lower and upper bounds of the 95% confidence interval ("LB" and "UB") for the ICC are shown, as well as the F-statistic, degrees of freedom ("df1", "df2"), and p-value for the hypothesis test on the significance of the calculated reliability. P-values that are significant after adaptive FDR correction are shown in bold.*

		ICC	1-ICC	LB	UB	F	df1	df2	p
Fz	Amplitude of peak	0.83	0.17	0.17	0.96	8.86	9	4.98	0.014
	Mean amplitude	0.31	0.69	-0.89	0.81	1.57	9	9.72	0.250
	Latency of peak	0.38	0.62	-0.65	0.82	1.86	9	8.38	0.193
	Mean Latency	0.69	0.31	-0.20	0.92	4.55	9	5.34	0.049
	Area under component	0.62	0.38	-0.31	0.90	3.45	9	6.17	0.070
FCz	Amplitude of peak	0.68	0.32	-0.26	0.92	4.67	9	4.69	0.058
	Mean amplitude	0.24	0.76	-0.67	0.76	1.50	9	8.71	0.281
	Latency of peak	-0.14	1.14	-1.24	0.63	0.79	9	3.24	0.653
	Mean Latency	-0.55	1.55	-12.05	0.70	0.62	9	2.13	0.747
	Area under component	0.24	0.76	-0.49	0.75	1.67	9	6.45	0.266
Cz	Amplitude of peak	**0.87**	**0.13**	**0.48**	**0.97**	**8.69**	**8**	**8.50**	**0.002**
	Mean amplitude	0.55	0.45	-0.46	0.88	2.45	9	9.46	0.094
	Latency of peak	0.68	0.32	-0.22	0.92	3.34	8	8.73	0.048
	Mean Latency	0.66	0.34	-0.66	0.92	2.74	8	8.34	0.084
	Area under component	0.77	0.23	-0.10	0.95	6.79	8	4.32	0.035
Pz	Amplitude of peak	0.31	0.69	-6.54	0.89	1.39	6	6.10	0.348
	Mean amplitude	0.50	0.50	-0.87	0.87	2.02	9	9.91	0.145
	Latency of peak	-0.52	1.52	48.85	0.78	0.70	6	5.87	0.660
	Mean Latency	0.80	0.20	-0.15	0.96	4.65	6	6.73	0.034
	Area under component	-0.24	1.24	-75.91	0.82	0.83	6	5.90	0.586

SART ERPs show excellent reliability across features and channels

Event-related responses to the SART were observed across all four channels of interest during "Go" and "No-Go" trials on both recording days (**Figure 2**). Day 1 and 2 waveforms show a high degree of morphological similarity, with the same components apparent across days for each trial-channel pair. As expected, larger amplitude responses are observed to "No-Go" trials than to "Go" trials. This effect is particularly apparent at electrodes FCz and Cz.

ERP measurements recorded during the SART were highly reliable. Significant ICC values ranged from 0.68 to 1.0 (**Table 4**). Of the 120 ICC values calculated (5 features x 3 components x 4 channels = 120 measurements), 109 demonstrated significant reliability. Of these 110 measures, 66 showed excellent reliability (ICC ≥ 0.90), 35 showed good reliability (0.75 ≤ ICC ≤ 0.90), and 9 showed acceptable reliability (0.50 ≤ ICC ≤ 0.75). No significant ICC values had a reliability rating of poor (ICC < 0.05).

Measures with insignificant reliability were the P2 "No-Go" peak amplitude and area at Cz and Pz and amplitude-weighted latency at Cz, N2 "No-Go" peak and area at Fz and latency, "No-Go" amplitude-weighted latency at Pz, and "Go" amplitude-weighted latency at Cz, and P3 "Go" and "No-Go" latency at FCz and Fz, respectively.

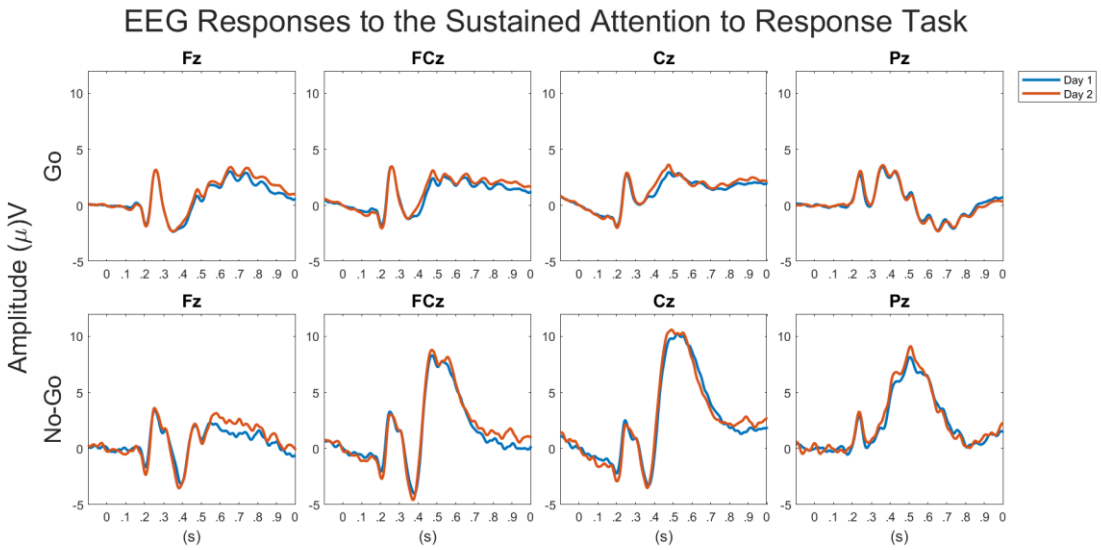


Figure 2. EEG Response to the Sustained Attention to Response Task (SART)*. Averaged EEG response to the sustained attention to response task (SART) across two days. Day 1 responses are shown in blue and Day 2 responses are shown in red. Responses to "Go" trials are shown in the first row and responses to "No-Go" trials are shown in the second row. P2, N2, and P3 components can be observed to varying degrees across trials, channels, and days.*

Table 4. ICCs for SART components along central midline. *Intraclass correlation coefficient (ICC) and 1-ICC values are shown for five waveform features from three ERP components at four channels of interest. P-values that are significant after adaptive FDR correction are shown in bold. Exact p-values are expressed to three decimal places. Exact values are not shown for p-values below 0.0005 and instead are represented as "<0.0005" for readability. Lower and upper bounds, F-statistics, and degrees of freedom are not shown here for legibility but can be found in* ***Supplementary Table 1****.*

			P2			**N2**			**P3**		
			ICC	1-ICC	p	ICC	1-ICC	p	ICC	1-ICC	p
Fz	Amplitude of peak	Go	0.93	0.07	**<0.0005**	0.90	0.10	**0.001**	0.90	0.10	**0.030**
		No-Go	0.79	0.21	**0.024**	0.34	0.66	0.277	0.79	0.21	**0.035**
	Mean amplitude	Go	0.91	0.09	**0.001**	0.93	0.07	**<0.0005**	0.79	0.21	**0.018**
		No-Go	0.69	0.31	**0.043**	0.64	0.36	**0.074**	0.85	0.15	**0.006**
	Latency of peak	Go	0.92	0.08	**0.001**	0.98	0.02	**<0.0005**	0.94	0.06	**0.011**
		No-Go	0.63	0.37	**0.067**	0.94	0.06	**<0.0005**	0.95	0.05	**0.001**
	Mean Latency	Go	0.81	0.19	**0.013**	0.90	0.10	**0.001**	0.93	0.07	**0.013**
		No-Go	0.95	0.05	**<0.0005**	0.81	0.19	**0.016**	0.96	0.04	**0.002**
	Area under component	Go	0.87	0.13	**0.003**	0.89	0.11	**0.003**	0.92	0.08	**0.015**
		No-Go	0.83	0.17	**0.013**	0.16	0.84	0.407	0.75	0.25	**0.051**
FCz	Amplitude of peak	Go	0.96	0.04	**<0.0005**	0.97	0.03	**<0.0005**	0.91	0.09	**0.006**
		No-Go	0.97	0.03	**<0.0005**	0.93	0.07	**0.001**	0.89	0.11	**0.002**
	Mean amplitude	Go	0.98	0.02	**<0.0005**	0.93	0.07	**<0.0005**	0.96	0.04	**<0.0005**
		No-Go	0.97	0.03	**<0.0005**	0.90	0.10	**0.001**	0.90	0.10	**0.002**
	Latency of peak	Go	0.94	0.06	**0.001**	0.96	0.04	**<0.0005**	-2.03	3.03	0.839
		No-Go	0.95	0.05	**0.001**	0.95	0.05	**<0.0005**	0.84	0.16	**0.007**
	Mean Latency	Go	0.69	0.31	**0.059**	0.92	0.08	**0.010**	0.85	0.15	**0.013**
		No-Go	0.91	0.09	**0.004**	0.92	0.08	**0.002**	0.86	0.14	**0.005**
	Area under component	Go	0.95	0.05	**<0.0005**	0.98	0.02	**<0.0005**	0.94	0.06	**0.002**
		No-Go	0.94	0.06	**0.001**	0.92	0.08	**0.001**	0.90	0.10	**0.001**
Cz	Amplitude of peak	Go	0.89	0.11	**0.011**	0.92	0.08	**0.033**	0.95	0.05	**<0.0005**
		No-Go	0.49	0.51	0.291	0.84	0.16	**0.017**	0.94	0.06	**<0.0005**
	Mean amplitude	Go	0.90	0.10	**0.002**	0.92	0.08	**<0.0005**	0.95	0.05	**<0.0005**
		No-Go	0.84	0.16	**0.004**	0.88	0.12	**0.002**	0.96	0.04	**<0.0005**
	Latency of peak	Go	0.91	0.09	**0.011**	0.85	0.15	**0.107**	0.97	0.03	**0.002**
		No-Go	0.86	0.14	**0.029**	0.94	0.06	**0.003**	0.61	0.39	**0.098**
	Mean Latency	Go	0.43	0.57	0.301	0.55	0.45	0.186	0.93	0.07	**0.008**
		No-Go	0.93	0.07	**0.017**	0.74	0.26	**0.079**	0.57	0.43	**0.087**
	Area under component	Go	0.76	0.24	**0.060**	0.92	0.08	**0.043**	0.95	0.05	**0.001**
		No-Go	-4.26	5.26	0.838	0.91	0.09	**0.003**	0.96	0.04	**<0.0005**
Pz	Amplitude of peak	Go	0.86	0.14	**0.015**	0.92	0.08	**0.054**	0.77	0.23	**0.055**
		No-Go	0.17	0.83	0.378	0.84	0.16	**0.013**	0.93	0.07	**<0.0005**
	Mean amplitude	Go	0.89	0.11	**0.001**	0.92	0.08	**<0.0005**	0.82	0.18	**0.011**
		No-Go	0.89	0.11	**0.001**	0.93	0.07	**<0.0005**	0.91	0.09	**0.001**
	Latency of peak	Go	0.98	0.02	**<0.0005**	0.93	0.07	**0.087**	0.99	0.01	**<0.0005**
		No-Go	0.92	0.08	**0.106**	0.48	0.52	0.369	0.87	0.13	**0.003**
	Mean Latency	Go	0.92	0.08	**0.016**	0.93	0.07	**0.055**	0.94	0.06	**0.004**
		No-Go	0.79	0.21	**0.098**	0.79	0.21	0.192	0.90	0.10	**0.001**
	Area under component	Go	0.86	0.14	**0.017**	0.91	0.09	**0.043**	0.79	0.21	**0.042**
		No-Go	0.19	0.81	0.268	0.91	0.09	**0.056**	0.91	0.09	**0.001**

Discussion

SART may be a better choice of paradigm than MMN for longitudinal research

We believe that this analysis is the first report on the reliability of ERP measurements obtained during the EEG-compatible sustained attention to response task (SART).

We demonstrated that the P2, N2, and P3 ERPs produced during this task are highly reliable over short-term repeat testing in healthy young adults with no cognitive, neurological, or psychological conditions. This indicates that these measures should not inherently vary with repeat testing. Therefore, we can measure these features longitudinally and interpret alterations as being the result of neurological or cognitive changes.

Limited reliability was observed for MMN features obtained during a passive auditory oddball task, apart from excellent reliability of the amplitude at Cz. One explanation for the difference in reliabilities of our methods is that our auditory oddball task is passive, requiring no input from the participant. In contrast, the SART requires active and specific engagement from the participant. Therefore, the SART may force a more similar pattern of cognitive (and therefore neural) activity among participants compared to the passive MMN. This could result in lower variability in neural activity during the SART than during the passive oddball task. Similarly, some studies of MMN reliability have used a two-frequency oddball task that requires a participant to respond to the infrequent tone, which may explain why the MMN was found to be reliable in these studies.

It is also of note that the only reliable MMN measure was seen at Cz. In a cap-based set up like the one used in this study, the Cz electrode is the only electrode that is placed according to direct measurements. Other electrodes are semi-fixed in relation to Cz due to being anchored to the fabric of the cap. Therefore, while Cz is in the same anatomical position on each participant, the other electrodes may vary slightly from their intended 10-20 position due to variations in participant head size or shape. This suggests that the same paradigm may produce more reliable MMN features if conducted with an EEG system where each electrode is placed individually. However, these types of EEG systems are uncommon in cognitive research applications, so the choice of experimental paradigm should reflect the equipment that is available for a given study.

Home-based EEG monitoring

The recent COVID-19 pandemic highlighted the utility of in-home options for medical treatment and research. One method that shows promise for use in longitudinal cognitive monitoring or research is mobile EEG that can be administered by a research participant or family member independently from the research team. Such EEG systems often include few electrodes (1-32), are wireless, and may be used to collect resting or task-based data. The technology, recording environments, and self-administration of these systems likely produce data of lower signal quality than data collected in a standard research EEG laboratory. However, previous research has shown that data aggregation and signal processing techniques can produce signal quality rivalling conventional EEG using these mobile systems (Barbey et al. 2022).

Another approach to improving the usability of these systems for research would be the selection of outcome measures that are highly robust and reproducible. Task-based data in at-home monitoring is frequently collected using variations of the oddball task to elicit a P300 or MMN, as these tasks are easy to administer and commonly reported in cognitive EEG literature.

Our results suggest that the SART could produce more reliable longitudinal ERP results than the oddball tasks typically used with these technologies. A longitudinal study comparing cognitive tracking using SART and cognitive tracking using standard oddball-based measures is warranted.

Future Directions

Longitudinal analysis

These results support the use of the EEG-compatible SART (McMackin et al. 2020) in a future longitudinal study of cognition in MS. The excellent reliability of the majority of the SART ERP markers assessed here indicates that any longitudinal changes in these variables should reflect changes in participants' neural function, rather than random variability. The study should select measures of interest showing high test-retest ICC values as the outcome variables in that study. For example, amplitude-weighted latency could be selected because it showed consistent reliability across channels and components in contrast to the latency of the peak, whose reliability varied across channels and components.

However, longitudinal studies based on these reliability findings should also account for the fact that the present results were obtained from a small sample of neurologically healthy younger adults and thus, no claim can be made regarding the test-retest reliability of these measures in people with multiple sclerosis. Due to the heterogeneity and variability of the disease, it is possible that people with MS would show more variation in these measures between individuals or within individuals over time than controls do. However, the presence of high retest reliability in healthy individuals provides sufficient justification for the initial selection of measures for longitudinal studies, and this selection can be further refined following reliability analysis in MS. Therefore, future longitudinal studies using these ERPs should measure and report inter- and intra-individual variation and retest reliability in people with MS.

Evaluate MMN reliability with an increased sample size

These results were collected using a relatively small sample size of ten participants. It is therefore possible that this study was underpowered to detect the reliability of MMN measures. However, repeating this analysis with a larger sample size should be undertaken with caution. The reliability of the MMN appears lower than the reliability of the SART-derived measures described here, so SART-derived measures may be a better choice for many applications. If the MMN is required for a particular research question, increasing the sample size may reveal significant reliability, but will not increase the underlying reliability of these measures.

Conclusions

ERP features along the central midline elicited by the EEG-compatible SART are highly reliable with repeat testing. Amplitude of the MMN at Cz also displays excellent reliability, but other measurements may not be as suitable for longitudinal applications. SART and auditory oddball ERP measurements with very high test-retest reliability are good choices for outcome variables for longitudinal study designs.

Chapter 6

Results: SART ERPs in MS

ERP responses to the sustained attention to response task are altered in MS

Chapter summary

This chapter aims to characterize behavioral performance and ERP responses during the sustained attention to response task (SART) in multiple sclerosis (MS). EEG was recorded from 81 participants with MS and 54 controls during a SART paradigm. P2, N2, and P3 ERPs were extracted from "Go" and "No-Go" trials and compared between groups. Reaction time and errors of commission, omission, and anticipation were compared between groups and with ERP measures and clinical features. Participants with RRMS made more total, omission, commission, and anticipation errors than HC on the SART. Participants with MS showed diminished amplitudes of the P2 and P3 and increased latencies of the P2, N2, and P3, though these alterations were not seen in all subgroups. These ERP impairments correlated with reaction time but not accuracy or neuropsychological screening scores.

Introduction

Cognitive impairment is a frequently reported and distressing symptom of multiple sclerosis (MS) often affecting processing speed, memory, attention, and executive function (Benedict et al. 2020; De Meo et al. 2021). These cognitive changes affect quality of life, employment, and caregiver burden, but may respond to cognitive rehabilitation (Figved et al. 2007; Hämäläinen and Rosti-Otajärvi 2016; Lancia et al. 2024; Macaron et al. 2020).

Electroencephalography (EEG) is a safe, cost-effective method of measuring direct neuronal activity which could address the need for repeatable, objective, pre-clinical measures of cognitive function. ERP indicators of cognitive dysfunction have been reported in MS, with decreased amplitude and increased latency of the P3 being the most frequently reported finding (Ferreira et al. 2024).

One paradigm that may be used to elicit the P3 is the Sustained Attention to Response Task (SART). This response inhibition task was developed to study "action slips" due to attentional lapses that are common after traumatic brain injury due to damage to frontal

regions and white matter (Robertson et al. 1997). Similar damage can be seen in multiple sclerosis, indicating that the test may be well-placed to detect attentional lapses in this condition. The SART has been used in multiple sclerosis research to increase cognitive load during a walking task (Yap et al. 2021) and to show the cognitive benefit of intrathecal compared to oral baclofen (Farrell et al. 2021), but the performance of people with multiple sclerosis on this potentially highly relevant task has not yet been characterized in comparison to controls. Furthermore, the neural signals underpinning performance on this task have not been investigated in multiple sclerosis.

ERPs elicited by the serial and random versions of the SART have been identified in healthy controls and in other neurodegenerative conditions like motor neuron disease (McMackin et al. 2020; Roche et al. 2005; Zordan et al. 2008). These studies generally describe increased amplitudes of the N2 and P3 ERPs over frontocentral or parietocentral regions during response inhibition. The P2 was also included in the present study as an earlier sensory component previously shown to be altered during a visual oddball task in MS (Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al. 2010).

This study aims to characterize the performance of people with multiple sclerosis on the sustained attention to response task (SART) and to validate the ERP correlates of this test in a population of people with multiple sclerosis. We also aim to correlate SART performance and ERP measures with other clinically and demographically relevant features.

Methods

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, with ethical approval from the Beaumont Hospital Ethics (Medical Research) Committee (REC reference: 18/63), the St. Vincent's University Hospital Research Ethics Committee (REC reference: RS19-054), and the St. James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (REC reference: 2017-02 Chairman's Action 18). Informed, voluntary consent was obtained from all study participants.

Participants

Recruitment

Participants with multiple sclerosis (n=81) were recruited from Beaumont Hospital, St. Vincent's University Hospital, and St. James's Hospital, Dublin, Ireland during routine neurology and specialist multiple sclerosis clinics. Participants with MS were also recruited through online advertisements distributed by MS Society Ireland. Neurologically healthy controls (n=54) were recruited through existing control banks in the Academic Unit of Neurology and advertisements on websites and social media.

Inclusion and exclusion

Adults with diagnosed RRMS, SPMS, or PPMS and no DMT changes or relapses within the prior 3 months were eligible for recruitment to the study. Control participants with no neurological, psychological, or muscular conditions and not taking CNS-acting medications were also recruited. Exclusion criteria for both participants with MS and controls included active psychiatric disease, history of seizures, head trauma causing a diagnosed concussion or loss of consciousness, metallic implants in the head, and pregnancy or breastfeeding.

Participant demographics

Characteristics of the participant samples are presented in **Table 5**. The subtype of MS was unknown for one participant. This participant was therefore excluded from group-level analyses but was included for correlation analysis.

Table 5. Demographics of the sample

	Patients	Controls
n	81	54
mean age (years) [SD]	48.8 [12.3]	60.2 [12.8]
age range (years)	27-82	21-72
Gender (f/m)	61/20	29/25
Handedness (R/L/A)	72/7/2	39/2/2
MS subtype (RRMS/SPMS/PPMS/unknown)	63/9/8/1	n/a
DMD status [no DMD/taking DMD]	23/58	n/a
Mean disease duration (years) [min-max]	14.7 [0-68]	n/a
Mean MSNQ score [*n* anormal]	27.4 [43]	n/a
Mean HADS- A [*n* abnormal]	6.9 [33]	n/a
Mean HADS-D [*n* abnormal]	4.7 [16]	n/a

Data acquisition

EEG recording

128 active electrodes were applied to an EEG cap (EASYCAP GmbH) selected to fit the participant's head by trained experimenters. EEG signals were recorded at 512Hz on a BioSemi ActiveTwo system in an electrically shielded room. Stimulus presentation and participant response events were saved in the continuous EEG data to facilitate accurate epoching.

Experimental paradigm: SART

Participants completed an EEG-compatible SART paradigm as reported by McMackin, et al. (2020). The test was administered using Presentation® software (Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com). Briefly, participants were seated approximately 1m in front of a standard computer screen in a darkened room and presented with a random series of single digits in light grey on a black background. Participants were instructed to click a standard computer mouse in response to an infrequent target digit ("3") and to withhold responses to all other digits, giving equal priority to speed and accuracy. Participants completed an unrecorded practice block (45 trials) with feedback from the experimenter followed by four blocks of 252 trials each with no experimenter in the recording booth.

Neuropsychological testing

Participants with MS completed the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (Benedict et al. 2003) and Hospital Anxiety and Depression Screening (HADS) (Zigmond and Snaith 1983).

Data analysis

Task performance

Reaction time, "Go" trial accuracy (percentage of non-3 digit presentations followed by a mouse click), "No-Go" accuracy (percentage of 3 digit presentations not followed by a mouse click) overall accuracy (percentage of "Go" and "No-Go" trials responded to correctly with either a mouse click or a response inhibition, respectively) and anticipation (percentage of correct "Go" trials with a response less than 150ms after stimulus presentation) were calculated for each participant. One control participant's response data was not saved during the experiment, so this participant was excluded from this part of the analysis. One-way ANOVAs were used to compare inverse normal transformed group means for these variables among controls and participants with RRMS, SPMS, and PPMS. Fisher's least significant difference (LSD) test was applied post-hoc to localize differences in means, and a 5% adaptive false discovery rate correction was applied to account for multiple comparisons.

EEG signal preprocessing

Data were cleaned and filtered according to methods in Chapter 4. The continuous EEG signal was epoched from 200 pre-stimulus to 900ms post-stimulus, and trials with responses less than 150ms after stimulus presentation were eliminated (anticipation errors). The remaining trials were averaged using a 10% trimmed mean to create ERP responses for each participant at each channel.

ERP analysis

Signals were baseline-subtracted and referenced to the common average. The P2, N2, and P3 ERP components were extracted from 100-300ms, 150-350ms and 350-550ms post-stimulus, respectively, and the maximum amplitude, mean amplitude, latency, amplitude-weighted latency, and area under the ERP component were calculated and subjected to an inverse normal transformation to approximate normality. A five-factor ANCOVA was conducted for each waveform feature to understand the impact of group

(RRMS, SPMS, PPMS, and HC), gender, channel location (Fz, FCz, Cz, Pz), and trial type ("Go", "NoGo") while controlling for age. The ANOVA was corrected within ERPs for multiple comparisons using a 5% adaptive FDR.

Significant effects in group, gender, channel, and trial were then localized with Fisher's least significant difference (LSD) test and a 5% adaptive false discovery rate (FDR) correction was applied to account for multiple comparisons. Effects of age were localized post-hoc using Spearman's rank correlation across all participants and corrected using a 5% adaptive FDR (AFDR). Significant results are presented with uncorrected p-values.

Correlations with neuropsychological screening

Spearman's rank correlation coefficients were calculated for each pairing of the waveform features (P2, N2, and P3 amplitude, mean amplitude, latency, amplitude-weighted latency, and area under the ERP component for Go and NoGo trials at Fz, FCz, Cz, and Pz) with clinical cognitive and psychological screening scores (MSNQ score, HADS-A score, HADS-D score) in participants with MS. P-values were corrected within screening scores and ERPs using a 5% AFDR.

Correlations with task performance

Spearman's rank correlation tests were conducted between SART performance metrics (go accuracy, no-go accuracy, total accuracy, anticipation, reaction time) and waveform features, and p-values were corrected within performance metrics and ERPs using a 5% AFDR. A separate Spearman's rank correlation analysis was conducted between SART performance metrics and age (MS and HC) and neuropsychological screening tools (MS only). P-values were corrected within performance metrics using a 5% AFDR.

Results

Overall waveform responses from healthy controls and participants with MS to "Go" and "No-Go" trials are shown in **Figure 3**. Compared to "Go" trials, "No-Go" trials produced

faster P2 responses, slower and larger N2 responses, and larger P3 responses (**Table 6**).

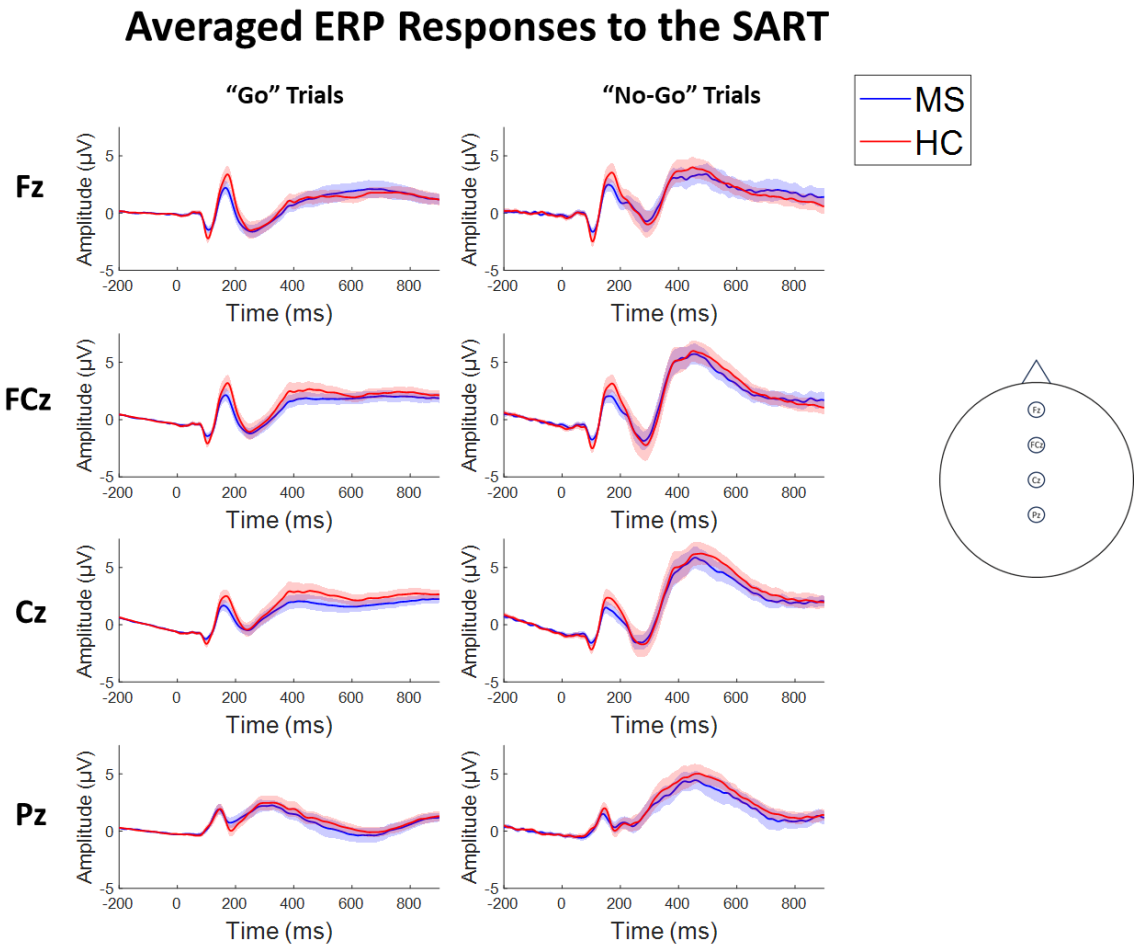


***Figure 3. SART ERP responses**. Averaged EEG potentials in response to the SART in participants with MS and healthy controls. Responses from participants with MS are shown in blue, and responses from healthy controls are shown in red. The solid line corresponds to the mean of the SART ERP across participants and the shaded region indicates the 95% confidence interval of this mean. Plots were generated based on plotting steps initially drafted by Etain O'Meara.*

***Table 6. Summary of differences between SART Go and No-Go trials across ERPs.** Compared to Go trials, No-Go trials produced faster P2 responses, slower and larger N2 responses, and larger P3 responses.*

	Size Measures	Latency Measures
P2		Standard: No-Go < Go (p = 0.021)
N2	Peak: No-Go > Go (p < 0.0005) Area: No-Go > Go (p < 0.004)	Standard: No-Go > Go (p = 0.004) Amplitude-weighted: No-Go > Go (p = 0.021)
P3	Peak: No-Go > Go (p < 0.0005) Area: No-Go > Go (p < 0.0005) Mean: No-Go > Go (p < 0.0005)	

Task performance

ANOVA identified differences among participant groups in "Go" trial accuracy ($F_{3, 126}$= 8.33, p < 0.0005), "No Go" trial accuracy ($F_{3, 126}$= 5.57, p=0.001), total accuracy ($F_{3, 126}$= 6.92, p < 0.0005), anticipation ($F_{3, 126}$= 8.57, p < 0.0005), and reaction time ($F_{3, 126}$= 6.27, p=0.001), which were driven by differences in participants with RRMS (**Figure 4**). No differences were identified between participants with SPMS or PPMS and controls. Participants with RRMS showed lower overall accuracy (p < 0.0005) on the task (with increased errors of both commission (p < 0.0005) and omission (p < 0.0005) and more anticipation errors (p < 0.0005) compared to controls. Participants with RRMS also had faster reaction times than participants with SPMS (p = 0.007), PPMS (p = 0.002), and healthy controls (p = 0.002), which may correspond to the higher level of anticipation made by this group.

Increasing age was associated with slower reaction times in both participants with MS (ρ= 0.41, p < 0.0005) and controls (ρ = 0.39, p = 0.004) (**Table 7**). Increased age was also associated with increased "No-Go" accuracy (fewer errors of commission) in participants with MS (ρ = 0.32, p = 0.004).

Additionally, aspects of SART performance were associated with scores on cognitive, anxiety, and depression screening tools (

Table 8). Increased accuracy on SART "Go" trials is correlated with lower self-reported cognitive impairment as measured by the MSNQ (ρ = - 0.38, p = 0.001). Higher self-reported anxiety (HADS-A) is associated with faster reaction times (ρ = - 0.24, p = 0.03), and higher self-reported depression (HADS-D) is associated with slower reaction times (ρ = 0.41, p < 0.0005).

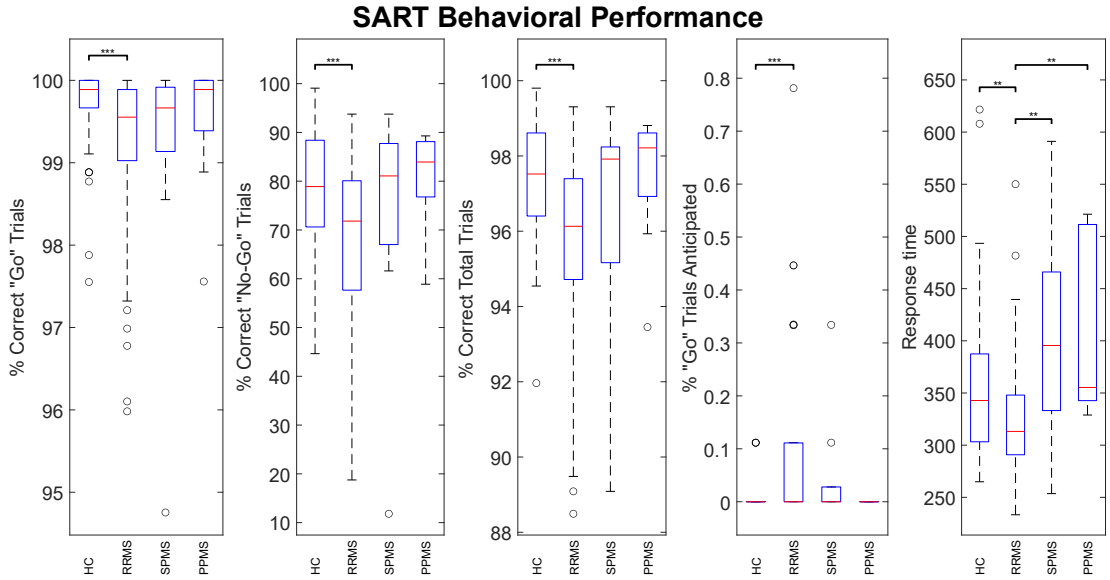


Figure 4. Behavioral performance on the SART. *Participants with RRMS showed impaired SART performance compared to controls, with more total errors ($p < 0.0005$), errors of omission ($p < 0.0005$), errors of commission ($p < 0.0005$), and errors of anticipation ($p < 0.0005$). Participants with RRMS showed faster reaction times compared to participants with SPMS ($p = 0.007$), PPMS ($p = 0.002$), and controls ($p = 0.002$).*

Table 7. Associations between SART performance and age. *Increased age is associated with increased "No-Go" accuracy in participants with MS and increased reaction time in people with MS and controls. Significant p-values are shown in bold.*

	MS age		**HC age**	
	rho	p	rho	p
"Go" accuracy	0.10	0.376	-0.18	0.196
"No-Go" accuracy	**0.32**	**0.004**	0.11	0.420
total accuracy	0.26	0.018	0.09	0.512
anticipation	-0.26	0.017	-0.19	0.187
reaction time	**0.41**	**p<0.0005**	**0.39**	**0.004**

***Table 8. Associations between SART performance and screening scores**. SART "Go" accuracy is negatively associated with self-reported cognitive impairment. Reaction time is negatively associated with self-reported anxiety and positively associated with self-reported depression. Significant p-values are shown in bold.*

	MSNQ		HADS-A		HADS-D	
	rho	p	rho	p	rho	p
"Go" accuracy	**-0.38**	**0.001**	-0.12	0.298	-0.22	0.054
"No-Go" accuracy	-0.03	0.822	-0.12	0.288	-0.13	0.245
total accuracy	-0.12	0.287	-0.11	0.343	-0.19	0.095
anticipation	0.11	0.346	0.23	0.043	0.24	0.032
reaction time	0.15	0.194	**-0.24**	**0.030**	**0.41**	**p<0.0005**

P2 responses

P2 size is diminished in MS and males

The area under the P2 was smaller in participants with RRMS ($p < 0.025$), SPMS ($p < 0.0005$), and PPMS ($p = 0.042$) than in controls. The area of the P2 did not differ among participants with different subtypes of MS. Participants with SPMS also showed reduced P2 peak amplitudes compared to participants with RRMS ($p = 0.016$) and controls ($p < 0.0005$). Males showed lower mean amplitudes ($p < 0.0005$) compared to females.

P2 areas and means were largest at electrode Pz compared to responses at Fz ($p = 0.001$, $p < 0.0005$), FCz ($p = 0.003$, $p < 0.0005$), and Cz ($p < 0.0005$, $p < 0.0005$).

P2 latency varies among MS subgroups

Participants with SPMS had slower conventional latency P2 responses than participants with RRMS ($p = 0.010$) or PPMS ($p = 0.009$), and responses in people with RRMS or PPMS were faster than in controls ($p = 0.040$, $p = 0.037$). Participants with SPMS and healthy controls did not differ in P2 latency.

The amplitude-weighted latency of the P2 was slower in males compared to females ($p < 0.0005$) and at Pz compared to Fz ($p < 0.0005$), FCz ($p < 0.0005$), and Cz ($p < 0.0005$).

Older age is associated with larger, slower frontal P2 responses

Age post-hoc results for all ERPs are shown in **Table 11**. Increased age was weakly correlated with higher mean amplitudes at Fz in participants with MS during "Go" trials ($\rho = 0.31$, $p = 0.004$) and in controls during "Go" ($\rho = 0.38$, $p = 0.005$) and "No-Go" trials ($\rho =$

0.42, p = 0.002). In contrast, older age was weakly correlated with lower mean amplitudes (ρ = -0.36, p = 0.001) and P2 areas (ρ = -0.33, p = 0.007) at Pz in "Go" trials in participants with MS.

Older age was also weakly-to-moderately associated with slower standard latencies in "Go" trials at Fz and FCz in participants with MS (Fz: ρ = 0.33, p = 0.004; FCz: ρ = 0.42, p < 0.0005) and controls (Fz: ρ = 0.59, p < 0.0005; FCz: ρ = 0.48, p = 0.001). Similarly, the amplitude-weighted latency at Fz (ρ = 0.31, p = 0.006) and FCz (ρ = 0.36, p = 0.002) during "Go" trials showed a weak positive association with age in participants with MS. Control participants showed weak-to-moderate associations between older age and slower weighted-latencies at Fz in both "Go" (ρ = 0.41, p = 0.004) and "No-Go" (ρ = 0.36, p = 0.009) trials.

N2 responses

N2 peaks are faster in RRMS and SPMS, younger participants, males, and posteriorly

Faster N2 responses were observed in RRMS and SPMS. Standard latency was decreased compared to controls in participants with RRMS (p = 0.008) and SPMS (p = 0.007). Likewise, amplitude weighted latencies were also smaller in participants with RRMS (p = 0.010) and SPMS (p = 0.043) compared to controls. Participants with SPMS and RRMS did not differ from each other in standard or amplitude-weighted latency, and participants with PPMS did not differ from other participants with MS or healthy controls.

Decreased amplitude weighted latency was associated with younger age in some electrodes and trial types. In participants with MS, lower age was weakly associated with faster "Go" N2 responses at Cz (ρ = 0.27, p = 0.037) and "No-Go" responses at Pz (ρ = 0.37, p = 0.003). Lower age was also weakly-to-moderately associated with faster N2 "Go" responses in healthy controls at Fz (ρ = 0.46, p = 0.001) and FCz (ρ = 0.40, p = 0.007) and "No-Go" responses at FCz (ρ = 0.38, p = 0.010), and Cz (ρ = 0.40, p = 0.010).

Males showed faster standard (p = 0.011) and amplitude-weighted latency (p = 0.012) responses than did females.

N2 responses were fastest posteriorly. Amplitude-weighted latencies were shortest at Pz compared to Cz (p = 0.041), FCz (p < 0.0005), and Fz (p < 0.0005). Amplitude-weighted latencies were also faster at Cz than at FCz (p = 0.001) and Fz (p = 0.002). Standard latencies were faster at Pz and Cz than at FCz (p < 0.0005; p = 0.002) and Fz (p = 0.001; p =

0.010). No differences in standard latency were found between Cz and Pz or between Fz and FCz.

N2 responses are larger fronto-centrally, in males, and in older participants

The peak amplitude and area under the N2 were larger at Fz, FCz, and Cz than at Pz ($p < 0.0005$ for all). The size of the N2 did not differ among electrodes Fz, FCz, and Cz. Males showed larger N2 areas ($p = 0.011$) compared to females.

Older age was also associated with larger frontal N2 (**Table 11**). Older age was correlated with larger magnitude N2 peak amplitudes at Fz in "Go" trials and at Fz and FCz in "No-Go" trials in participants with MS and controls ($\rho = 0.33 - 0.48$, $p < 0.026$; individual results in **Table 11**). Similarly, older age was associated with larger magnitude N2 mean amplitudes at Fz in "Go" and "No-Go" trials in participants with MS and controls and at FCz in "Go" trials in participants with MS ($\rho = 0.26 - 0.41$, $p < 0.017$; individual results in **Table 11**). Likewise, younger age was correlated with smaller areas under the N2 at Fz during "Go" and "No-Go" trials in both groups, and at FCz during "No-Go" trials in participants with MS ($\rho = 0.32 - 0.54$, $p < 0.031$; individual results in **Table 11**).

Mean amplitude reveals possible weaknesses of the peak selection method

Estimates of the marginal means for N2 mean amplitude were positive, indicating that this measure may have been affected by other (positive) ERP peaks within the selection window in addition to the N2.

Unlike the decreased N2 peak and area seen at Pz, the mean amplitude of the N2 was larger at Pz than at Fz, FCz, or Cz (all $p < 0.0005$). Mean amplitudes were also larger in female than in male participants ($p < 0.0005$). Additionally, the positive relationship between age and N2 size described above was not seen at Pz. Conversely, older age was associated with decreased N2 mean amplitudes at Pz across trial types and groups ($\rho = -0.43$ to -0.29, $p < 0.033$; individual results in **Table 11**).

P3 responses

P3 is diminished in SPMS, enhanced in PPMS, and slowed in SPMS and PPMS

The mean amplitude across the 350-550ms time window was lower in participants with SPMS than in participants with RRMS ($p < 0.0005$) or controls ($p < 0.0005$). In contrast, P3 amplitude and area were increased in participants with PPMS compared to participants with RRMS ($p < 0.0005$, $p = 0.001$) and controls ($p = 0.002$, $p = 0.002$).

The latency of the P3 was also altered in SPMS and PPMS. Both participants with SPMS and PPMS showed slower standard and amplitude-weighted latencies of the P3 peak compared to controls and participants with RRMS (all $p < 0.002$, individual values in **Table 9**). P3 latencies did not differ between participants with SPMS and PPMS and were not altered participants with RRMS.

Table 9. P3 latency group effect post-hoc p-values

P3 Latency			
post-hoc p-values		**RRMS**	**HC**
standard	**PPMS**	0.001	< 0.0005
	SPMS	0.002	< 0.0005
amplitude-weighted	**PPMS**	< 0.0005	< 0.0005
	SPMS	0.001	< 0.0005

Older age is associated with slower P3 responses

Age showed weak positive correlations with standard and amplitude-weighted latencies across most electrodes, trials, and participant groups. At Fz, increased age in healthy controls was associated with increased P3 standard and amplitude-weighted latency during both "Go" ($\rho = 0.43$, $p = 0.003$; $\rho = 0.34$, $p = 0.028$) and "No-Go" trials ($\rho = 0.51$, $p < 0.0005$; $\rho = 0.45$, $p = 0.001$). Older age was associated with longer standard latencies at FCz in participants with MS and controls during "Go" ($\rho = 0.30$, $p = 0.016$; $\rho = 0.45$, $p = 0.001$) and "No-Go" trials ($\rho = 0.32$, $p = 0.006$; 0.44, $p = 0.001$). Older age was also associated with longer amplitude-weighted latencies at FCz in participants with MS and controls during "No-Go" trials ($\rho = 0.29$, $p = 0.015$; $\rho = 0.43$, $p = 0.002$) but only in controls during "Go" trials ($\rho = 0.42$, $p = 0.003$). Age and both latency measures were positively correlated at Cz during both trials in both participant groups ($\rho = 0.33$ - 0.53, $p < 0.006$; individual results in **Table 11**). Increased Pz standard and amplitude-weighted latencies were associated with increased age in "No-Go" trials only ($\rho = 0.37$ - 0.40, $p < 0.009$; individual results in **Table 11**).

The P3 is fastest and smallest at Pz, but does not show a clear directional gradient in size

Faster standard and amplitude-weighted latencies were seen at Pz than at Fz, FCz, or Cz ($p < 0.0005$ for all). The P3 recorded at Pz also showed lower peak amplitudes and areas under the component than the P3 at Fz, FCz, or Cz. Peak amplitudes and areas were also smaller at Fz than at FCz. These effects are summarized in **Table 10**. P3 mean amplitudes

were lower at Fz than at Pz (0.041), Cz ($p < 0.0005$), and FCz ($p < 0.0005$). P3 mean amplitudes were also lower at Pz than at Cz ($p < 0.0005$) or FCz ($p = 0.002$), which did not differ from each other in mean amplitude.

Table 10. Summary of electrode differences in P3 peaks and areas. *P3 responses showed increasing size from Pz to Fz, to FCz and Cz, with no differences between FCz and Cz.*

		Fz	FCz	Cz
P3 sizes were	**smaller at Pz than at…**	Peak: p = 0.001 Area: p = 0.002	Peak: p < 0.0005 Area: p < 0.0005	Peak: p < 0.0005 Area: p < 0.0005
	smaller at Fz than at…		Peak: p = 0.045 Area: p = 0.037	

Table 11. Correlations between ERPs and age. *P-values are shown to three decimal places unless they are below 0.0005, in which case they are listed as "0.0005". P-values that are significant after adaptive FDR correction are shown in bold.*

			PwMS				Controls			
			Go		NoGo		Go		NoGo	
			rho	p	rho	p	rho	p	rho	p
P2	peak amplitude	Fz	0.22	0.054	0.11	0.333	0.14	0.349	0.18	0.219
		FCz	0.18	0.138	0.08	0.501	0.06	0.696	0.07	0.650
		Cz	0.08	0.529	0.15	0.230	-0.16	0.292	-0.17	0.278
		Pz	-0.20	0.105	-0.17	0.178	-0.33	0.033	-0.33	0.052
	mean amplitude	Fz	0.31	**0.004**	0.28	0.013	0.38	**0.005**	0.42	**0.002**
		FCz	0.19	0.086	0.24	0.033	0.26	0.062	0.32	0.021
		Cz	-0.02	0.861	0.04	0.705	0.00	0.983	0.08	0.579
		Pz	-0.36	**0.001**	-0.23	0.038	-0.35	0.011	-0.33	0.017
	area amplitude	Fz	0.21	0.064	0.16	0.181	0.20	0.162	0.28	0.044
		FCz	0.17	0.168	0.07	0.536	0.10	0.480	0.14	0.318
		Cz	-0.01	0.956	0.12	0.342	-0.09	0.582	-0.10	0.504
		Pz	-0.33	**0.007**	-0.20	0.125	-0.39	0.012	-0.42	0.013
	standard latency	Fz	0.33	**0.004**	0.16	0.169	0.59	**<0.0005**	0.11	0.434
		FCz	0.42	**<0.0005**	0.19	0.107	0.48	**0.001**	-0.03	0.860
		Cz	0.25	0.043	0.01	0.933	0.32	0.037	0.27	0.070
		Pz	-0.05	0.708	0.00	0.971	-0.08	0.631	-0.19	0.285
	amplitude-weighted latency	Fz	0.31	**0.006**	0.16	0.168	0.41	**0.004**	0.36	**0.009**
		FCz	0.36	**0.002**	0.15	0.188	0.27	0.063	0.15	0.311
		Cz	0.08	0.547	-0.05	0.663	0.04	0.783	0.24	0.120
		Pz	-0.03	0.785	-0.10	0.435	-0.16	0.330	-0.34	0.046
N2	peak amplitude	Fz	0.39	**0.001**	0.48	**<0.0005**	0.35	**0.017**	0.36	**0.023**
		FCz	0.16	0.185	0.38	**0.001**	0.25	0.095	0.33	**0.026**
		Cz	-0.25	0.055	0.12	0.311	0.06	0.713	0.08	0.628
		Pz	-0.26	0.074	-0.05	0.726	0.06	0.738	-0.15	0.373
	mean amplitude	Fz	0.38	**<0.0005**	0.39	**<0.0005**	0.33	**0.016**	0.41	**0.002**
		FCz	0.26	**0.017**	0.21	0.063	0.20	0.147	0.20	0.157
		Cz	0.00	0.987	-0.10	0.377	-0.08	0.558	-0.10	0.462
		Pz	-0.29	**0.008**	-0.32	**0.003**	-0.29	**0.033**	-0.43	**0.001**
	area	Fz	0.33	**0.005**	0.54	**<0.0005**	0.32	**0.031**	0.35	**0.029**
		FCz	0.18	0.132	0.35	**0.003**	0.20	0.198	0.27	0.072
		Cz	-0.26	0.045	0.06	0.652	0.00	0.983	0.05	0.775
		Pz	-0.28	0.049	-0.17	0.200	0.09	0.620	-0.27	0.107
	amplitude-weighted latency	Fz	0.14	0.239	-0.14	0.287	0.46	**0.001**	0.09	0.592
		FCz	-0.06	0.606	0.21	0.085	0.40	**0.007**	0.38	**0.010**
		Cz	0.27	**0.037**	0.15	0.234	0.27	0.097	0.39	**0.010**
		Pz	0.15	0.298	0.37	**0.003**	0.09	0.632	0.13	0.450
P3	standard latency	Fz	-0.05	0.742	0.08	0.527	0.45	**0.003**	0.51	**<0.0005**
		FCz	0.30	**0.016**	0.32	**0.006**	0.45	**0.001**	0.44	**0.001**
		Cz	0.37	**0.002**	0.33	**0.006**	0.53	**<0.0005**	0.49	**0.001**
		Pz	0.20	0.088	0.39	**<0.0005**	0.07	0.618	0.40	**0.005**
	amplitude-weighted latency	Fz	-0.10	0.466	0.00	0.982	0.34	**0.028**	0.45	**0.001**
		FCz	0.17	0.180	0.29	**0.015**	0.42	**0.003**	0.43	**0.002**
		Cz	0.39	**0.001**	0.41	**0.001**	0.45	**0.002**	0.50	**<0.0005**
		Pz	0.18	0.139	0.37	**0.001**	-0.06	0.686	0.38	**0.009**

Correlations with clinical features

No relationship between ERPs and clinical screening tools

No correlations between P2, N2, or P3 ERP features and the MSNQ or HADS (A or D) were significant after correction for multiple comparisons using adaptive FDR (**Supplementary Table 2**, **Supplementary Table 3**, **Supplementary Table 4**).

Diminished P3 size is associated with increased accuracy in controls but not in MS

No P2 or N2 characteristics were associated with SART accuracy measures in people with MS or healthy controls (**Supplementary Table 5**, **Supplementary Table 6**). No latency

measures showed significant correlations with SART performance in controls or people with MS. P3 peak amplitude, mean amplitude, and area were correlated with “No-Go” trial accuracy and overall accuracy in controls, but not in people with MS (**Table 12**). No ERP measures showed associations with “Go” accuracy or anticipation errors.

In controls, increased “No-Go” and total accuracy was associated with lower peak amplitudes of the P3 during “No-Go” trials at Fz, FCz, and Cz (ρ = - 0.47 to - 0.38, $p < 0.006$, individual results in **Table 12**). Higher “No-Go” and total accuracy were also correlated with lower mean amplitudes at FCz and Cz during “Go” trials and at Fz and FCz during “No-Go” trials (ρ = - 0.42 to - 0.36, $p < 0.008$, individual results in **Table 12**). Decreased P3 areas during “No-Go” trials at Fz and FCz were associated with increased “No-Go” and overall accuracy (ρ = - 0.38 to - 0.34, $p < 0.014$, individual results in **Table 12**). Increased “No-Go” accuracy was also associated with decreased “No-Go” P3 area at Cz (ρ = - 0.36, $p < 0.014$).

SART reaction time correlates with ERP characteristics

Correlations were found between SART reaction time and P2 and P3 ERP characteristics in participants with MS and P2, N2, and P3 characteristics in controls **Table 13**. Slower behavioral reaction times were generally associated with smaller and slower ERP responses.

The P2 peak amplitude, mean amplitude, area, and amplitude-weighted latency during “Go” trials at Pz were negatively associated with reaction time in controls (ρ = - 0.54 to - 0.40, $p < 0.003$, individual results in **Table 13**). In participants with MS, longer reaction times were correlated with longer “Go” and “No-Go” trial standard latencies at Fz, “Go” trial standard latencies at FCz, and “Go” trial amplitude-weighted latencies at Fz.

No associations between reaction time and N2 ERP characteristics were found in participants with MS. In controls, longer reaction times were correlated with smaller and slower N2 responses. The mean amplitude of the N2 at Pz during “Go” trials was negatively correlated with reaction time ρ = - 0.44, $p = 0.001$. Reaction time was positively associated with the amplitude-weighted latency of the N2 during “Go” trials at FCz (ρ = 0.47, $p = 0.001$) and during “Go” and “No-Go” trials at Cz (ρ = 0.63, $p < 0.0005$; ρ = 0.49, $p = 0.001$).

Reaction time was negatively associated with the peak amplitude of the P3 at Cz and Pz in both groups and at FCz in controls only (ρ = - 0.50 to -0.23, p < 0.053, individual results in **Table 13**). Reaction time also showed negative correlations with P3 mean amplitude at Cz in both trials and groups and at FCz and Pz during "No-Go" trials in both groups and during "Go" trials in controls only (ρ = - 0.52 to -0.26, p < 0.025, individual results in **Table 13**). Similarly, longer reaction times were associated with lower P3 areas at Cz in both groups, at FCz in controls, at Pz during "No-Go" trials in both groups, and at Pz during "Go" trials in controls (ρ = - 0.53 to - 0.24, p < 0.048, individual results in **Table 13**).

Standard and amplitude-weighted latencies at P3 showed an identical pattern of positive correlations with reaction time. Longer reaction times were associated with longer latencies at FCz and Cz, at Fz during "Go" trials in controls, and at Fz and Pz during "No-Go" trials in both groups. (ρ = 0.30 – 0.73, p < 0.025, individual results in **Table 13**). The relationship between reaction time and P3 latency appears to be stronger in controls (median ρ = 0.67) than in participants with MS (median ρ = 0.39).

Table 12. Correlations between P3 ERP characteristics and SART accuracy in MS and controls. *Spearman's correlation tests were conducted for each pairing of P3 waveform feature (peak and mean amplitude, standard and amplitude-weighted latency, and area) for "Go" and "No-Go" trials at Fz, FCz, Cz, and Pz and SART accuracy measures ("Go" accuracy, "No-Go" accuracy, total accuracy, and anticipation errors). Spearman's rank coefficients are shown to two decimal places and p-values that were significant after adaptive FDR correction are shown in bold.*

				"Go" accuracy				"No-Go" accuracy				total accuracy				anticipation			
				MS		Control		MS		Control		MS		Control		MS		Control	
				rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
P3	Go	peak amplitude	Fz	0.12	0.406	-0.27	0.094	0.04	0.776	-0.16	0.335	0.04	0.792	-0.23	0.150	-0.10	0.483	-0.02	0.891
			FCz	0.13	0.289	-0.01	0.945	0.10	0.425	-0.23	0.112	0.10	0.426	-0.27	0.071	-0.24	0.052	0.10	0.509
			Cz	0.04	0.777	0.06	0.694	0.03	0.826	-0.24	0.109	0.04	0.765	-0.25	0.094	-0.18	0.141	0.13	0.391
			Pz	0.09	0.446	0.02	0.889	-0.06	0.621	-0.19	0.199	-0.02	0.864	-0.21	0.157	-0.17	0.149	0.16	0.282
		mean amplitude	Fz	0.04	0.742	-0.16	0.253	0.05	0.628	-0.18	0.189	0.03	0.770	-0.22	0.121	-0.06	0.624	0.02	0.862
			FCz	0.13	0.260	-0.06	0.686	0.06	0.612	-0.37	**0.007**	0.07	0.557	-0.38	**0.005**	-0.15	0.196	0.12	0.401
			Cz	0.03	0.805	0.04	0.761	-0.08	0.495	-0.36	**0.008**	-0.04	0.700	-0.37	**0.007**	-0.07	0.551	0.14	0.302
			Pz	0.05	0.663	0.11	0.422	-0.06	0.591	-0.15	0.278	-0.01	0.937	-0.15	0.274	-0.11	0.332	0.19	0.181
		standard latency	Fz	-0.13	0.333	-0.19	0.239	-0.01	0.949	-0.11	0.492	-0.02	0.877	-0.09	0.600	0.15	0.284	-0.21	0.194
			FCz	-0.03	0.819	-0.22	0.129	0.15	0.227	-0.04	0.783	0.09	0.483	-0.03	0.837	0.01	0.960	-0.15	0.311
			Cz	-0.11	0.355	-0.11	0.489	0.14	0.263	0.27	0.076	0.06	0.613	0.26	0.084	-0.03	0.809	-0.20	0.182
			Pz	-0.10	0.418	0.11	0.439	-0.07	0.535	0.27	0.058	-0.08	0.518	0.27	0.058	0.02	0.844	0.31	0.033
		amplitude-weighted latency	Fz	-0.16	0.262	-0.09	0.602	-0.05	0.724	0.07	0.674	-0.07	0.622	0.07	0.671	0.18	0.203	-0.27	0.086
			FCz	-0.11	0.373	-0.26	0.083	0.15	0.227	0.12	0.413	0.08	0.543	0.11	0.479	0.14	0.266	-0.13	0.389
			Cz	0.09	0.486	-0.12	0.420	0.18	0.134	0.27	0.074	0.16	0.204	0.27	0.071	-0.08	0.503	-0.09	0.536
			Pz	-0.15	0.214	0.04	0.785	-0.13	0.258	-0.05	0.756	-0.14	0.250	-0.04	0.785	0.04	0.728	0.30	0.034
		area	Fz	0.15	0.273	-0.21	0.203	0.09	0.526	-0.12	0.472	0.09	0.536	-0.17	0.282	-0.13	0.337	-0.11	0.484
			FCz	0.11	0.373	0.00	0.985	0.10	0.406	-0.21	0.165	0.10	0.426	-0.23	0.119	-0.24	0.055	0.08	0.575
			Cz	-0.01	0.956	0.04	0.775	-0.02	0.856	-0.26	0.084	-0.02	0.892	-0.27	0.071	-0.10	0.406	0.12	0.443
			Pz	0.01	0.903	0.08	0.565	-0.07	0.554	-0.16	0.285	-0.05	0.680	-0.16	0.265	-0.16	0.183	0.17	0.248
	NoGo	peak amplitude	Fz	0.20	0.091	-0.39	0.004	0.15	0.221	-0.44	**0.001**	0.19	0.115	-0.47	**<0.0005**	-0.21	0.078	0.23	0.097
			FCz	0.20	0.100	-0.05	0.721	-0.03	0.791	-0.38	**0.006**	0.06	0.601	-0.39	**0.006**	-0.07	0.549	0.16	0.281
			Cz	0.16	0.182	0.07	0.635	-0.08	0.509	-0.44	**0.003**	0.03	0.784	-0.42	**0.004**	-0.02	0.867	0.13	0.391
			Pz	0.08	0.519	0.35	0.019	-0.09	0.439	0.05	0.741	-0.01	0.898	0.08	0.594	-0.06	0.637	-0.09	0.541
		mean amplitude	Fz	0.25	0.025	-0.41	0.002	0.16	0.159	-0.37	**0.007**	0.20	0.074	-0.41	**0.003**	-0.20	0.074	0.17	0.226
			FCz	0.21	0.065	-0.04	0.758	-0.01	0.898	-0.41	**0.002**	0.07	0.545	-0.42	**0.002**	-0.08	0.504	0.17	0.222
			Cz	0.12	0.278	0.16	0.263	-0.16	0.153	-0.27	0.048	-0.06	0.602	-0.26	0.057	0.07	0.510	0.14	0.300
			Pz	0.10	0.354	0.36	0.009	-0.09	0.431	-0.01	0.932	-0.01	0.937	0.02	0.890	-0.02	0.863	-0.13	0.371
		standard latency	Fz	0.09	0.445	-0.34	0.015	0.16	0.177	0.20	0.155	0.18	0.128	0.18	0.213	-0.02	0.884	-0.18	0.192
			FCz	-0.19	0.107	-0.31	0.027	0.19	0.113	0.29	0.038	0.03	0.791	0.24	0.087	-0.14	0.244	-0.21	0.146
			Cz	-0.08	0.503	-0.28	0.064	0.22	0.076	0.13	0.380	0.10	0.395	0.11	0.460	-0.10	0.420	-0.13	0.378
			Pz	-0.01	0.946	-0.13	0.401	0.11	0.331	-0.01	0.968	0.07	0.575	0.00	0.983	-0.12	0.316	-0.02	0.890
		amplitude-weighted latency	Fz	0.09	0.483	-0.39	0.005	0.19	0.114	0.15	0.289	0.19	0.113	0.11	0.440	-0.18	0.139	-0.17	0.235
			FCz	-0.09	0.437	-0.32	0.025	0.27	0.020	0.16	0.255	0.14	0.253	0.13	0.380	-0.23	0.050	-0.20	0.169
			Cz	-0.04	0.751	-0.25	0.095	0.28	0.020	0.20	0.183	0.16	0.188	0.18	0.229	-0.18	0.149	-0.14	0.346
			Pz	-0.04	0.731	-0.20	0.186	0.14	0.211	0.03	0.843	0.09	0.421	0.03	0.841	-0.14	0.235	0.18	0.240
		area	Fz	0.23	0.052	-0.40	0.003	0.20	0.094	-0.34	**0.014**	0.25	0.039	-0.38	**0.005**	-0.27	0.021	0.17	0.240
			FCz	0.26	0.029	-0.07	0.649	0.07	0.542	-0.37	**0.009**	0.17	0.156	-0.38	**0.006**	-0.14	0.230	0.15	0.285
			Cz	0.24	0.045	0.12	0.431	-0.05	0.696	-0.36	**0.014**	0.08	0.491	-0.35	0.019	-0.06	0.642	0.12	0.414
			Pz	0.07	0.550	0.35	0.017	-0.10	0.392	0.02	0.920	-0.03	0.787	0.05	0.762	-0.03	0.803	-0.17	0.271

Table 13. Associations between SART reaction time and ERP features at P2, N2, and P3. *Spearman's rank correlation coefficients and p-values for the relationship between reaction time on the SART and peak amplitude, mean amplitude, standard latency, amplitude-weighted latency, and area of the P2, N2, and P3 at Fz, FCz, Cz, and Pz for "Go" and "No-Go" trials. Significant p-values after adaptive FDR correction are shown in bold.*

			P2				N2				P3			
			MS		Control		MS		Control		MS		Control	
			rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
peak amplitude	Fz	Go	-0.08	0.503	-0.22	0.129	0.22	0.068	0.15	0.318	-0.06	0.672	-0.12	0.466
		No-Go	-0.10	0.397	-0.08	0.604	0.26	0.045	0.13	0.415	0.13	0.287	-0.11	0.425
	FCz	Go	-0.04	0.765	-0.23	0.121	0.16	0.189	0.04	0.803	-0.05	0.702	-0.41	**0.004**
		No-Go	-0.05	0.674	-0.14	0.354	0.17	0.149	0.28	0.058	-0.19	0.118	-0.49	**<0.0005**
	Cz	Go	-0.10	0.450	-0.27	0.071	-0.01	0.925	-0.24	0.134	-0.26	**0.035**	-0.49	**0.001**
		No-Go	0.07	0.580	-0.16	0.301	0.19	0.125	0.11	0.492	-0.31	**0.009**	-0.50	**<0.0005**
	Pz	Go	-0.15	0.229	-0.54	**<0.0005**	-0.31	0.029	0.14	0.445	-0.23	**0.053**	-0.38	**0.007**
		No-Go	-0.17	0.186	-0.32	0.062	0.10	0.429	-0.09	0.617	-0.33	**0.004**	-0.35	**0.017**
mean amplitude	Fz	Go	0.13	0.239	0.08	0.580	0.15	0.178	0.05	0.719	0.02	0.881	-0.07	0.601
		No-Go	0.09	0.446	0.07	0.620	0.09	0.447	0.02	0.901	0.06	0.585	-0.07	0.631
	FCz	Go	-0.01	0.902	-0.05	0.703	-0.03	0.822	-0.17	0.226	-0.10	0.389	-0.43	**0.001**
		No-Go	0.08	0.472	0.11	0.437	-0.08	0.501	-0.08	0.566	-0.26	**0.018**	-0.48	**<0.0005**
	Cz	Go	-0.23	0.042	-0.21	0.126	-0.29	0.010	-0.34	0.013	-0.28	**0.012**	-0.51	**<0.0005**
		No-Go	0.05	0.683	0.03	0.818	-0.18	0.116	-0.17	0.213	-0.44	**<0.0005**	-0.52	**<0.0005**
	Pz	Go	-0.27	0.017	-0.40	**0.003**	-0.28	0.013	-0.44	**0.001**	-0.19	0.084	-0.31	**0.025**
		No-Go	-0.16	0.163	-0.19	0.171	-0.25	0.025	-0.35	0.011	-0.31	**0.005**	-0.33	**0.014**
standard latency	Fz	Go	0.46	**<0.0005**	0.29	0.044	-0.01	0.939	0.05	0.762	-0.10	0.490	0.35	**0.025**
		No-Go	0.33	**0.004**	-0.20	0.164	-0.02	0.884	0.16	0.316	0.31	**0.009**	0.65	**<0.0005**
	FCz	Go	0.44	**<0.0005**	0.20	0.188	0.04	0.721	0.18	0.229	0.37	**0.002**	0.48	**0.001**
		No-Go	0.31	0.008	-0.22	0.128	0.09	0.441	0.26	0.079	0.54	**<0.0005**	0.70	**<0.0005**
	Cz	Go	0.28	0.027	0.08	0.616	0.31	0.016	0.35	0.031	0.42	**<0.0005**	0.73	**<0.0005**
		No-Go	0.20	0.103	0.02	0.893	0.18	0.146	0.41	0.006	0.45	**<0.0005**	0.59	**<0.0005**
	Pz	Go	-0.16	0.197	-0.34	0.026	0.01	0.970	0.33	0.062	0.10	0.387	0.05	0.754
		No-Go	-0.04	0.768	-0.15	0.374	0.12	0.381	0.14	0.405	0.30	**0.009**	0.40	**0.006**
weighted latency	Fz	Go	0.34	**0.002**	0.02	0.896	0.13	0.292	0.29	0.052	-0.05	0.728	0.49	**0.001**
		No-Go	0.24	0.037	-0.02	0.883	0.02	0.897	0.13	0.448	0.32	**0.007**	0.68	**<0.0005**
	FCz	Go	0.28	0.019	-0.09	0.546	0.18	0.149	0.47	**0.001**	0.33	**0.007**	0.72	**<0.0005**
		No-Go	0.24	0.036	-0.17	0.249	0.19	0.107	0.37	0.012	0.59	**<0.0005**	0.69	**<0.0005**
	Cz	Go	-0.12	0.340	-0.23	0.137	0.36	0.005	0.63	**<0.0005**	0.41	**0.001**	0.73	**<0.0005**
		No-Go	0.11	0.377	0.03	0.848	0.22	0.071	0.49	**0.001**	0.63	**<0.0005**	0.69	**<0.0005**
	Pz	Go	-0.16	0.186	-0.47	**0.002**	0.15	0.315	0.41	0.018	-0.03	0.813	-0.09	0.538
		No-Go	-0.05	0.711	-0.20	0.239	0.20	0.135	0.30	0.076	0.33	**0.004**	0.37	**0.011**
area	Fz	Go	-0.02	0.848	-0.24	0.096	0.15	0.214	0.13	0.386	-0.01	0.957	-0.12	0.470
		No-Go	-0.06	0.582	-0.14	0.332	0.28	0.032	0.08	0.610	0.15	0.213	-0.02	0.891
	FCz	Go	-0.06	0.623	-0.25	0.088	0.10	0.418	-0.03	0.853	-0.04	0.767	-0.32	**0.031**
		No-Go	-0.06	0.605	-0.16	0.287	0.09	0.475	0.20	0.190	-0.11	0.375	-0.42	**0.002**
	Cz	Go	-0.19	0.139	-0.27	0.072	-0.12	0.372	-0.33	0.038	-0.24	**0.048**	-0.43	**0.003**
		No-Go	0.07	0.587	-0.17	0.273	0.03	0.781	-0.02	0.897	-0.33	**0.007**	-0.53	**<0.0005**
	Pz	Go	-0.19	0.124	-0.54	**<0.0005**	-0.35	0.013	-0.03	0.881	-0.19	0.119	-0.36	**0.012**
		No-Go	-0.17	0.176	-0.34	0.049	0.04	0.741	-0.19	0.257	-0.32	**0.005**	-0.34	**0.021**

Discussion

SART performance is impaired in RRMS

Participants with RRMS made increased errors of omission, commission, and anticipation on the SART, reflecting an impairment in sustained attention and response inhibition in this group. O'Connell et al. (2009) propose that, in comparison to the sequential SART paradigm, the random SART paradigm used here may be more reflective of response inhibition processes than sustained attention processes (O'Connell et al. 2009). Response inhibition, which is a component of executive function, has previously been reported to be impaired in MS using other paradigms (Clough et al. 2015; McCarthy et al. 2005;

Simani et al. 2023). However, other studies do not find impairments in response inhibition, suggesting that these results may vary by factors like MS type, disease duration, or even task choice (Elosúa and Villadangos 2023; Santiago et al. 2007).

Unexpectedly, no impairment on SART performance scores was observed in SPMS or PPMS groups. This may be a lack of power due to the relatively small sample size (n=9; n=8) in these groups or could reflect the development of some compensatory change that is not present in RRMS.

Similarly, no group showed impairments in reaction time, despite the motor impairment associated with multiple sclerosis. In contrast, participants with RRMS showed a faster reaction time relative to controls. However, this effect is likely to relate to the more prevalent errors of anticipation made by this group, rather than a true advantage in motor or processing function relative to controls.

Therefore, SART reaction time appears to be insensitive to MS-related motor impairment and is therefore a good choice for longitudinal use in clinical trials to assess changes in cognition independently of changes in motor function.

SART-related potentials are altered in MS

We observed the previously reported increase in N2 and P3 amplitudes during SART "No-Go" trials in both controls and PwMS (McMackin et al. 2020; Zordan et al. 2008). Future work should explore interactions between this effect and participant group to assess whether the size of this increase varies among groups.

In this study, we investigated two measures of latency and three measures of size of the P2, N2, and P3 ERPs and found decreased latencies of the P2 and N2, increased latencies of the P3, diminished P2 amplitudes, and both diminished and enhanced P3 amplitudes in subgroups of participants with MS. These ERP alterations were not consistent between subgroups, suggesting that this paradigm can detect clinically relevant distinctions in brain function.

Previous studies have reported similar, but generally less comprehensive, sets of alterations. The larger number of alterations detected in this study may support the suitability of the SART for detecting cortical changes related to cognitive impairment in this population compared to other paradigm choices:

For example, Kimiskidis et al. (2016) reported increased P3 latency and decreased P2 and N2 amplitudes (but not decreased P2 or N2 latency or altered P3 amplitude), during a semi-passive auditory oddball paradigm. The authors also describe a positive association between P3 latency and age, as we report here.

Whelan et al. (2010) found altered N2 latency and P2 and P3 amplitude on an active visual oddball task and altered P2, N2, and P3 latency during an active auditory oddball task. The study did not find associations between these alterations and age. In a separate study, this group identified latency and amplitude differences in the P3a subcomponent that varied between subtypes (Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al. 2010).

In our study, performance on the MSNQ and HADS-A/D did not correspond to any ERP measure, suggesting that these ERPs are able to detect alterations that are not captured by current clinical tools. These ERPs may reflect impairment in domains not assessed by these screening questionnaires or may represent pre-clinical or sub-clinical changes not detectable by the screening tools.

Limitations and future directions

Sample size and selection

Our sample included relatively small numbers of participants with SPMS (n=9) and PPMS (n=8), meaning that the study was underpowered to examine interactions between subgroups and other factors. An increased sample size would also allow us to better account for disease heterogeneity by considering factors like disease duration, EDSS, and cognitive profiles. However, no correlations with disease duration, EDSS, or education were reported in a previous study ERP study including P2, N2, and P3 (Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al. 2010).

The control group was also older and more male than our MS sample. We accounted for this by including age and gender as covariates in the analysis. The weak but significant correlations of age with several ERP measures suggests that age should continue to be explicitly included as a covariate in these analyses and supports the hypothesis that the observed changes are not wholly due to aging.

Fatigue and sleep disturbances

Fatigue is one of the most commonly reported symptoms in MS and can impact clinical measurements of cognition (Braley et al. 2016; Guillemin et al. 2022). Fatigue has been shown to impact P300 latency in MS (Pokryszko-Dragan et al. 2016). Additionally, sleep disturbances may impact sustained attention and response inhibition in this group (Braley et al. 2016; Lehmann et al. 2013). While we did not have data on the fatigue status of this sample, future studies should examine the impact of fatigue on the ERPs described here.

Source localization

Localizing these scalp-level ERPs to their sources (as described in McMackin et al. (2020)) could increase the power of this analysis and provide mechanistic explanations for the ERP changes and behavioral impairments observed in this population.

Conclusion

This study characterizes for the first time the performance of people with multiple sclerosis on the sustained attention to response task and provides evidence that ERP responses to this task are altered in line with previous ERP alteration findings in this population.

Chapter 7

Results: MMN in MS

Mismatch negativity is unaffected in MS

Chapter summary

This chapter investigates the use of the mismatch negativity (MMN) ERP, which is a classic EEG biomarker of cognitive dysfunction, in multiple sclerosis. Prior literature on the MMN's utility in this condition is inconclusive. We do not find evidence of the MMN's ability to distinguish between participants with MS and controls, among subgroups of MS, or between people with varying degrees of cognitive impairment. This suggests that the MMN may not be the best avenue for further investigation of cognitive impairment or subtyping in MS.

Introduction

As discussed in previous chapters, cognitive dysfunction in multiple sclerosis is frequent and impactful, but often not assessed as part of regular clinical visits due to limitations of time, staffing, or equipment. Thus, any proposed EEG biomarker of cognitive function must be both clinically relevant and clinically practical. This means that any task-based measures should be fast and completed easily by patients with significant motor or cognitive impairments. One solution to this challenge is the use of passive ERP tasks, where the repetitive stimulus is delivered without the need for a cognitive or physical response from the participant.

Oddball tasks

"Oddball" tasks, in which infrequent "deviant" stimuli are presented in a stream of "standard" stimuli are one such potentially passive task. Some oddball task designs ask participants to respond (e.g. with a button click) to the deviant stimulus (the "oddball"), but ERP responses to these stimuli also can be generated in the absence of a response. Certain designs, like the one used in this study, also employ a distractor task or stimulus (in this case, a movie) to present the task stimuli outside of the participant's direct attention. The fully passive versions of these tasks are a good option for use with patient groups whose motor symptoms, cognitive impairment, or fatigue could hamper their ability to engage with an active cognitive task. ERPs generated from such tasks have been

shown to reflect not only sensory engagement with the task, but also aspects of unconscious cognitive processing (Näätänen et al. 2014).

Mismatch Negativity

The mismatch negativity (MMN) is one such ERP that was first described by Nääntänen and Michie (1979) and reflects the sensory and early cognitive aspects of change detection (Näätänen et al. 2007). It is a difference waveform obtained by subtracting responses to standard stimuli from responses to deviant stimuli. Early analysis of ERP topographies suggested that the signal is generated temporally in or near the auditory cortex with input from right frontal sources (Giard et al. 1990; Scherg et al. 1989). These sources were confirmed with later intracranial and MEG analyses (Kropotov et al. 1995; Halgren et al. 1995; Näätänen et al. 2012; Baudena et al. 1995). The signal is generally observed to peak approximately 100-300ms after stimulus presentation and is maximal at electrodes over the frontocentral cortex (Giard et al. 1990).

MMN in multiple sclerosis

The MMN remains under-researched in MS with studies reporting variable results. Of the three prior published studies of the MMN in MS, only one found amplitude or latency abnormalities in MS. In this study, reduced area and latency to a duration deviant was seen at Fz (Jung et al. 2006). This study also found smaller MMN responses in cognitively impaired (n=6) than cognitively unimpaired (n=12) participants, though the sample size was small. Two other studies measuring the MMN at Fz and Cz (Santos et al. 2006) and F4, Fz, F3, C4, Cz, and C3 (Bissonnette et al. 2023) did not find amplitude or latency differences between people with MS and controls. However, both studies report associations between MMN amplitude and clinically relevant metrics. Santos et al. (2006) found a correlation between an absent MMN response and low PASAT score, and Bissonnette et al. (2023) found a correlation between lower MMN to a volume-change stimulus and higher EDSS. These results suggest that while the MMN may not show differences between people with MS and controls, it may still reflect clinically relevant distinctions among people with MS.

MMN in other neurodegenerative conditions

MMN EEG amplitude and latency changes have also been reported in several other conditions, including neurodegenerative conditions. The association between these MMN

alterations and cognitive changes varies. In ALS, some studies find decreases in amplitude (Raggi et al. 2008) and increases in latency (Iyer et al. 2017). Other studies report no differences between groups on the MMN's amplitude or latency (Mannarelli et al. 2014; Pinkhardt et al. 2008). However, ERP differences between participants with and without ALS may be more apparent at their brain sources rather than at electrodes (McMackin et al. 2019; McMackin, Dukic, Costello, Pinto-Grau, McManus, et al. 2021).

Reduced amplitude and increased latency MMNs have also been found in Parkinson's disease (Brønnick et al. 2010; Pekkonen et al. 1995), though other studies find no difference between this group and controls (Solís-Vivanco et al. 2011; De Groote et al. 2021).

Similarly varied reports are seen in Alzheimer's disease, with some studies showing decreased MMN amplitude and increased latency (Papadaniil et al. 2016; Pekkonen et al. 1994), and other studies finding no MMN alterations (Gaeta et al. 1999), or alterations only in specific stimulus conditions (Kazmerski et al. 1997).

In Huntington's disease, higher MMN EEG amplitudes have been observed in people with manifest disease compared to both pre-manifest participants and controls (Beste et al. 2008). In contrast, the MMNm (magnetic MMN, obtained using MEG) showed decreased amplitude and increased latency (Cheng et al. 2014). Decreased global field power (GFP) of the EEG MMN (with no changes in amplitude or latency) has also been reported (Delussi et al. 2024).

Aims

The widespread use of the MMN as a marker of cognition in these conditions suggests that further investigation of the MMN in MS is needed. This study aims to quantify the frequency deviant MMN in MS relative to healthy controls and to understand the relationship between this ERP and a cognitive screening tool (MSNQ).

Methods

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, with ethical approval from the Beaumont Hospital Ethics (Medical Research) Committee (REC reference: 18/63), the St. Vincent's University Hospital Research Ethics Committee (REC

reference: RS19-054), and the St. James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (REC reference: 2017-02 Chairman's Action 18). Informed, voluntary consent was obtained from all study participants.

Participants

Recruitment

Participants with multiple sclerosis (PwMS) (n=81) were recruited from Beaumont Hospital, St. Vincent's University Hospital, and St. James's Hospital, Dublin, Ireland during routine neurology and specialist multiple sclerosis clinics. PwMS were also recruited through online advertisements distributed by MS Society Ireland. Neurologically healthy controls (n=54) were recruited through existing control banks in the Academic Unit of Neurology and advertisements on websites and social media.

Inclusion and exclusion

Adult PwMS with diagnosed RRMS, SPMS, or PPMS and no DMT changes or relapses within the prior 3 months were eligible for recruitment to the study. Control participants with no neurological, psychological, or muscular conditions and not taking CNS-acting medications were also recruited. Exclusion criteria for both PwMS and controls included active psychiatric disease, history of seizures, head trauma causing a diagnosed concussion or loss of consciousness, metallic implants in the head, and pregnancy or breastfeeding.

Participant demographics

Characteristics of the participant samples are presented in **Table 14**.

Table 14. Demographics of the sample

	Patients	Controls
n	81	54
mean age (years) [SD]	48.8 [12.3]	60.2 [12.8]
age range (years)	27-82	21-72
Gender (f/m)	61/20	29/25
Handedness (R/L/A)	72/7/2	39/2/2
MS subtype (RRMS/SPMS/PPMS/unknown)	63/9/8/1	n/a
DMD status [no DMD/taking DMD]	23/58	n/a
Mean disease duration (years) [min-max]	14.7 [0-68]	n/a
Mean MSNQ score [*n* anormal]	27.4 [43]	n/a
Mean HADS- A [*n* abnormal]	6.9 [33]	n/a
Mean HADS-D [*n* abnormal]	4.7 [16]	n/a

Data acquisition

EEG recording

128 active electrodes were applied to an EEG cap (EASYCAP GmbH) selected to fit the participant's head by trained experimenters. EEG signals were recorded at 512Hz on a BioSemi ActiveTwo system in an electrically shielded room. Stimulus presentation and participant response instances were saved into the continuous EEG data to facilitate accurate epoching. The recording room was darkened during recording blocks to minimize distracting visual input.

Experimental paradigm

As described in Iyer et al. (2017), participants were instructed to sit in a relaxed manner and pay attention to a silenced black-and-white movie (Hazanavicius 2011) while a series of tones was presented through headphones. The tone sequence consisted of frequent "standard" and infrequent "deviant" tones of 720 and 800Hz, respectively. Deviant tones comprised approximately 10% of the delivered tones. Three blocks of tones were presented for approximately seven minutes each.

Neuropsychological screening

Participants with MS completed the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) (Benedict et al. 2003) and Hospital Anxiety and Depression Screening (HADS) (Zigmond and Snaith 1983).

Data analysis

EEG signal preprocessing

Data were cleaned according to the methods in Chapter 4. The continuous EEG signal was epoched from 200 pre-stimulus to 600ms post-stimulus and averaged across trials using a 10% trimmed mean to create ERP responses for each participant at each channel.

ERP analysis

Signals were again low-pass filtered below 15Hz (dual-pass 5^{th}-order Butterworth), baseline-subtracted, and referenced to the common average. Auditory evoked potentials in response to standard and deviant stimuli were extracted from between 150-350ms post-stimulus and subtracted to obtain the MMN component. The maximum amplitude, mean amplitude, latency of the peak, amplitude-weighted latency of the peak, and area under the MMN were calculated at each channel for each participant. A normal distribution was approximated using an inverse normal transform.

Group comparisons

A four-factor ANOVA was conducted for each waveform feature to understand the impact of group (RRMS, SPMS, PPMS, and HC), gender, channel location (Fz, FCz, Cz, Pz) and age on these features. Outputs were corrected with a 5% FDR, and remaining significant effects in group, gender, and channel were localized with Fisher's least significant difference (LSD) test with 5% adaptive false discovery rate (FDR) correction (Benjamini et al. 2006). Effects of age were localized post-hoc using Spearman's rank correlation in both PwMS and controls and corrected using a 5% adaptive FDR (AFDR).

Correlations with neuropsychological screening and clinical characteristics

Spearman's rank correlation coefficients were calculated for each pairing of the waveform features (amplitude, mean amplitude, latency, amplitude-weighted latency, and area under the MMN at Fz, FCz, Cz, and Pz) with clinical cognitive and psychological screening scores (MSNQ score, HADS-A score, HADS-D score) in participants with MS. Correlations were also calculated between waveform features and age at diagnosis and

disease duration. P-values were corrected using a 5% adaptive FDR correction for each measure. Uncorrected p-values are shown for significant detections.

Results

MMN responses

Mismatch negativity responses were seen in both people with MS and healthy controls at electrodes Fz, FCz, and Cz (**Figure 5**). No consistent MMN response was seen at Pz.

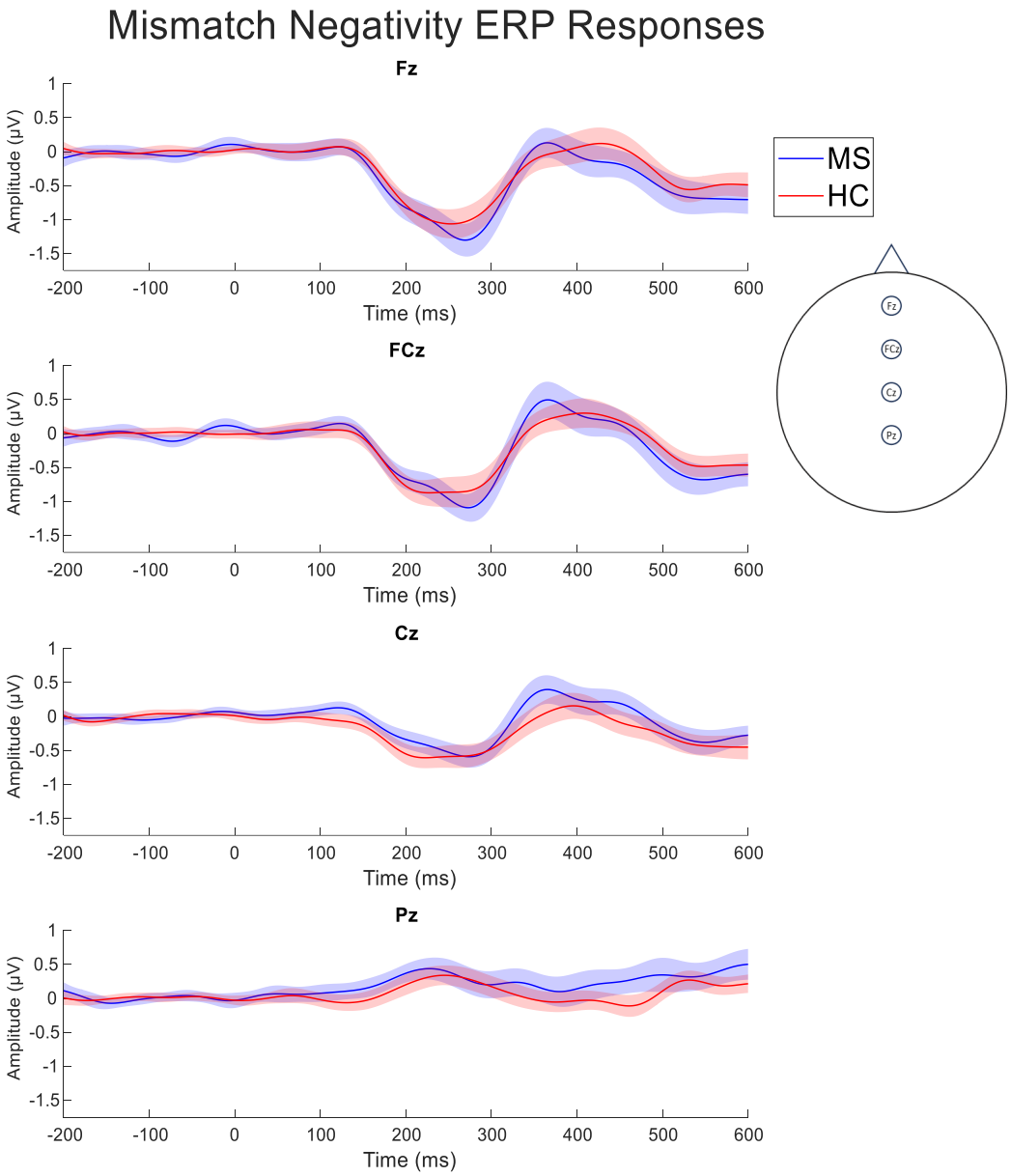


Figure 5. Mismatch negativity responses to a passive auditory frequency oddball*. Subtracted mismatch negativity waveforms are shown for participants with MS and healthy controls. Responses from participants with MS are shown in blue, and responses from healthy controls are shown in red. The solid line corresponds to the mean of the MMN across participants and the shaded region indicates the 95% confidence interval of this mean. Plots were generated based on plotting steps initially drafted by Etain O'Meara.*

MMN measures do not distinguish people with MS from healthy controls

No differences were observed between RRMS, SPMS, PPMS, or controls in the peak or mean amplitude, latency or mean latency, and area under the component of the MMN (all ANOVA group effects insignificant after adaptive FDR correction).

The MMN is largest at Fz

Significant effects of electrode were observed for peak amplitude ($F_{3,467} = 58.66$, $p < 0.0005$), mean amplitude ($F_{3,467} = 34.99$, $p < 0.0005$), area ($F_{3,467} = 54.38$, $p < 0.0005$), and amplitude-weighted latency ($F_{3,467} = 50.21$, $p < 0.0005$) of the MMN. Post-hoc tests revealed that MMN responses were larger (more negative) anteriorly than posteriorly. The peak, mean amplitude and area under the component of the MMN were each significantly different at each electrode, with amplitude decreasing moving posteriorly. The largest peaks, mean amplitudes, and areas were seen at Fz, followed by FCz, Cz, and then Pz (**Table 15**). However, the MMN mean amplitude at Pz was positive, suggesting that an MMN may not have been reliably found at this electrode. A follow-up analysis revealed that no MMN was found for 11 participants with MS and 11 controls at Pz, compared to 0-3 missed MMN peaks at the other channels.

Table 15. P-values for MMN post-hoc tests of size

		FCz	Cz	Pz
Peak	**Fz**	0.039	p < 0.0005	p < 0.0005
	FCz		p < 0.0005	p < 0.0005
	Cz			p < 0.0005
	Pz			
Mean	**Fz**	0.004	p < 0.0005	p < 0.0005
	FCz		0.091	p < 0.0005
	Cz			p < 0.0005
	Pz			
Area	**Fz**	0.014	p < 0.0005	p < 0.0005
	FCz		0.003	p < 0.0005
	Cz			p < 0.0005
	Pz			

Amplitude-weighted latency is increased at Pz and in males.

The amplitude-weighted latency of the MMN peak was slower at Pz than at Fz ($p < 0.0005$), FCz ($p < 0.0005$), and Cz ($p < 0.0005$), which did not differ from one another. This could be due to a prolongation of the MMN response in this region or (as discussed

above) could reflect a failure to find an MMN peak at this electrode. Additionally, males showed a longer amplitude-weighted latency MMN compared to females across controls and participants with MS (p = 0.004).

Age does not affect the latency of the MMN

A post-hoc correlation test was conducted between age and the features that showed a significant effect for age on the ANOVA: MNN peak, latency, and amplitude-weighted latency. No effects of age could be localized post-hoc after adaptive FDR correction (**Table 16**).

Table 16. Age post-hoc correlation test. *Correlations are shown between age and the MMN features that showed significant main effects of age on ANOVA. No correlations remained significant after correction for multiple comparisons.*

MMN	channel	Age	
		rho	p
Peak Amplitude	Fz	0.09	0.328
	FCz	0.06	0.515
	Cz	-0.10	0.286
	Pz	-0.22	0.032
Latency	Fz	0.12	0.193
	FCz	0.16	0.078
	Cz	0.13	0.151
	Pz	0.18	0.077
Amplitude-Weighted Latency	Fz	0.19	0.044
	FCz	0.21	0.023
	Cz	0.21	0.024
	Pz	-0.06	0.586

MMN standard latency at Pz is associated with onset age and disease duration

Slower standard latencies of the MMN at Pz were associated with younger age at diagnosis (ρ = - 0.46, p = 0.002) and longer disease duration (ρ = 0.41, p = 0.005) (**Table 17**). No significant correlations were seen between age at diagnosis or disease duration and MMN peak or mean amplitude, area, or amplitude-weighted latency. Furthermore, no associations were found between MMN waveform features and scores on the MSNQ, HADS-A, or HADS-D (**Supplementary Table 7**).

***Table 17. MMN feature associations with age at diagnosis and disease duration**. Spearman's correlation coefficients are shown for correlations between MMN characteristics at Fz, FCz, Cz, and Pz and age at diagnosis and disease duration. Significant p- values after adaptive FDR correction are shown in bold.*

MMN		age at diagnosis		disease duration	
	channel	rho	p	rho	p
peak	Fz	-0.08	0.570	-0.05	0.707
	FCz	0.08	0.575	-0.18	0.198
	Cz	0.11	0.443	-0.03	0.850
	Pz	0.21	0.163	-0.16	0.301
mean	Fz	-0.05	0.730	-0.20	0.161
	FCz	0.15	0.289	-0.33	0.016
	Cz	0.15	0.285	-0.16	0.259
	Pz	0.28	0.045	-0.15	0.281
delay	Fz	-0.07	0.632	0.00	0.995
	FCz	-0.22	0.121	0.17	0.223
	Cz	-0.14	0.343	0.18	0.194
	Pz	-0.46	**0.002**	0.41	**0.005**
centre	Fz	-0.06	0.652	0.13	0.360
	FCz	-0.15	0.277	0.27	0.056
	Cz	-0.22	0.113	0.17	0.246
	Pz	-0.20	0.188	0.03	0.826
area	Fz	-0.08	0.560	-0.17	0.223
	FCz	0.10	0.466	-0.31	0.025
	Cz	0.13	0.375	-0.05	0.724
	Pz	0.33	0.029	-0.25	0.105

Discussion

Variability of the MMN

Unlike Jung et al. (2006), we did not observe altered MMN responses in people with MS. We also did not see differences between subgroups of MS on any MMN measure. This is in agreement with the results of Santos et al. (2006) and Bissonnette et al. (2023), who did not find differences between participants with and without MS on MMN measures.

Like previous studies, we observed the MMN over frontocentral locations: Fz, FCz, and Cz. Among these electrodes, the MMN was largest at Fz and decreased moving posteriorly, supporting the activation of a frontal source by this paradigm. Our finding of a positive average amplitude across the MMN window at Pz indicates that we likely did not capture a MMN component at this electrode. This also suggests that the decreased latency we observed at Pz reflects the activity of other ERP components, rather than the MMN.

Other studies failing to find MMN alterations in MS did report associations between the MMN and clinical or cognitive scores. We found an association between slower MMN responses at Pz and both younger MS onset and longer disease duration, suggesting that the MMN latency could reflect the increased risk of cognitive impairment in this group. This effect should be confirmed with follow up studies due to the potential limitations of recording at Pz discussed above.

We also assessed the correlation between twenty (five characteristics at four electrodes) MMN features and the MSNQ and HADS and found no association. This suggests that the MSNQ reflects impairment in cognitive processes other than change detection and involuntary attention switching.

Electrode selection

This study investigated MMN signals at four electrodes along the central midline (Fz, FCz, Cz, and Pz) selected based on previous analysis of control data by this group (Iyer et al. 2017). While many studies do report this ERP over the midline, the MMN has been found to show hemispheric asymmetry, with higher amplitude responses over the right hemisphere (Giard et al. 1990; Scherg et al. 1989).

Future studies using this data should independently assess the locations of maximal MMN response in patients and controls to select optimal channels for analysis. The use of source localization measures could also avoid the challenges associated with electrode selection and determine the locations of MMN generation in this sample.

Stimulus selection

The MMN shows variable responses to different types of stimulus oddballs (Wunderlich and Cone-Wesson 2001; Tervaniemi 2022), so it is possible that our choice of stimulus and paradigm did not elicit maximally discriminatory signals. However, Bissonnette et al. (2023) studied the effects of five different types of oddball stimuli in MS and found no significant effects in amplitude or latency for any stimulus.

Medication

Evidence suggests that the MMN is affected by escitalopram (Oranje et al. 2008; Wienberg et al. 2010), raising the question of whether this and other medications commonly taken by participants with MS may affect these results. We did not account for medication status in this study but excluded participants taking medications other than

SSRIs or SNRIs. However, unpublished work[18] from this lab suggests that these medications do not affect the ERPs studied here (O'Meara 2024). The other MMN studies in MS discussed above did not include medication as an exclusion criterion, so we do not expect the inclusion of these participants in our study to significantly alter our results in relation to these prior studies.

Fatigue and sleep disturbances

Fatigue and sleep disturbances are common in multiple sclerosis (Bhattarai et al. 2023) and are known to reduce the MMN in people without MS (Evstigneeva et al. 2010; Yang et al. 2013; Zerouali et al. 2010). Our study and the studies summarized here did not assess fatigue. Future research on the MMN in MS should include participants' level of fatigue and sleep disturbances as covariates.

Conclusion

These results, in conjunction with prior literature, suggest that the MMN is not a robust marker of cognitive or sensory dysfunction in MS. Furthermore, the MMN does not appear to show significant potential as a diagnostic or stratification biomarker. Follow-up analyses could assess whether the previously reported associations between reduced MMN and impaired performance on detailed neuropsychological measures exist in this study's sample. However, extensive additional investigation or dataset expansion is not currently warranted.

[18] Undergraduate thesis

Chapter 8

Results: Microstates in MS

Microstate properties are affected in SPMS

Chapter summary

This chapter replicates previous microstate analyses of resting-state EEG data in MS. This work represents the first analysis of EEG microstate characteristics in people with secondary progressive and primary progressive multiple sclerosis (SPMS, PPMS). Participants with SPMS are shown to have altered microstate properties. Other previously reported microstate alterations were not observed in this sample.

Introduction

Many proposed EEG biomarkers of cognition in MS are event-related potentials (ERPs), which involve recording EEG measurements during the presentation of repetitive stimuli, the responses to which are then averaged. These "task-based" paradigms generally involve long recording sessions to obtain sufficient trials for adequate signal-to-noise ratios and may require a verbal or motor response from the participant if needed to ensure particular types of cognitive processing, for example attention or memory. Long recording times limit clinical feasibility and patients' willingness to engage with these tests. Additionally, paradigms requiring motor responses could be biased by physical disability levels in the absence of cognitive impairment.

In contrast, resting-state EEG (RS-EEG), during which EEG signals are recorded from a person sitting at rest and not engaging in an active mental task, can be recorded in a matter of minutes post-set-up from participants with severe motor or cognitive limitations. RS-EEG biomarkers of cognitive impairment have been proposed in MS including altered alpha power, frontal theta/beta ratios, graph parameters, and mutual information (Keune et al. 2017; Shirani and Mohebbi 2022; Lenne et al. 2013). Another promising avenue for RS-EEG evaluation of MS cognitive impairment is resting state EEG microstate analysis.

Microstates

Microstates are recurring, transient, quasi-stable topographies (spatial patterns of activity) of EEG scalp potentials lasting approximately 60-120ms (Michel and Koenig

2018). They can be extracted from resting state recordings of multi-channel electroencephalographic activity and represent the dominant whole-brain activations during a given window of time.

These semi-stable topographies can be grouped into a small number of microstate classes. Spatial clustering methods can be used to group activity patterns into topographic classes, ignoring the polarity of the signal (Pascual-Marqui et al. 1995). These clustered topographies, or classes, are then fitted back to the data to determine a sequence of dominant microstate activations for each time point.

The number of microstate classes identified or selected varies. The number of classes should be a balance between overexplaining and oversimplifying the data. Criteria to determine the optimal number of microstates vary, but many studies report 4 "canonical" microstates initially described by Koenig et al. (1999) and labelled Classes A, B, C, and D. Briefly, these classes have been associated with auditory and visual networks (A), visual networks (B), self-referential thought (C), and attention and executive functioning (D) (Tarailis et al. 2024).

Each of these aspects are altered in multiple sclerosis to varying degrees. Executive function and attention (Class D) are commonly reported cognitive impairments in MS (Chiaravalloti and DeLuca 2008). Interruptions of the visual network (Classes A and B) have also been found (Sacco et al. 2013). Auditory processing (Class A) is a less common impairment in MS but has been seen (Gür et al. 2022). Some evidence of alterations to interoception (Class C) also exists (Salamone et al. 2018) and this could be hypothesized to relate to symptoms of MS such as depression and deficits in social cognition.

Microstate alterations in neurological and psychiatric conditions

Altered EEG microstate properties have been identified across several neurological and psychological conditions. Increased frequency and coverage of Class A and lower coverage and duration of Class D have been observed in schizophrenia (Koenig et al. 1999). Increased Class A coverage and decreased Class D coverage were also observed in Huntington's disease, along with increases in Class B coverage, decreases in Class C occurrence, and decreases in Class D occurrence (Faber et al. 2021). Similarly, increased coverage and occurrence of Classes A and B, increased duration of Class A, and decreased duration of Class D were seen in ALS (Metzger et al. 2023).

Microstates in multiple sclerosis

Three studies have previously investigated microstate characteristics in MS. These studies looked specifically at participants with relapsing-remitting MS (RRMS). To date, no published work has reported the characteristics of microstates in people with secondary progressive or primary progressive MS (SPMS, PPMS).

Gschwind et al. (2016) were the first to identify the four canonical microstate classes in multiple sclerosis. Using a similar analysis pipeline to the one used in this chapter, they found longer durations and higher global explained variance (GEV) of Classes A and B in participants with RRMS than in controls. They also observed greater coverage of class B in RRMS. The authors also found associations between microstate properties and clinical characteristics. Longer Class A duration predicted longer disease duration, and shorter Class A duration predicted higher depression scores. Shorter Class B duration was associated with a higher two-year annualized relapse rate, more cognitive fatigue, and a higher EDSS score. Increased cognitive fatigue and higher EDSS scores were also predicted by greater GEV of Class A.

Like the Gschwind study, Baldini et al. (2023) also found higher Class A GEV in RRMS in addition to greater coverage and occurrence of Class A. The authors also report higher Class B occurrence and lower coverage, duration, GEV, and occurrence of class D in RRMS. This study also replicated the association between Class A duration disease duration, though the size of this association was small ($r = 0.29$). The study also found small correlations ($r = 0.32$-0.34) between increased performance on the symbol-digit modalities test (a test of information processing speed) and higher coverage, occurrence, and GEV of Class A. It is possible that this association of higher Class A GEV with both increased cognitive fatigue (Gschwind et al. 2016) and better SDMT performance (Baldini et al. 2023) could reflect a compensatory increase in cognitive effort in people with RRMS.

A follow-up study by the same group found increased Class B occurrence in fatigued participants with MS, as well as correlations between increased occurrence, coverage, duration, and GEV of Class B and increased cognitive fatigue (Baldini et al. 2024). This contradicts the association between decreased Class B duration and increased cognitive fatigue reported previously by Gschwind et al. (2016). However, these groups used

different analysis methods (prototypes calculated on all participant data vs. within groups) and fatigue scales (FSMC vs. MFIS), which may explain some variation in these results.

Aims

This study aims to evaluate whole-brain measures of network activity in subgroups of MS and understand relationships between these measures and clinical and demographic variables.

Methods

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, with ethical approval from the Beaumont Hospital Ethics (Medical Research) Committee (REC reference: 18/63), the St. Vincent's University Hospital Research Ethics Committee (REC reference: RS19-054), and the St. James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (REC reference: 2017-02 Chairman's Action 18). Informed, voluntary consent was obtained from all study participants.

Participants and data

Recruitment and inclusion

Participants with multiple sclerosis (n=71) were recruited from specialist and general neurology clinics (Beaumont, St. Vincent's, and St. James' Hospitals, Dublin, Ireland), and through online advertisements on the MS Society of Ireland website and the I-VOL volunteer database (www.i-vol.ie). Neurologically, psychiatrically, and psychologically healthy controls (n=78) were recruited through existing pseudo-anonymized datasets within the Academic Unit of Neurology, outreach events, and the I-VOL platform.

Participants with MS over 18 years of age with diagnosed MS (RRMS, SPMS, or PPMS) and no change in disease activity or medication status within the prior 3 months were eligible for inclusion in the study. Participants without MS and with no neurological, psychiatric, or muscular conditions or CNS-acting medication use were also eligible for inclusion as controls. Potential participants (with and without MS) were excluded for active psychiatric disease, history of seizures, history of head trauma causing a diagnosed concussion or loss of consciousness, metallic implants in the head, current pregnancy, or

current breastfeeding. Participants with MS taking SSRIs and SNRIs (n= 10) were eligible for inclusion due to the large number of people with MS who take these medications. Control participants taking SSRIs or SNRIs were not eligible for this study.

Demographics

Data from 71 PwMS (76% female, mean age: 48.4 ± 12.3 years) and 78 HC (60% female, mean age: 60.0 ± 12.0 years) were included in this analysis. Additional demographic information on the study population is presented in (**Table 18**).

Table 18. Demographic features of the sample

	Patients	Controls
n	71	78
mean age (years) [SD]	48.4 [12.3]	60.0 [12.0]
age range (years)	21-71	27-83
Gender (f/m)	54/17	47/31
MS subtype (RRMS/SPMS/PPMS/unknown)	57/7/6/1	n/a
DMD status [no DMD/taking DMD]	18/52	n/a
Mean disease duration (years) [min-max]	10.5 [0-51]	n/a
Mean MSNQ score [*n* anormal]	26.9 [36]	n/a
Mean HADS- A [*n* abnormal]	7.1 [28]	n/a
Mean HADS-D [*n* abnormal]	4.7 [12]	n/a

Questionnaires

Participants with MS completed the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ) (Benedict et al. 2003) and the Hospital Anxiety and Depression Scale (HADS-R) (Zigmond and Snaith 1983) at recruitment.

EEG recording

EEG was recorded using a cap-based (EASYCAP GmbH) 128-channel BioSemi ActiveTwo system at 512Hz in an electrically shielded room with the lights on (to prevent sleep). Electrode offsets were maintained between ± 25µV and signals were monitored online for channel noise, movement, and sleep.

Two three-minute blocks of eyes-open resting state EEG data were obtained from all participants as part of a longer EEG assessment battery. Participants were seated upright in a supportive chair and instructed to relax their bodies and let their minds wander. A 6x8cm^2 black fixation cross on white A4 paper was provided to minimize eye movement during recording.

Microstate processing

Microstate processing was conducted in MATLAB (R2020a) with the Microstate EEGLab toolbox from Poulsen et al. (2018) using custom scripts designed for the analysis by Metzger et al. (2023). Minor methodological changes were made to this analysis as described below.

Preprocessing

The pre-processing steps were carried out following pipelines previously outlined in publications by our team (Dukic et al. 2019; 2022; Nasseroleslami et al. 2019). These steps are briefly summarized here. First, continuous EEG signals were segmented into 750ms epochs. Epochs with high amplitude, mean shift, variance, and band-variance of spectral power were excluded using a 3.5 Z-score cutoff to avoid bias from muscle and blink artefacts (Dukic et al. 2017). The EEG signals were then down sampled to 256 Hz. Next, a zero-phase band-pass filter (one-pass zero-phase FIR: 1–97 Hz) was applied to remove non-cortical activity (slow drifts and very high frequency noise) with minimal distortion of the temporal information in the signal. A notch filter (dual-pass third order Butterworth: 50 Hz) was also applied to remove power line noise by sharply reducing signals at the notch frequency. The signals were baseline corrected to remove DC offsets and drift, and noisy channels were removed using an algorithm based on Bigdely-Shamlo et al.'s PREP pipeline (2015). The removed channels were replaced with an interpolation of neighboring electrodes to preserve spatial coverage. As recommended by (Michel and Koenig 2018), the signals were then referenced to the common average and low-pass filtered at 30Hz (6th order, dual-pass, zero-phase, brick-wall filter) to remove muscle activity artefacts.

Microstate computation

The topography of the EEG signal was obtained at time points corresponding to peaks of the global mean-field power (GFP) function, which was calculated for each participant

using a smoothing window of 10ms as described in Al Zoubi et al. (2019). Peaks less than 10ms from other peaks or more than 1.5 standard deviations above the mean were excluded from the analysis. A maximum of 3000 peaks were randomly selected from the individual's total set of GFP peaks to reduce computation time. The selected peaks represent 38.4% ± 4.8% (mean ± standard deviation) of the total available peaks for each participant.

These topographies were clustered into four prototype classes using a modified K-means clustering algorithm as described in Metzger et al. (2023), resulting in polarity-invariant clusters of microstate topographies. The number of clusters was set at four based on the cross-validation analysis conducted by Metzger et al. (2023) on the same group of control participants[19]. Additionally, using four clusters maximizes interpretability in relation to prior microstate literature. Prototypes were constructed by clustering the topographies at the selected GFP peaks from all three groups before backfitting.

The four averaged prototype topographies were backfitted to the continuous EEG data to obtain a sequence of microstates for each individual. Short microstates (<23ms) were removed by reclassifying these segments to the next most probable class, as these very short duration states are likely to represent noise (Poulsen et al. 2018).

Microstate properties

For each microstate class, the length of individual instances ("duration"), number of instances ("occurrence"), proportion of the full signal spent in the class ("coverage"), global explained variance (GEV), and global field power (GFP) were calculated for each participant. The probability of a particular class following another class was also calculated for each pair of microstate classes (e.g. A→ B, B→A, …, 12 pairs total) for each participant. These probabilities were not corrected for differences in the overall occurrence or duration of the microstate classes.

[19] This analysis determined the optimal number of microstate clusters (between 3 and 11) by creating prototype maps from two thirds of the data and evaluating their performance on the remaining third with respect to GEV and cross-validation criteria (Pascual-Marqui et al. 1995). The cross-validation procedure reduces the likelihood of obtaining clusters that represent noise, thereby ensuring the stability of future data (Metzger et al. 2023).

Statistical analysis

Pair-wise comparisons

Pair-wise comparisons among controls and participants with relapsing-remitting, secondary progressive, and primary progressive MS were completed for each microstate parameter and class using Mann-Whitney U tests (Mann and Whitney 1947b). P-values were corrected within parameters (duration, occurrence, coverage, GEV, GFP, and transition probabilities) with a 10% adaptive FDR correction (Benjamini et al. 2006; Nasseroleslami 2018). Group averages for these parameters are presented as mean ± standard deviation. Due to the nature of FDR correction, the p-values shown are unadjusted. Significant detections are indicated in the text and tables.

Correlations with clinical and neuropsychological scores

Correlations between the microstate parameters and clinical and neuropsychological characteristics were assessed using Spearman rank correlations in participants with RRMS, SPMS, and PPMS. The characteristics assessed were age, age at onset, disease duration, MSNQ score, HADS-A subscore, and HADS-D subscore. Correlations with age were also calculated in healthy controls. Multiple comparisons correction was carried out using adaptive FDR correction within clinical characteristics (Benjamini et al. 2006; Nasseroleslami 2018).

Results

Canonical microstates observed in both samples

The four canonical microstates that are typically discussed in the literature (A, B, C, D) were observed in both controls and participants with MS (Michel and Koenig 2018) (**Figure 6**). The total explained variance (mean ± standard deviation) of these prototype maps across all four classes was 59.6% ± 1.7% for data from controls, 63.1% ± 2.2% for data from participants with RRMS, 49.8% ± 10.4% for participants with SPMS, and 68.3% ± 6.6% for participants with PPMS. The amount of data explained by the prototypes was not significantly different among participant groups (Kruskal-Wallis test, $H = 4.15$ $p = 0.245$).

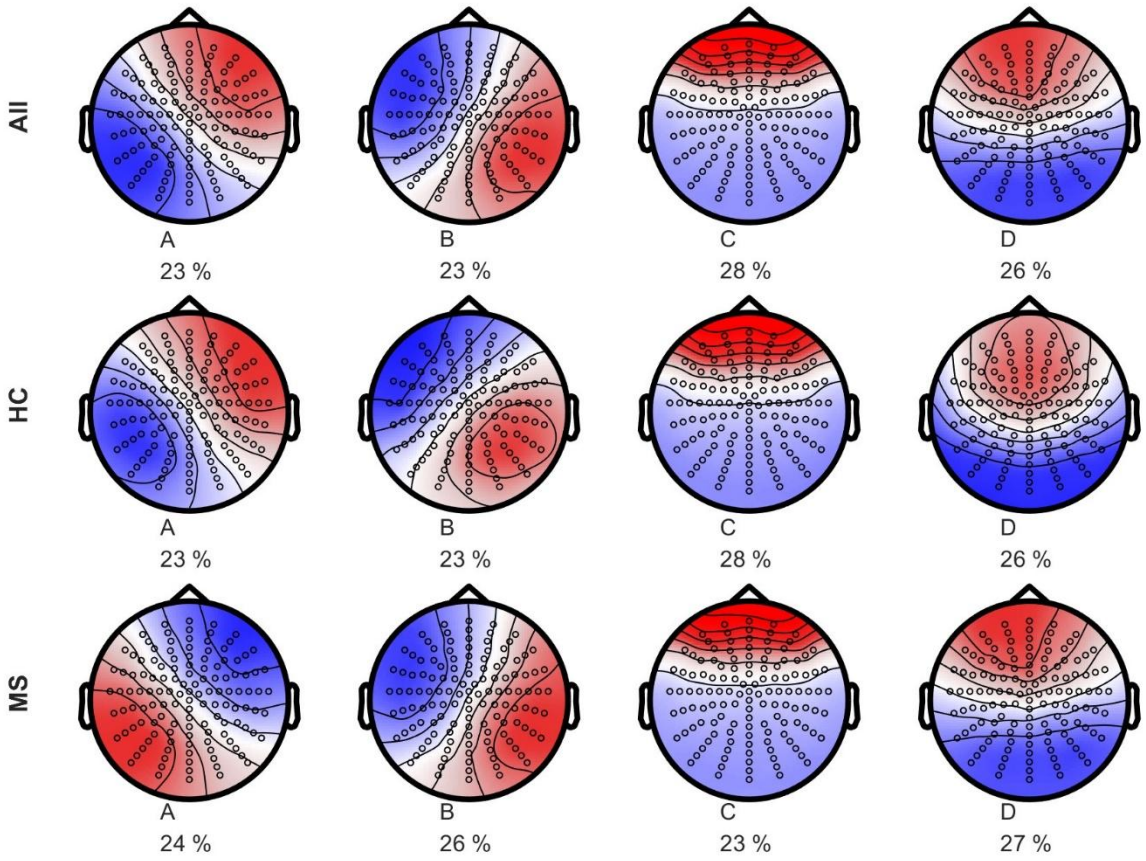


***Figure 6 Microstate prototype topographies**. Similar topographies are observed for each class in MS, HC, and combined groups. Percentages under each topographic map represent the coverage (percent of the total recording spent in that class) of that class. Microstates topographies are polarity invariant: topographies with opposite polarities are treated as the same microstate.*

Duration of Class B is altered in SPMS

Participants with SPMS showed an increase in the duration of Class B (68.82 ± 7.7ms) compared to both controls (60.21 ± 3.71ms, $p < 0.0005$) and participants with RRMS (61.03 ± 5.68ms, $p = 0.002$) (**Figure 7**). Class B duration did not differ between participants with SPMS and PPMS (61.43 ± 5.01ms, $p > 0.05$) or among participants with RRMS or PPMS and controls ($p > 0.05$).

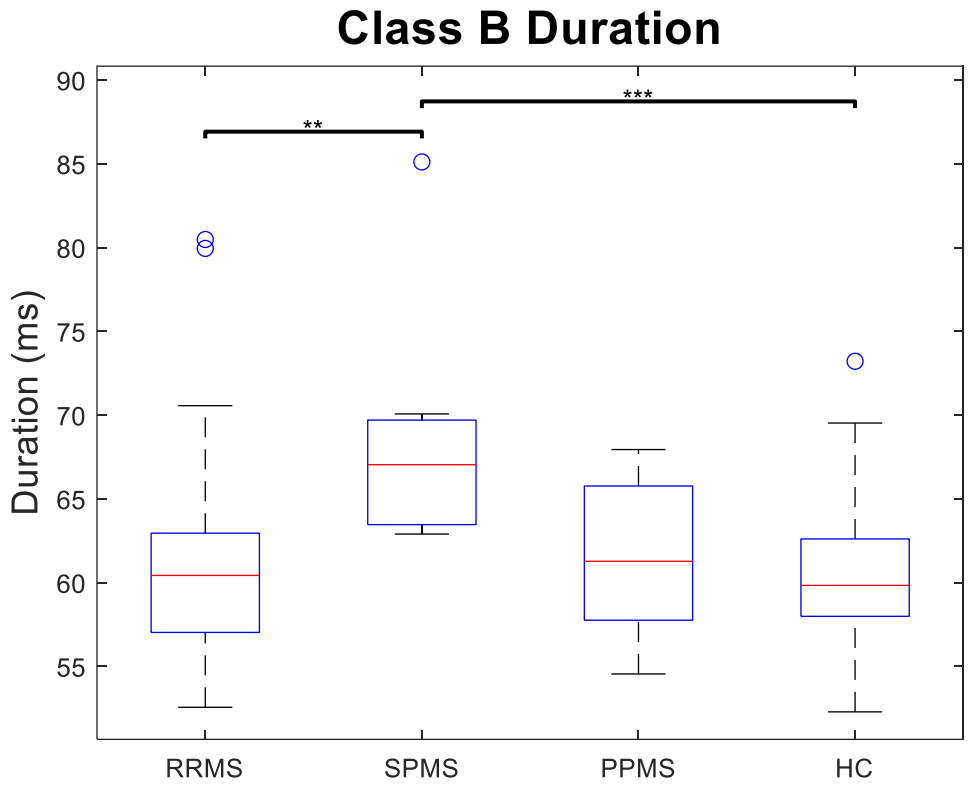


Figure 7. Duration of Class B. *The duration of microstate Class B in milliseconds is shown for RRMS, SPMS, PPMS, and HC groups. Significant differences were identified between RRMS and SPMS (p=0.002) and SPMS and HC (p<0.0005) groups.*

Occurrence, coverage, duration, GEV, and GFP are not altered in MS

After adaptive FDR correction, no significant differences were identified between healthy controls and participants with RRMS or PPMS on microstate occurrence, coverage, duration, GEV, or GFP in any microstate class. No differences other than increased Class B duration were seen in participants with SPMS.

Transition probabilities are not altered in MS

No differences in transition probabilities were found between participants with any subgroup of MS and healthy controls.

Microstate properties are correlated with age in controls only

Increased age in controls was generally associated with decreased activity in microstate Class D. Older controls showed lower Class D occurrence ($\rho = -0.28$, $p = 0.012$), duration ($\rho = -0.31$, $p = 0.007$), coverage ($\rho = -0.30$, $p = 0.005$), GEV ($\rho = -0.31$, $p = 0.005$), and transition probabilities from Class A to Class D ($\rho = -0.32$, $p = 0.004$) and from Class B to Class D ($\rho = -0.41$, $p < 0.0005$). Increased age was also associated with increased coverage

of Class C in controls (ρ = 0.26, p < 0.0005). No associations were seen between any microstate parameter and age, age at onset, disease duration, MSNQ score, HADS-A score, or HADS-D score in participants with RRMS, SPMS, or PPMS. Correlation coefficients and p values are given in **Table 19**.

Table 19. Microstate correlations with demographic and clinical features. *Significant correlations with age were observed in healthy controls for the occurrence, duration, coverage, and GEV of class D, transition probabilities from A and B to D, and coverage of class C. No associations were found between microstate properties and clinical characteristics in people with RRMS, SPMS, and PPMS. Results from people with RRMS, SPMS, and PPMS are shown collectively (i.e. "PwMS" rather than by subtype) for legibility. No significant effects were observed at either group or subtype level.*

		Controls		PwMS											
		Age		Age		Age at Onset		Disease Duration		MSNQ		HADS A		HADS D	
		rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
Occurrence	A	-0.13	0.244	0.00	0.975	-0.02	0.908	0.13	0.353	0.07	0.573	-0.06	0.648	0.01	0.908
	B	-0.23	0.047	0.09	0.463	-0.01	0.921	0.13	0.358	-0.09	0.447	-0.18	0.143	0.00	0.970
	C	0.13	0.251	-0.03	0.782	0.03	0.826	-0.07	0.608	0.00	0.995	0.24	0.046	0.12	0.307
	D	-0.28	**0.012**	-0.11	0.379	-0.12	0.405	-0.09	0.517	-0.21	0.085	-0.06	0.610	0.09	0.441
Duration	A	0.05	0.695	-0.04	0.770	-0.02	0.881	0.09	0.520	0.10	0.426	-0.05	0.709	-0.10	0.424
	B	-0.01	0.908	0.13	0.279	0.01	0.948	0.13	0.351	0.01	0.962	-0.17	0.166	-0.08	0.486
	C	0.25	0.030	0.04	0.772	0.03	0.816	-0.12	0.421	0.11	0.375	-0.01	0.965	-0.12	0.326
	D	-0.30	**0.007**	-0.13	0.289	-0.10	0.510	-0.16	0.272	-0.15	0.197	0.07	0.548	0.15	0.224
Coverage	A	-0.11	0.320	-0.03	0.826	-0.03	0.848	0.12	0.398	0.11	0.343	-0.03	0.793	0.00	0.982
	B	-0.18	0.117	0.12	0.317	0.00	0.981	0.15	0.304	-0.09	0.457	-0.22	0.072	-0.07	0.584
	C	0.26	**0.022**	0.01	0.916	0.02	0.884	-0.13	0.365	0.08	0.506	0.10	0.397	-0.06	0.639
	D	-0.30	**0.008**	-0.15	0.228	-0.15	0.305	-0.11	0.450	-0.20	0.094	-0.01	0.950	0.12	0.330
GEV	A	-0.18	0.115	-0.09	0.477	0.11	0.429	-0.14	0.350	0.07	0.580	-0.01	0.939	0.06	0.611
	B	-0.24	0.033	-0.06	0.603	0.01	0.918	0.00	0.996	-0.12	0.324	-0.11	0.350	0.10	0.407
	C	0.20	0.080	-0.05	0.657	0.03	0.845	-0.14	0.344	0.03	0.781	-0.05	0.684	-0.14	0.250
	D	-0.31	**0.005**	-0.22	0.068	0.07	0.639	-0.26	0.066	-0.10	0.408	0.04	0.750	0.20	0.098
Gfp	A	-0.03	0.796	-0.03	0.826	0.04	0.794	0.02	0.911	0.19	0.118	0.15	0.226	0.16	0.192
	B	-0.05	0.637	-0.04	0.728	-0.03	0.845	0.07	0.612	0.18	0.123	0.14	0.239	0.14	0.254
	C	0.09	0.444	0.06	0.613	-0.03	0.823	0.09	0.532	0.16	0.192	0.13	0.290	0.04	0.744
	D	-0.04	0.726	-0.02	0.874	0.02	0.879	0.07	0.634	0.21	0.081	0.22	0.062	0.23	0.059
Transition probabilities	BA	0.11	0.330	0.10	0.426	0.05	0.717	0.18	0.220	0.11	0.342	-0.07	0.572	-0.07	0.581
	CA	0.17	0.132	0.08	0.493	0.07	0.642	0.27	0.058	0.10	0.409	-0.14	0.249	-0.18	0.142
	DA	-0.12	0.313	-0.06	0.598	-0.11	0.449	0.18	0.208	0.14	0.239	0.01	0.965	-0.02	0.841
	AB	0.08	0.512	0.10	0.391	0.02	0.871	0.15	0.288	0.00	0.982	-0.14	0.238	-0.07	0.573
	CB	-0.09	0.433	0.19	0.106	-0.01	0.951	0.22	0.131	-0.09	0.465	-0.24	0.045	-0.15	0.215
	DB	-0.20	0.086	0.10	0.416	-0.05	0.740	0.13	0.352	-0.13	0.288	-0.28	0.019	-0.12	0.328
	AC	0.22	0.054	0.05	0.666	0.07	0.623	-0.01	0.959	0.10	0.427	0.16	0.179	0.01	0.917
	BC	0.21	0.070	0.00	0.972	0.06	0.658	-0.09	0.555	0.08	0.491	0.18	0.143	0.00	0.974
	DC	0.18	0.107	-0.06	0.633	0.01	0.953	-0.20	0.174	0.00	0.974	0.19	0.111	0.06	0.610
	AD	-0.32	**0.004**	-0.24	0.045	-0.23	0.101	-0.17	0.231	-0.09	0.448	-0.03	0.780	-0.01	0.948
	BD	-0.41	**<0.0005**	-0.10	0.414	-0.08	0.566	-0.18	0.213	-0.16	0.188	-0.03	0.782	0.04	0.746
	CD	-0.04	0.756	-0.15	0.218	0.02	0.897	-0.35	0.012	-0.02	0.882	0.21	0.079	0.19	0.116

Discussion

Class B duration as a marker of SPMS

We observed an increased duration of microstate Class B in participants with SPMS in relation to both controls and participants with RRMS. Class B duration has previously been shown to be increased in RRMS (Gschwind et al. 2016). The implications of this increase are unclear, with evidence of associations both with decreased (Gschwind et al. 2016) and increased (Baldini et al. 2024) cognitive fatigue. However, the study reporting

increased cognitive fatigue calculated prototype maps separately for patients and controls, which may introduce bias (Murphy et al. 2024).

It is also possible that the observed prolongation of Class B reflects Wallerian degeneration in visual networks due to prior optic neuritis. Optic neuritis is a common first symptom of MS, and has been shown to cause anterograde degeneration farther downstream the visual system (Chapelle 2025). Class B activity has been proposed to originate in the occipital cortex and thus to reflect visual processing (Britz et al. 2010; Custo et al. 2017; Tarailis et al. 2024). Therefore, the observed prolongation of Class B in SPMS could reflect visual system damage from several sources, including prior optic neuritis or fronto-parietal lesions. This damage could cause a prolonged Class B through either a compensatory increase in neural resources to maintain visual processing or a loss of network efficiency needed to exit this particular functional state.

Activity in Class B is also increased during verbalization (Milz et al. 2016). Visuospatial processing and memory, verbal fluency, and verbal memory are commonly impaired in MS, and some evidence suggests these functions may be more significantly impacted in SPMS than in RRMS (Brochet et al. 2022; Planche et al. 2016). Therefore, the increased duration of Class B seen in this analysis could reflect a compensatory increase in visual and verbal effort through prolonged activation of these networks.

Furthermore, the observation of microstate alterations between participants with SPMS and RRMS warrants further investigation. The diagnosis of SPMS following RRMS is made retrospectively based on clinical observation of disease course changes. This leads to uncertainty and delay for clinicians and people with MS. The search for a diagnostic or prospective biomarker for this transition remains underway, but has not yet included EEG candidates (Maier et al. 2023). The analysis should be expanded to include additional participants with SPMS to assess microstate Class B's potential as a biomarker of the RRMS to SPMS transition.

Replication of previous work

We failed to replicate the increase in Classes A and decreases in Class D as well as increases in other Class B properties found by Gschwind et al. and Baldini et al. (2023; 2024). These differences may be due to the methodological differences detailed above or differences in the participants sampled. For example, the participant group in Gschwind

et al.'s study was younger (RRMS: 37.7 ± 7.1 years; HC: 36.4 ± 8.2 years) than the sample included in this study (MS: 48.4 ± 12.3 years; HC; 60.0 ± 12.0 years) by a substantial margin. Microstate properties have been shown to vary with age (Koenig et al. 2002), so these samples may have exhibited different characteristics, though no associations with age were observed in this sample.

Future directions

This study was limited by a small sample size in the SPMS and PPMS groups. This could limit the statistical power of the analyses or bias our results if the participants included are not representative of the wider population with their subtype. Participants were recruited to this resting state study as part of a larger battery of task-based EEG experiments. This meant that only participants with a relatively low level of physical or cognitive disability could be included in the sample. Future studies using only RS-EEG (or RS-EEG in conjunction with a more accessible selection of tasks) could be conducted to facilitate the inclusion of additional participants with progressive forms of MS.

Conclusion

This study characterized the microstate properties of resting-state EEG in relapsing-remitting, secondary progressive, and primary progressive multiple sclerosis. Shorter duration of microstate Class B was seen in participants with SPMS, which may be an indicator of greater disease burden and relapse risk. Future work will expand the sample size and explore the biomarker potential of Class B duration as an indicator of transition from RRMS to SPMS.

Chapter 9

Results: ERPs in MS and ALS

ERP impairments diverge in MS and ALS

Chapter summary

This chapter presents a direct comparison of auditory oddball and sustained attention to response task (SART) ERP data from people with MS, ALS, and healthy controls. The pattern of cognitive impairments revealed through neuropsychological testing shows similarities between these conditions. However, this analysis shows that the pattern of cognitive ERP impairments is different between people with MS and ALS. This indicates that ERP measures can provide additional information beyond neuropsychological batteries and that the similar cognitive outcomes in these conditions are the result of different neural processes.

Introduction

Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) are neurodegenerative conditions affecting the motor neurons. ALS is an upper and lower motor neuron (UMN, LMN) condition, while MS mainly impacts UMNs, though LMNs can be affected as well (Shefner et al. 1992; Vogt et al. 2009). Though the motor symptoms of each condition are generally focus of research and clinical management, cognitive impairment can occur in both conditions as well.

Meta-analyses suggest an any-domain rate of cognitive impairment of around 30% in ALS (Beeldman et al. 2016) and around 41% in MS (Askari et al. 2024), though the severity and prevalence of impairment varies widely among patient subgroups. The profile of cognitive impairments seen in these conditions show some similarities. The most commonly reported impairments in ALS are in executive function, language, and verbal memory (Jellinger 2023; Abrahams 2023). In MS, the most affected domains are information processing speed, learning, and memory (Benedict et al. 2020). However, deficits in executive function (Migliore et al. 2018; Abrahams et al. 2000), verbal fluency (França et al. 2024; Delgado-Álvarez et al. 2020), working memory (Vacchi et al. 2017; Hammer et al. 2011), and social cognition (Bora 2017; Bora et al. 2016) are seen in both conditions.

Because these groups can show similar cognitive changes on neuropsychological testing, the use of cognitive EEG measures could allow us to understand whether these changes are the result of common or divergent neural alterations. The purpose of this study is to directly compare ERP data from people with ALS and MS obtained using the same collection and analysis methods to understand whether ERP alterations in these groups reflect general effects of neurodegeneration or disease-specific changes.

A brief review of the literature generated from the same data and methods used in this chapter is provided below. Therefore, the previous effects listed here reflect results obtained by this lab rather than a summary of the literature. This approach was chosen to maximize interpretability between previous and current analyses. No previous work in this group has evaluated these ERPs in MS, so this summary pertains only to findings in ALS. A summary of these findings is presented in **Table 22**, which also provides a direct comparison between the literature, the findings from earlier in this thesis, and the results of this chapter in ALS and MS.

Mismatch negativity

Increased amplitude-weighted latency, but not decreased amplitude, was seen in ALS (Iyer et al. 2017). This study used some of the same passive auditory frequency oddball recordings studied in this chapter, but the peak selection method was not identical to the method used here. The calculation of waveform features after peak selection was the same for each study, but the Iyer et al. study did not measure mean amplitude. This study was chosen as the closest comparison despite these differences because no analysis using the current methods has been undertaken.

Sustained attention to response task

Behavioral changes

In ALS, only anticipation errors were increased compared to controls, while accuracy and reaction time remained unaffected (McMackin et al. 2020).

P2

The P2 was not assessed in this group's prior analyses of the SART in ALS.

N2

No latency changes were found in ALS. Smaller peak amplitudes were seen in response to "No-Go" trials at Cz and FCz (McMackin et al. 2020).

P3

No differences in P3 characteristics between controls and people with ALS were reported (McMackin et al. 2020).

In summary, increased MMN latencies and decreased N2 amplitudes are seen in ALS using these stimuli and methods. The pattern of ERP alterations may differ between participants with ALS and MS.

Methods

This chapter is a secondary analysis of data discussed elsewhere in this thesis and data from existing databanks within the lab. All data were collected according to the methods detailed in the Materials and Methods, Chapter 6, and Chapter 7. Details of deviations from the analysis methods mentioned previously are given below.

Data

This study used data from three groups of participants: those with MS, those with ALS, and healthy controls. The data from people with MS and healthy controls has been discussed elsewhere in this thesis. Additional data from people with ALS was obtained from existing repositories within the lab. This extra data was collected and pre-processed according to the same methods detailed in this thesis. The combined datasets are described briefly below.

MMN

Data from 56 participants with ALS, 67 participants with MS, and 54 healthy controls were included in this study (**Table 20**). The group averaged ERP responses were visually inspected to select the optimal time window for MMN analysis (**Figure 8**). The MMN was extracted from 150-350ms post stimulus and the amplitude and latency of the peak, amplitude-weighted latency, mean amplitude, and area under the component were compared among groups.

MMN ERPs in this chapter were processed using a 100ms baseline, as opposed to the 200ms baseline used elsewhere in this thesis. This was done to ensure compatibility with the ALS dataset, which had been processed using a shorter baseline.

Table 20. Demographic characteristics: MMN

	ALS	MS	HC
n	56	67	54
mean age (years) [SD]	59.9 [9.7]	48.2 [11.8]	50.8 [15.6]
age range (years)	38-80	21-72	20-71
Gender (f/m)	18/37	52/15	33/20

SART

Data from 68 participants with ALS, 81 participants with MS, and 54 healthy controls were included in this analysis (**Table 21**). P2, N2, and P3 ERPs were extracted from EEG averaged waveforms between 100-300ms, 150-350ms and 350-550ms post-stimulus, respectively. The amplitude and latency of the peak, amplitude-weighted latency, mean amplitude, and area under the component were calculated for each component and compared among groups.

Table 21. Demographic characteristics: SART

	ALS	MS	HC
n	68	81	54
mean age (years) [SD]	60.1 [9.5]	48.8 [12.3]	60.2 [12.8]
age range (years)	38-80	27-82	21-72
Gender (f/m)	22/44	61/20	29/25

Group comparisons

Group means for each waveform feature were compared using four- or five-way ANOVAs with electrode, trial type (SART only), sex, and age included as covariates after normality correction of the data using an inverse normal transformation. Participants with MS or ALS were not divided by subtype or site of onset. A Fischer's least significant difference (LSD) test was applied to significant group effects to localize pairwise differences, and p-values were corrected using a 5% adaptive false discovery rate (FDR) correction (Benjamini et al. 2006). Group means for each behavioral task score were compared using an ANOVA with age included as a covariate on inverse normal transformed data. As above, ANOVA outputs were corrected for multiple comparisons using a 5% adaptive FDR

correction, significant group effects were localized using Fisher's LSD, and these pairwise tests were corrected using a 5% adaptive FDR.

Results

The MMN is differentially impaired in ALS and MS

A MMN response was seen between 150 and 350ms at Fz, FCz, and Cz in all participant groups (**Figure 8**). No clear MMN was seen at Pz, so this electrode was excluded from further analysis. Group differences between controls, participants with ALS, and participants with MS were seen in the amplitude of the peak ($F_{2,505} = 4.84$, $p = 0.008$), the area under the MMN ($F_{2,505} = 10.49$, $p < 0.0005$), the standard latency ($F_{2,505} = 13.00$, $p < 0.0005$), and the amplitude-weighted latency of the peak ($F_{2,505} = 4.42$, $p < 0.012$). Participants with MS showed larger amplitude MMN peaks compared to both participants with ALS ($p = 0.002$) and healthy controls ($p = 0.052$). In contrast, participants with ALS showed diminished MMN areas compared to participants with MS ($p < 0.0005$) and healthy controls ($p < 0.0005$). Both participants with ALS ($p < 0.0005$) and participants with MS ($p = 0.058$) showed slowed amplitude-weighted MMN responses compared to healthy controls. In contrast, the standard latency of the P3 was faster in ALS than in HC ($p < 0.0005$) or MS ($p < 0.0005$).

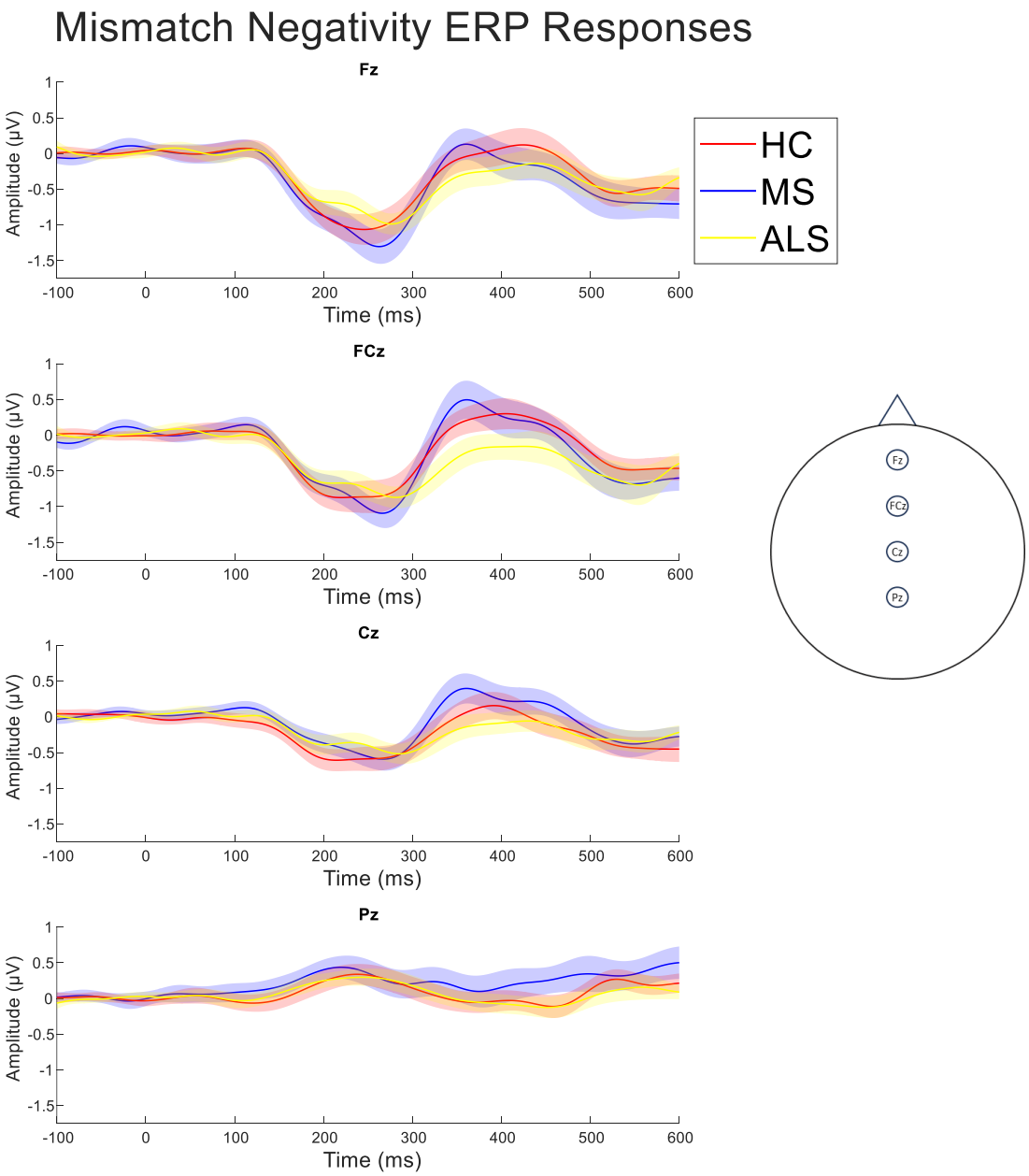


***Figure 8. MMN responses along the central midline**. Responses from healthy controls are shown in blue. Responses from participants with ALS are shown in red. Responses from participants with MS are shown in yellow. Solid lines represent the mean of the MMN response from each participant, and the shaded cloud represents the 95% confidence interval of this measurement. Plots were generated based on plotting steps initially drafted by Etain O'Meara.*

ERPs from the SART differ in MS and ALS

ERP waveforms in response to the SART show similar morphologies among participants with MS, participants with ALS, and healthy controls (**Figure 9**).

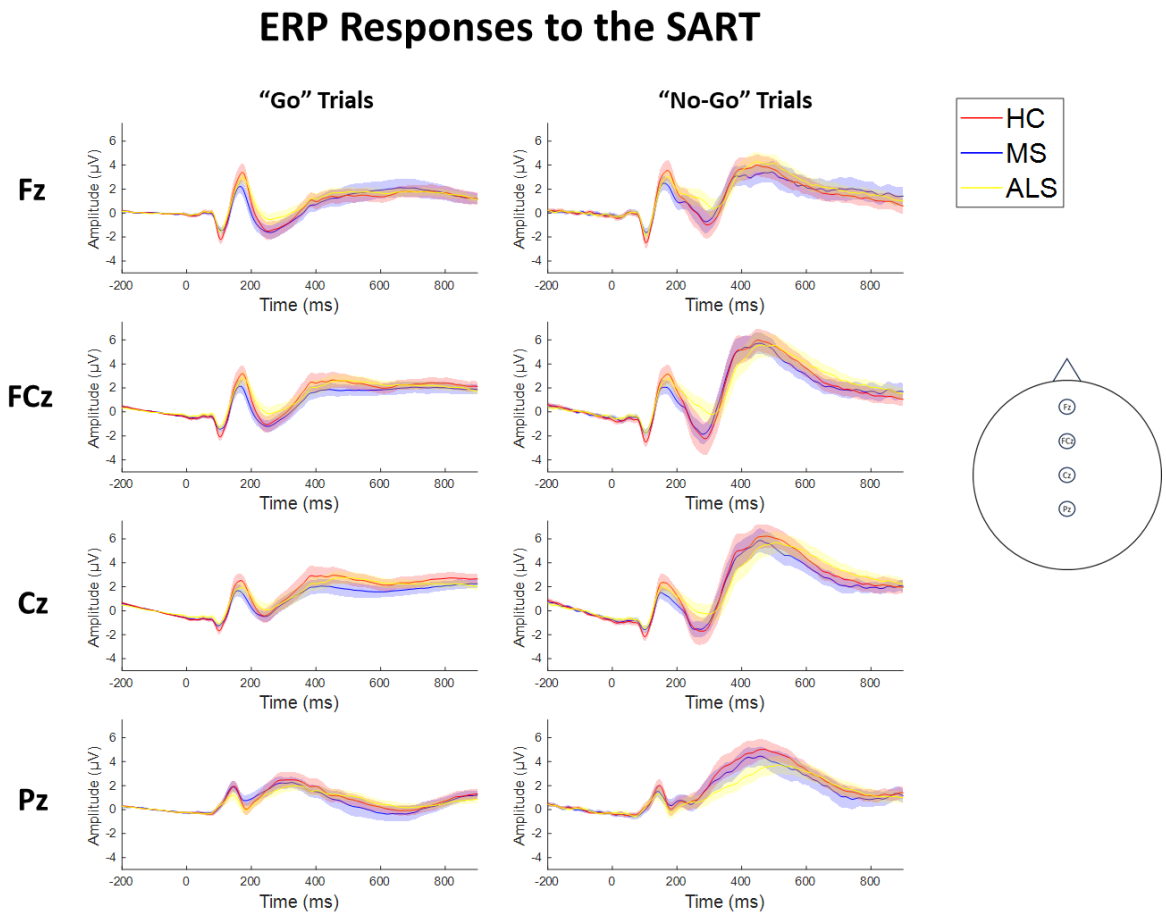


Figure 9. SART response waveforms in MS, ALS, and controls at Fz, FCz, Cz, and Pz*. Responses from healthy controls are shown in blue. Responses from participants with ALS are shown in red. Responses from participants with MS are shown in yellow. Plots were generated based on plotting steps initially drafted by Etain O'Meara.*

P2 area is reduced in MS, while N2 area is reduced in ALS

Group level differences were observed in the area under the P2 ($F_{2,1591} = 6.92$, $p = 0.001$) and N2 ($F_{2,1591} = 9.50$, $p < 0.0005$). P2 areas were decreased in participants with MS ($p < 0.0005$) and N2 areas were decreased in participants with ALS ($p = 0.001$) relative to controls. N2 areas in participants with ALS were smaller than those in participants with MS ($p < 0.0005$).

Group differences were also found in P2 ($F_{2,1591} = 7.06$, $p = 0.001$) and N2 peak amplitudes ($F_{2,1591} = 9.23$, $p < 0.0005$), though the pattern of alterations was not as distinct as for P2 and N2 areas. P2 amplitudes were lower in both participants with ALS ($p = 0.003$) and participants with MS ($p = 0.001$), and no differences were observed between these groups. N2 amplitudes were lower only in participants with ALS compared to controls ($p = 0.001$) and participants with MS ($p < 0.0005$).

P2 latency is reduced in ALS and increased in MS

The standard ($F_{2,1591} = 4.28$, $p = 0.014$). and amplitude-weighted latency of the P2 differed among groups ($F_{2,1591} = 3.32$, $p = 0.036$). In comparison to P2 latencies in controls, standard latencies were shorter in ALS ($p = 0.004$) and unaffected in MS, and amplitude-weighted latencies were longer in MS ($p = 0.013$) and unaffected in ALS. Participants with MS and ALS did not differ from each other in the standard or amplitude-weighted latency of the P2.

N2 standard and weighted latency differ in MS and ALS

The groups also showed differences in the standard ($F_{2,1591} = 5.46$, $p = 0.004$) and amplitude weighted ($F_{2,1591} = 3.83$, $p = 0.022$) latencies of the N2. Both participants with MS ($p = 0.001$) and participants with ALS ($p = 0.032$) showed faster N2 peaks compared to controls when measured using a standard latency of the peak. When comparing the amplitude-weighted latency of this peak, participants with ALS and MS differed from each other (ALS > MS, $p = 0.006$), though neither group was impaired relative to controls.

P3 latency is altered in MS but not in ALS

P3 responses were delayed in participants with MS. Participants with MS showed longer standard ($p = 0.003$) and amplitude-weighted ($p = 0.018$) latencies of the P3 compared to control latencies. Participants with ALS showed no impairment in standard or amplitude-weighted latency and did not differ from participants with MS in these measures.

Mean amplitudes are decreased in MS and increased in ALS across ERPs

In contrast to the results described above, mean amplitude showed a consistent pattern across ERP components, with decreases in the MS group in P2 ($p = 0.042$), N2 ($p = 0.019$), and P3 ($p = 0.004$), and increases in the ALS group in P2 ($p = 0.006$) and N2 ($p = 0.039$) compared to controls. In addition, participants with MS and ALS differed in mean amplitude of the P2 (ALS > MS, $p < 0.0005$) and N2 (ALS > MS, $p < 0.0005$). As discussed previously, calculation of this waveform component does not require the presence of the peak of interest, so this measure may be more reflective of total EEG activity across the ERP search window than of ERP-specific changes.

SART "Go" accuracy differs between ALS and MS

Participants with ALS and MS also showed different behavioral impairments on the SART (**Figure 10**). Controls and participants with ALS and MS differed in overall accuracy ($F_{2,145} =$

4.93, p = 0.008), with both participants with ALS (p = 0.003) and MS (p = 0.016) responding less accurately than controls. “Go” trial accuracy also differed among groups ($F_{2,145}$ = 14.32, p < 0.0005), with lower accuracy compared to controls in ALS (p < 0.0005) and MS (p = 0.001). Participants with ALS and MS also directly differed from each other in response accuracy to “Go” trials (p = 0.057).

Anticipation errors varied among groups ($F_{2,145}$ = 8.93, p < 0.0005), with both participants with ALS and MS producing fewer anticipation errors than controls. Anticipation errors were less frequent in participants with ALS compared to controls (p < 0.0005) and participants with MS (p < 0.023), and less frequent in participants with MS than in controls (p = 0.060).

Finally, reaction times differed among groups ($F_{2,145}$ = 4.33, p = 0.015), with participants with ALS producing longer reaction times than controls (p = 0.056) and participants with MS (p = 0.006).

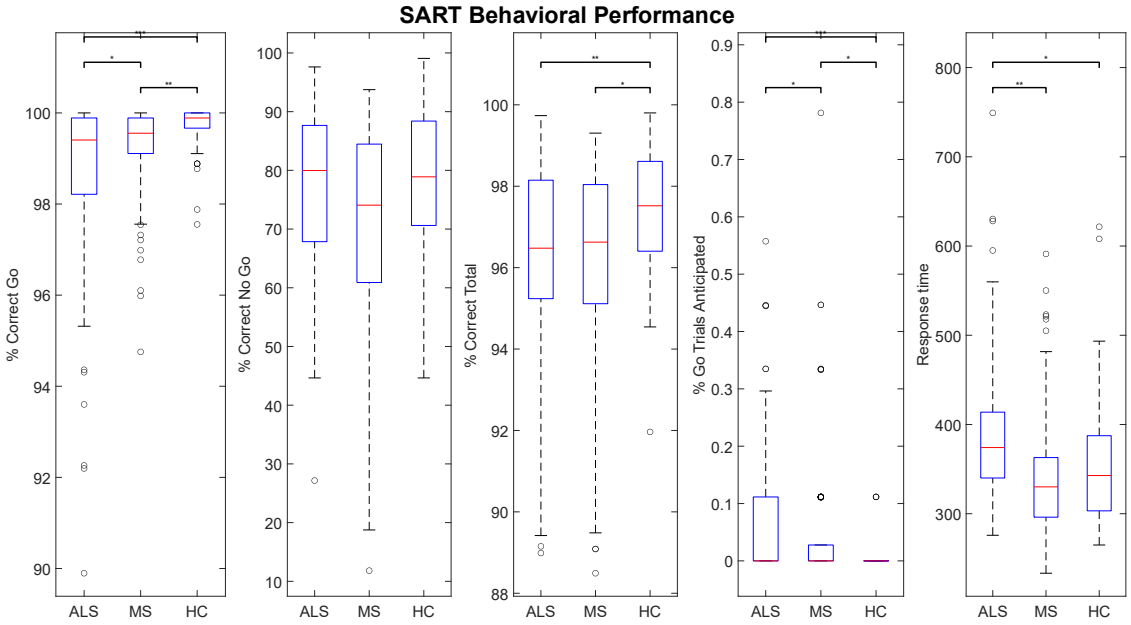


***Figure 10. SART behavioral performance scores across groups**. Significantly different performance among groups was seen in total accuracy, “Go” trial accuracy, anticipation, and response times. Participants with ALS and MS showed impairments in total accuracy, “Go” trial accuracy, and anticipation. Participants with ALS also showed impairments in reaction time that were not observed in the group with MS.*

Discussion

A summary of the results observed in this study and previous results is given in **Table 22**. The results in this chapter show slight deviations from previous findings, despite identical

methodology[20] and overlaps in the datasets assessed. Some of these could be attributed to variations in the samples of participants included or artefacts of the statistical analysis procedures. For example, pairwise post-hoc comparisons were only conducted in the case of significant group-level effects on an ANOVA. This could lead to some missed pairwise effects (in either the prior or current studies), if, for example, one participant group had very high within-group variation masking differences between the two remaining groups. In this case, the high within-group variation could result in a low F-value and high p-value for the ANOVA group effect, preventing further investigation in the form of a post-hoc test according to our method.

Additionally, results discussed in Chapter 6

and Chapter 7

were separated by MS subtype, while results in the present study pertain to participants with RRMS, SPMS, and PPMS collectively. Our previous results show that ERP alterations differ among subtypes of MS (Chapter 6), so effects seen in one or two subgroups may not be apparent when considering MS participants as a unified group. Conversely, the increased sample size of the combined group may increase the statistical power of some tests, allowing us to observe effects at a group level that were underpowered when studied within subtypes.

[20] With the exception of the MMN study mentioned above.

***Table 22. Results overview: comparison with previous findings**. The results of this analysis are shown in blue, while the results shown earlier in this thesis or published elsewhere are shown in black. The waveform characteristics of the MMN and P2 ERPs are shown in grey because these ERPs were not assessed using these same methods in this group's prior studies of ALS. The P2 was not assessed, and the MMN was assessed using a different method (including omission of mean amplitude). The previous MMN results are included on the table in parentheses to reflect the fact that this was not a direct replication study.*

	Auditory Oddball	**SART**		
ERP	**MMN**	**P2**	**N2**	**P3**
Peak amplitude	↑MS	↓MS ↓ALS ↓SPMS	↓ALS ↓ALS	↑PPMS
Mean amplitude		↓MS ↑ALS	↓MS ↑ALS	↓MS ↓SPMS
Area under the component	↓ALS	↓MS ↓RRMS ↓SPMS ↓PPMS	↓ALS	↑PPMS
Latency of the peak	↓ALS	↓ALS ↓RRMS ↓PPMS	↓ALS ↓MS ↓SPMS ↓RRMS	↑MS ↑SPMS ↑PPMS
Amplitude-weighted latency	↑MS ↑ALS (↑ALS)	↑MS	↓SPMS ↓RRMS	↑MS ↑SPMS ↑PPMS

The MMN is enhanced in MS, diminished in ALS

In contrast to previous results, we found an increase in the amplitude of the MMN peak and a decrease in its amplitude-weighted latency in participants with MS. In a previous direct comparison of people with MS and controls (Chapter 7), no group level effects were observed with an ANOVA. Therefore, no post-hoc testing was carried out, which could account for the differences in effect seen here. Additionally, the analysis in Chapter 7 was broken down by MS subtype, while the present chapter analyzed all participants with MS together. Therefore, increased amplitude and delayed weighted latency of the

MMN may be a feature observable in participants with MS generally, rather than within individual subtypes. These results also contradict the finding of a smaller, faster MMN in MS reported by Jung et al. (2006). However, this study employed a duration deviant rather than the frequency deviant used here. As MMN is highly variable and affected by stimulus choice, the difference in paradigms could account for this difference in findings.

The amplitude-weighted latency was also found to be increased in ALS, which corresponds to previous work by this group (Iyer et al. 2017). In contrast, standard latency was found to be decreased in ALS, which was not reported previously. This could reflect an alteration in MMN morphology in ALS, with a faster peaking, more persistent waveform. Additionally, the previous analysis did not find alterations in MMN size, in contrast to the decreased MMN area seen here. The peak selection method used in this chapter does differ from the one used by Iyer et al., which could account for the difference in findings. Iyer et al. calculated the MMN as the timepoints of significant difference between the standard and deviant waveforms, while the present analysis looked for a negative deflection between 150 and 350ms. This could lead to differences in what part of the waveform was defined as the "MMN" for a participant. The Iyer et al. significant difference method found a MMN from 102-268ms in controls and from 125-500ms (the end of the epoch) in participants with ALS. The morphology of this peak in participants with ALS suggests that this method may have captured later peaks in addition to the MMN, because two distinct peaks are seen in this waveform (between approximately 100-300ms and 400-500ms). Waveform characteristics were calculated between 100 and 300ms, as opposed to the 150-350ms window used here. Another potential cause of this difference is that Iyer et al. observed increased latencies compared to controls in spinal, bulbar, and C9ORF72-negative ALS subgroups. If the ALS group used in this study had a different distribution of participant subgroups than the group studied in Iyer et al., then this could account for some of the variation in the results.

Mean amplitudes are decreased in MS and increased in ALS across SART ERPs

Consistent changes in mean amplitude were seen across the P2, N2, and P3 elicited during the SART. Participants with MS in this study showed a decreased mean amplitude across all three ERPs. In contrast, participants with ALS showed an increased mean amplitude of the P2 and N2. Other than a decrease in P3 mean amplitude in participants with SPMS, none of these effects were observed previously. Further investigation is

needed to determine the cause and meaning of this effect. However, reductions in amplitude in MS may result from fewer neurons responding to the stimulus due to atrophy or dysfunctional cortical organization. While greater levels of neuronal loss (and therefore a lower mean amplitude) would be expected in ALS relative to MS, the increases in mean amplitude seen here could also reflect the well-known cortical hyperexcitability in ALS (Vucic, Pavey, et al. 2021).

As a more diffuse measure of ERP size, this measurement may be more sensitive to differences in waveform morphology compared the amplitude of the peak, which is based on a single time-point only. For instance, a quickly peaking P2 could have a lower mean amplitude across the 100-300ms time window compared to a more slowly peaking P2 with the same peak amplitude. However, we would expect that such morphological differences might also be reflected in changes in the area under the component. Instead, P2 area and mean amplitude were both decreased in participants with MS, but no other group-ERP pairs showed matched effects in area and mean amplitude. On the contrary, N2 area was decreased and N2 mean amplitude was increased in ALS. Directly comparing amplitudes across waveform timepoints as was done for standard and deviant trials in Iyer et al. (2017) may be a more direct option for investigating relative changes to ERP component morphology in ALS and MS.

The following discussion sections pertain to the peak-specific ERP features: amplitude and latency of the peak, amplitude-weighted latency, and area under the component.

P2 amplitude and latency are differentially altered in MS and ALS

We found decreases in P2 amplitude in both MS and ALS groups. However, a lower P2 area was seen only in MS and not in ALS. Additionally, participants with ALS showed a faster P2 response (standard latency) while participants with MS showed a slower P2 response (amplitude-weighted latency) relative to controls. The P2 alterations in ALS seen in this study were not found in previous analyses of this data (McMackin et al. 2020), possibly due to the inclusion of additional participants or methodological differences in the statistical analysis.

In MS, decreases in peak amplitude and area under the component correspond to our earlier results (Chapter 6). Participants with SPMS showed decreased peak amplitudes and areas of the P2 and participants with RRMS and PPMS showed decreased areas of the

P2. However, we did not observe the decreased P2 standard latency in participants with MS seen in Chapter 6. Instead, we observed a delayed amplitude-weighted latency. In the previous analysis, we had seen both an increased standard latency in participants with SPMS and a decreased latency in participants with RRMS and PPMS, so these changes may have averaged out in a combined group. Likewise, the combined all-MS grouping may have provided additional power to detect the delayed amplitude-weighted latency seen here.

Therefore, we can conclude that the P2 is affected in both MS and ALS, though the pattern of alteration may differ. Further consideration of component morphology may allow better dissociation of these groups from P2 data.

N2 latency is altered in ALS and MS, but amplitude is altered in ALS only

Participants with ALS showed diminished amplitudes and areas of the N2, corresponding to the decrease in N2 amplitude reported previously (McMackin et al. 2020). The N2 standard latency was decreased in both ALS and MS groups in this analysis, corresponding to the decreased N2 latency seen in RRMS and SPMS (Chapter 6). A decreased latency of the peak could reflect a flattened N2 peak that does not continue to rise for as long as peaks in healthy controls do. Participants with ALS also showed greater amplitude-weighted latencies compared to participants with MS, though neither group differed from controls. In ALS, a decreased standard latency and increased mean latency supports the hypothesis of a broad and early peaking N2 component in participants with ALS. The alterations in N2 amplitude-weighted latency in RRMS and SPMS reported in Chapter 6 were not reflected in decreased MS group N2 amplitude-weighted latencies in this analysis.

The P3 is altered in MS, but not in ALS

No changes were seen in this analysis in ALS in the amplitude or latency of the peak, amplitude-weighted latency, or area under the component of the P3. This supports the lack of P3 alterations in ALS reported previously (McMackin et al. 2020). In contrast, the P3's mean amplitude was lower, and standard and amplitude-weighted latencies were higher in participants with MS. This reflects the decreased mean amplitude seen in SPMS and delayed standard and amplitude weighted latencies in SPMS and PPMS (Chapter 6).

CHAPTER 9

Conclusions

Different patterns of impairments can be seen in ERPs related to cognitive functions between ALS and MS. Though similarities exist between the cognitive changes observed in these conditions, these results suggest that different neural processes produce these changes. The results also support the use of ERPs to provide additional information about clinical cognitive functioning that is not revealed by standard neuropsychological testing.

Chapter 10

Discussion

Chapter summary

This chapter synthesizes the novel findings from the thesis and discusses these in the context of the state of the field and potential future applications. Limitations and other considerations for the interpretation of this work are also examined.

Introduction

The results obtained during this thesis project provided evidence of impaired executive function in MS, identified biomarker candidates for the RRMS-to-SPMS transition, showed that cognitively related neural dysfunction is disease-specific and highlighted the importance of paradigm selection for EEG quantification of cognition. These results suggest interesting avenues for further research into cognitive impairment in MS.

ERP responses to cognitive task-based paradigms were altered in people with MS, varied among subgroups, and differed between groups with MS and ALS. No MMN characteristic was altered in subgroups of MS, but MMN characteristics were differently altered in MS and ALS at a group level. However, MMN features did not show good test-resest reliability. P2, N2, and P3 responses to the SART did vary among subgroups of MS and also showed different patterns of alterations in MS and ALS. Characteristics of these ERPs did show high test-restest reliability. Resting state microstates were largely unaffected in subgroups of MS, with the exception of a prolonged Class B duration in SPMS.

Complex executive function is impaired in MS

Prior evidence from neuropsychological testing has shown that many people with MS display impairments in executive function, which encompasses processes like attention, inhibition, and task-switching. These effects have been supported with evidence from structural and functional brain imaging techniques.

This thesis assessed aspects of executive function through task-based EEG and resting state EEG microstates. The mismatch negativity (MMN) was found to be a poor indicator of MS-related cognitive dysfunction (Chapter 7, Chapter 9). Furthermore, it was determined that the MMN would not be a good choice for longitudinal tracking of

cognition in MS or other conditions due to its poor test-retest reliability (Chapter 5). Only one MMN measure was found to have significant reliability, and the location of this finding at the Cz electrode only (the only electrode on a cap EEG system placed according to direct measurements) suggests that the MMN may be more impacted than SART ERPs by anatomical location.

The findings support the literature showing that MMN is a highly variable ERP impacted by location, paradigm, and neurological dysfunction. In addition, no amplitude or latency differences (across the five measures assessed) were found at Fz, FCz, Cz, or Pz, corroborating previous reports that the MMN is not affected in MS. In previous studies of the MMN in MS, MMN characteristics correlated with clinical and cognitive scores (Bissonnette et al. 2023; Santos et al. 2006), so we assessed the correlation between the MMN and the MSNQ, age at diagnosis, disease duration, and HADS. No significant associations between the MMN and these measures were identified. Furthermore, the frontocentral midline is expected to be the site of maximal MMN response, so it is unlikely that selection of different electrodes would alter these results. These results, in combination with the literature, suggest that the auditory oddball is not the most suitable task for the assessment of cognitive impairment in MS.

The MMN is generally used as an indicator of auditory processing and memory, but may also reflect early activity in attention-switching networks (Näätänen et al. 2014). Therefore, this aspect of executive function does not appear to be substantially impacted in people with MS. Early attention-switch processes may be spared in MS cognitive decline, or these basic processes may be sustained through compensation from other neural mechanisms. The compensation hypothesis is contradicted by the observation of no change in microstate Class A (Chapter 8), which represents activity in audiovisual networks. If compensatory auditory network processes were active, we would expect to see an increase in Class A activity as indicated through increased duration, occurrence, or coverage of Class A. However, microstate network activation may be quite broad in comparison to the specificity of the neural mechanisms generating the MMN response. Additionally, the MMN is a focused response generated during a task-based paradigm as opposed to the more variable brain activity observed at rest. Therefore, possible compensatory activity related to this task may not be visible using resting state

microstate analysis. Future source localization[21] of MMN responses or other whole-brain measures may better characterize network activity during this task.

In contrast to these relatively spared basic attentional processes, complex executive functions like sustained attention and inhibition appeared to be impaired in MS. In Chapter 6, evidence was given of impaired performance and ERP responses to the sustained attention to response task (SART), a complex task of executive function involving aspects of sustained attention, change detection, performance monitoring, inhibition, and processing speed. The complexity of the task minimizes ceiling effects and makes the task well-suited to identifying subtle cognitive impairment. Performance on and EEG responses to the SART had not previously been characterized in MS.

People with RRMS (but not SPMS or PPMS) showed increased errors of omission, commission, and anticipation on the task, but no slowing in reaction time. These results indicate that the test could be a useful measurement of cognitive impairment in RRMS. Further investigation with additional participants is needed to clarify whether performance on the SART is unimpaired in people with SPMS or PPMS, or if our study was underpowered to detect such impairment. If people with progressive forms of MS do indeed perform normally on the SART, then the test may provide a behavioral indicator of transition from RRMS to SPMS. In this case, unimpaired performance could reflect the development of a compensatory neural or cognitive strategy that is not present in RRMS. However, such a finding would be unexpected, as people with SPMS would be more likely to have more significantly impacted cognition than those with RRMS.

Additionally, while the effect should be confirmed in those with a more advanced disease stage, the lack of reaction time impairment suggests that the task could be a good tool to

[21] EEG source localization is an umbrella term referring to a variety of mathematical methods used to infer the probable origin of EEG signals recorded at the scalp. Source localization of the same auditory oddball and SART signals studied in this thesis revealed alterations in ALS (McMackin et al. 2019; 2020). Source localization of ERP signals increases the spatial resolution of EEG and thus can provide further information about what underlying brain changes are contributing to cognitive changes in neurodegenerative diseases like MS. This thesis includes data collected at 128 EEG channels, making it suitable for future source localization. A follow-up analysis should identify the brain source generators of the scalp ERP signals reported in this thesis in people with MS and controls.

measure and track cognition without bias from motor dysfunction. Other commonly used screening tools like the PASAT and SDMT can be affected by dysarthria and fine motor impairment (Tombaugh 2006; Nygaard et al. 2015).

This study also documented altered ERP responses to this task for the first time in MS. Decreased amplitudes and increased latencies of these ERPs indicate quantifiable changes in neural activity associated with task switching, sustained attention, performance monitoring, and response inhibition. These results correspond to prior reports in the literature of loss of inhibitory control in MS and of alterations of the same ERPs elicited with different paradigms. Response inhibition failures in MS are proposed to be related to failures of executive function rather than global disinhibition (Ternes et al. 2019). This is supported by observations that increased CSF parvalbumin (a marker of inhibitory neuron loss) is associated with global cognitive dysfunction rather than attention, processing speed, or executive function (Ziccardi et al. 2024).

The SART and its ERP correlates therefore appear to be robust indicators of inhibitory failure related to executive function impairment in MS. Furthermore, the peak and mean amplitude, latency and mean latency, and area under the component of the P2, N2, and P3 were shown to have almost uniformly high test-retest reliability across Fz, FCz, Cz, and Pz, making these measures good choices for future longitudinal studies. Measures that show insignificant reliability (11 out of 120 potential biomarkers) can be avoided in future longitudinal analyses.

Future research should assess whether variations in these tasks or their ERPs correspond to clinically meaningful distinctions in cognitive impairment severity. The cognitively related EEG changes reported here were found to have greater associations with MS presence or subtype than with scores on cognitive and psychiatric screening tools. Many of the participants with MS and some control participants also completed full-battery neuropsychological testing through a connected research group. A follow-up study could seek to compare the EEG results from this thesis with neuropsychological scores to assess the biomarker potential of these candidate markers in determining clinical cognitive impairment.

In addition to assessing the biomarker potential of these signals to diagnose cognitive impairment, future studies could seek to assess their suitability as prognostic biomarkers

of cognitive impairment. Participants from the studies described here can be invited to complete additional follow-up EEG visits. Alternatively, data could be collected longitudinally from a new cohort. First, these longitudinal data could be compared between time cohorts to understand the typical progression of these signals over time in MS. Then, the signals could be evaluated within an individual over time to understand whether changes in the signals reflect clinically meaningful progression of cognitive symptoms. Additionally, the prognostic biomarker potential of these signals could be evaluated by comparing cognitive outcomes longitudinally between participants showing impaired and unimpaired signals at baseline. Differences observed between participants with RRMS and SPMS could also be investigated longitudinally as candidate biomarkers of the RRMS-to-SPMS transition.

ERP biomarkers could identify the RRMS to SPMS transition

At present, no objective indicators of the transition from relapsing-remitting to secondary progressive MS have been identified. This is a particularly interesting area of research because the diagnosis of SPMS is made after observing the presence of steady disease progression over a span of time, often six months. This means that the transition to SPMS is usually diagnosed retrospectively, and so people developing SPMS likely remain classed as having RRMS during and after this transition.

A good objective biomarker for SPMS would be measurable routinely at home or during clinic visits to identify transition as early as possible. A better objective biomarker would be able to predict this transition before it happens. If these biomarkers could identify people at the point of this transition (or even before it occurs), then an “early SPMS” subtype could be identified. Very early SPMS is a critical subset that is currently unidentifiable until after SPMS has progressed. Better identification of early SPMS could permit clinical trials to target this group directly and accelerate the development of treatments tailored specifically to progressive MS. Early treatment has been linked to better outcomes in RRMS, so it is conceivable that early treatment with a medication specifically for SPMS could yield similar results. Additionally, predicting and identifying SPMS faster would reduce stress and uncertainty for patients.

For these reasons, the identification of biomarkers of SPMS development is an active area of research. However, to date, such research has focused on methods such as serum and

CSF assays, MRI, and OCT (Maier et al. 2023). As discussed elsewhere in this thesis, EEG provides complimentary information to these methods and, in some cases, has advantages in cost and patient acceptability. Therefore, an EEG biomarker of RRMS to SPMS would be advantageous to the field.

The pattern of EEG alterations relative to controls differed between MS subtypes for several markers in this thesis, suggesting that some markers could be investigated further as indicators of the RRMS-to-SPMS transition. Specifically, participants with RRMS showed decreased P2 size and P2 and N2 latency. Participants with SPMS showed diminished and slowed P2 and P3 responses, faster N2 responses, and higher microstate Class B duration. P2 and P3 amplitude and latency differed between participants with RRMS and SPMS.

These markers may indicate differences in stimulus monitoring, change detection, and visual network activation between people with RRMS and SPMS. These candidate biomarkers should be evaluated further in a larger group of people with SPMS (in comparison to RRMS) to evaluate their biomarker potential. If candidate biomarkers are identified, then a prospective study of the measures could be conducted with a group of people with RRMS who are highly likely to transition to SPMS over the study period (e.g. long disease duration, older age, presence of other prospective transition biomarkers). This group could be followed longitudinally, and EEG measures could be compared between progressors and non-progressors. Additionally, data from participants with SPMS and PPMS could be grouped to identify features most associated with a progressive phenotype. These features could then be assessed both for ability to identify transition to SPMS and to identify progression independent of relapse activity (PIRA) within participants with RRMS. Development of biomarkers for PIRA is an active area of research, and no EEG biomarkers of the phenomenon have been identified to-date (Calabrese et al. 2024; Bsteh et al. 2025).

However, it must be noted that these biomarker candidates are related to cognition, so they may show lower utility in people who do not have cognitive symptoms or whose cognitive symptoms do not progress throughout the disease. There is significant debate over whether the prevalence and severity of cognitive impairment increases over time in MS (Literature Review). However, these markers reflect the neural activity underpinning cognition rather than cognitive outcomes themselves. Therefore, it is possible that these

may change during progression to SPMS even if clinically observable cognitive performance does not. Future longitudinal analysis of biomarker potential should consider completing detailed cognitive phenotyping on participants at baseline to evaluate whether the utility of the markers depends on the presence of cognitive impairment at baseline.

Cognitive ERP alterations are disease-specific

The patterns of cognitive impairment seen in neurodegenerative conditions overlap. For example, both MS and ALS have been linked to varying degrees of dysfunction in attention, memory, verbal fluency, and social cognition. While each condition shows a different prevalence of these and other impairments at a group level, it would be difficult to distinguish individuals based on which cognitive domains are impaired. Therefore, cognitive impairment is not currently used in the differential diagnosis of these conditions. It is possible that better understanding and more specific measurements of cognitive impairments could allow these patterns to be considered as part of diagnosis in the future.

Currently, it is more relevant to understand whether the overlapping patterns of cognitive impairments seen in different neurodegenerative diseases are due to the same or different underlying neural changes. Knowing whether the neurodegenerative changes causing cognitive impairment are general or specific to a particular disease could help ensure that cognitive rehabilitation or medications are tailored to the underlying neural dysfunction.

This question is incompletely answered by direct, between-condition comparison of cognitive and EEG changes reported in the literature because of inter-study variations in study participants, experimental paradigms, analysis methodologies, and more. Thus, the datasets available within the Academic Unit of Neurology provide an excellent opportunity to address this question. These data were collected from people with MS and ALS in the same location with the same equipment, experimental paradigms, and processing methodologies. Therefore, similarities or differences in these measures should reflect similarities or differences in the conditions.

Just as ERP characteristics were found to differ among MS subtypes, ERP characteristics differed between neurodegenerative conditions as well (Chapter 9). For example,

participants with ALS showed smaller MMN responses, while those with MS showed larger ones. Among the four ERPs studied (MMN, P2, N2, and P3), MMN amplitude, area, and latency, P2 area, latency, and weighted-latency, N2 amplitude and area, and P3 latency and weighted latency alterations differed between those with ALS and MS. Therefore, these markers likely reflect impaired cognitive neural activity that is specific to each condition rather than neurodegeneration in general. In contrast, the ERP features that showed the same changes in each condition (e.g. MMN weighted latency, P2 amplitude, N2 latency) may reflect the effects of common neurodegenerative processes between the two conditions. These results can be used to inform choices of condition-specific biomarkers for future research.

Additionally, the results suggest that associations between ERP measurements and cognitive outcomes should be evaluated within the context of a specific condition, rather than among neurodegenerative conditions as a whole. This also highlights the need for condition-specific approaches to cognitive rehabilitation and drug discovery. In other words, interventions that are tailored to the underlying neural dysfunction rather than to the symptomatic outcome may be more effective.

Appropriate paradigms are essential for EEG analysis of cognition

The results discussed above underscore the need for the considered selection of appropriate EEG experimental paradigms and analysis methods. To capture cognitive impairment in highly heterogeneous conditions, paradigms must activate the impaired process and candidate biomarkers must accurately reflect the activity of these processes. This section provides some reflections on appropriate avenues for the future use of paradigms and markers discussed in this thesis.

To evaluate executive function in MS

The ERP correlates of the SART are better biomarker candidates than the MMN for the detection of executive function impairments in MS. The MMN reflects sensory components of attention and early attention-switching mechanisms that do not appear to be impaired in MS. In contrast, the SART reveals impairments in more complex aspects of attention and inhibition.

Performance on the sustained attention to response task is impaired in MS and does not appear to be affected by motor impairment. These effects should be investigated

longitudinally and compared to detailed neuropsychological testing to evaluate whether the task can track or predict cognitive progression within an individual. Furthermore, the study should be expanded to include more participants with advanced EDSS to confirm its insensitivity to fine-motor impairment.

ERP alterations in P2, N2, and P3 can also be seen in response to the SART. Further study could investigate the longitudinal biomarker potential of these candidates. Using the current analysis methods described in this thesis, the P2 and P3 may be more suitable choices due to peak-finding difficulties with the N2.

To study cognition longitudinally

Biomarkers for longitudinal tracking of cognition should have suitable test-retest reliability. Good test-retest reliability means that changes in the marker can be interpreted as changes to neural activity, rather than random variation between measurements. The MMN as measured in this thesis generally does not show acceptable reliability for longitudinal use. However, the amplitude of the MMN at Cz was found to have excellent test-retest reliability and could be considered for longitudinal use to study the evolution of sensory attention.

Unlike the MMN, ERPs recorded during the SART show generally high test-retest reliability, making this paradigm an excellent choice for longitudinal application. The test measures cognition in MS-relevant domains, and so should be sensitive to longitudinal cognitive decline in MS. The evolution of SART ERPs should be investigated as potential predictive biomarkers of cognitive decline.

To study the activity of brain networks

The MMN and SART ERPs described in this thesis reflect the summed activity of discrete neural processes at set locations, rather than whole-brain activation across networks. In contrast, rsEEG microstates (Chapter 8) reflect broader, whole-brain activation patterns. If information about whole-brain networks is desired, rsEEG microstates could be a better starting point. From there, task-evoked activity can be investigated within altered networks. On the other hand, these broad networks reflect the interaction of numerous processes, only some of which may be impaired. In this way, microstate analysis could miss cognitive neural impairment if it is very specific or variable within a sample. This may be why numerous alterations were seen in SART ERPs while few alterations in microstates

were observed. Therefore, both whole-brain and sensor ERP measurements can play a role in the quantification of activity within a network.

Limitations and considerations

Some limitations that may have impacted the results presented in this thesis are discussed below. These limitations do not represent errors in the current analyses, but rather, considerations that may guide the application of these results. The section discusses how these limitations were addressed in the present studies and opportunities to further address them in future research.

Clinical characteristics of MS

The participants included in these studies were approximately representative of the wider population of people with MS with respect to MS subtype. The proportion of the study samples made up of people with RRMS varied from around 75-80%. However, we did not directly assess disease stage (e.g. EDSS) beyond distinguishing between RRMS, SPMS, and PPMS, so these analyses may have missed EEG alterations that were specific to people with high or low levels of physical disability. Nevertheless, age, age of onset, and disease duration were assessed for correlation in each analysis, and no associations were found between the candidate markers in these features, which would be expected to show some association with EDSS. Future applications of this research seeking to track cognition on an individual rather than group level should measure EDSS, as disability level may contribute to inter-individual variability in EEG measures.

We also did not measure fatigue, which is a common and disabling symptom of MS affecting between 36-78% of people with MS and decreasing quality of life (Oliva Ramirez et al. 2021). Though we did not measure fatigue, we did measure self-reported depression, which often co-occurs with fatigue in MS (Wood et al. 2013) and showed no associations with ERP measures in our studies.

Additionally, conflicting reports have been made regarding whether fatigue affects ERP measurements in MS. No studies have investigated the impact of fatigue on the SART in MS, because the SART has not been previously characterized in MS. One study has looked at fatigue in relation to the MMN in MS, finding delayed latencies in people with higher fatigue. Only one study has investigated the impact of fatigue on microstates in MS, reporting increases in Class F and Class B (Baldini et al. 2024). In Chapter 8, increased

Class B duration was observed in SPMS. Expansion of this SPMS dataset in conjunction with fatigue assessment could help clarify whether these effects may be reflective of increased fatigue in SPMS.

Self-report measures of cognition

The analyses included in this theses assessed the relationships between EEG measures and cognition using the multiple sclerosis neuropsychological questionnaire (MSNQ) (Benedict et al. 2003). Self-report measurements of cognitive dysfunction are sometimes criticized as non-objective and influenceable by mood, fatigue, or physical disability. Validated anxiety and depression scales were included in these studies to account for some of this variability and showed no association with ERP measures. As discussed above, disability and fatigue scales could further improve these measurements.

The lack of concordance between the MSNQ and individual objective cognitive tests was identified from the point of the tool's development (Benedict et al. 2003). In this study, the screening score did not correlate well with any individual cognitive test. However, the screen had a sensitivity and specificity of 0.83 and 0.97, respectively, for the overall identification of cognitively impaired patients. Therefore, while self-report measures may not reflect impairment within a particular domain, they can still accurately identify people who have affected cognition. Most of the participants with MS included in this thesis project have completed full-battery neuropsychological assessments with linked research teams. Therefore, future analyses could assess the relationship between self-report and objective measures with our own data.

However, self-report scales like the MSNQ may not only be useful as a prompt for further cognitive evaluation. Rather, these tools contain important information of their own: a person's perception of their own cognition. Therefore, abnormal MSNQ scores should be taken both as an indication for further cognitive testing and as a statement of an individual patient's experience, whether or not this corresponds to objectively measurable changes.

Impact of COVID-19

The research reported here was conducted from 2020-2024 and was consequently impacted by the COVID-19 pandemic. Initial plans for longitudinal analyses were quickly changed to methodological assessment of laboratory methods (Chapter 5).

It is also possible that the pandemic impacted the research after data collection resumed. Fatigue and “brain fog” (cognitive impairment and cognitive fatigue) were frequently reported symptoms of COVID-19 infection, both during the acute illness and longer-term. No data on the presence or number of prior COVID-19 infections was obtained during these studies. It is therefore possible that some of the cognitive and neural effects described in this thesis were due to COVID-19 related cognitive dysfunction rather than MS-related cognitive dysfunction. However, these effects should have impacted both people with MS and healthy controls, unless the impact of COVID-19 on the brain is different between these groups. Additionally, some evidence suggests that the overall rate of COVID infection was lower in people with MS, possibly due to earlier access to vaccines and increased attention to social distance and isolation because of the greater risks of infection in this population (Moreno-Torres et al. 2021). Therefore, COVID-19 brain dysfunction likely does not explain the results obtained in this thesis but could be an interesting avenue for further research.

Conclusion

As discussed throughout this thesis, cognitive impairment is a frequently reported and distressing symptom of several neurodegenerative diseases, including multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). Successful longitudinal tracking of cognitive impairment for research and treatment could be aided by the development of robust biomarkers that more directly reflect underlying neural activity than methods like neuropsychological assessment.

This thesis applied novel and under-utilized EEG methods to study cognitive dysfunction in multiple sclerosis. The goal of this research program was to identify EEG biomarker candidates of cognitive impairment in MS, or EEG signatures that are altered in MS and could be assessed in relation to cognitive impairment in the future. This revealed new EEG signatures of cognitive impairment in MS. These signatures (e.g. P3 elicited by the SART, microstate Class B) have been associated with cognitive outcomes in other conditions like ALS. Therefore, these novel candidates have the potential to serve as robust biomarkers of cognitive impairment in MS.

The biomarker candidates identified point to the existence of impaired executive function in MS. Some candidates also differ among subtypes of MS, suggesting that these could be

developed into phenotypic biomarkers in MS. Additionally, the identification of biomarkers that differ between RRMS and SPMS (e.g. P2 latency, microstate B duration) indicates that these markers could reflect neural changes relevant to the progression from RRMS to SPMS. No prospective clinical test for this transition currently exists, so these results highlight an interesting avenue for further research.

This project also provides practical advances to facilitate future longitudinal study of cognition in MS and other neurodegenerative conditions. Firstly, it provides the first evaluation of the test-retest reliability of ERPs generated from the EEG-compatible implementation of the sustained attention to response task (SART). The test interrogates MS-relevant cognitive domains, and the resulting ERPs were shown to be highly reliable with repeat testing. This will support the future use of this paradigm in a longitudinal study of cognition in MS. In addition, the assembly of a large, representative dataset of EEG recordings in people with MS provides an initial basis for such a longitudinal study. Other analysis methodologies such as source analysis, oscillatory band power, and EEG connectivity analysis can be applied to this rich dataset to further understand the neural signals underpinning cognition in this group.

The thesis also facilitates cognitive research in neurodegeneration by showing that the observed EEG signal alterations in conditions like MS and ALS are not solely due to neurodegenerative processes that are shared between the conditions. Patterns of EEG alterations differed between participants with MS and ALS, showing that these signals can reflect disease-specific alterations in cognitively related neural processes. This will encourage future studies to differentiate between shared and divergent alterations among neurodegenerative conditions. Such distinctions could increase the specificity of research on treatments and interventions for cognitive impairment, increasing their chances of success.

In conclusion, this thesis project investigated novel and under-studied EEG biomarker candidates of cognitive impairment in MS and identified a set of candidate biomarkers of impaired executive function and the RRMS to SPMS transition. The project also showed the disease-specificity of these alterations. The collection of a large dataset of task-based and resting state EEG recordings and the validation of the test-retest reliability of the EEG-compatible SART facilitates future work in this area.

References

Abdel Naseer, Maged, Shereen Fathi, Nagwa K. Roshdy, et al. 2019. 'Cognitive and Physical Disability in Egyptian Patients with Multiple Sclerosis: Genetic and Optical Coherence Tomography Study'. *Neurological Research* 41 (7): 644–51. https://doi.org/10.1080/01616412.2019.1609203.

Abrahams, Sharon. 2023. 'Neuropsychological Impairment in Amyotrophic Lateral Sclerosis-Frontotemporal Spectrum Disorder'. *Nature Reviews. Neurology* 19 (11): 655–67. https://doi.org/10.1038/s41582-023-00878-z.

Abrahams, Sharon, P. N Leigh, A Harvey, G. N Vythelingum, D Grisé, and L. H Goldstein. 2000. 'Verbal Fluency and Executive Dysfunction in Amyotrophic Lateral Sclerosis (ALS)'. *Neuropsychologia* 38 (6): 734–47. https://doi.org/10.1016/S0028-3932(99)00146-3.

Abrahams, Sharon, Judith Newton, Elaine Niven, Jennifer Foley, and Thomas H. Bak. 2014. 'Screening for Cognition and Behaviour Changes in ALS'. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 15 (1–2): 9–14. https://doi.org/10.3109/21678421.2013.805784.

Akbar, Nadine, Kimia Honarmand, and Anthony Feinstein. 2011. 'Self-Assessment of Cognition in Multiple Sclerosis: The Role of Personality and Anxiety'. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology* 24 (3): 115–21. https://doi.org/10.1097/WNN.0b013e31822a20ae.

Al Zoubi, Obada, Ahmad Mayeli, Aki Tsuchiyagaito, et al. 2019. 'EEG Microstates Temporal Dynamics Differentiate Individuals with Mood and Anxiety Disorders From Healthy Subjects'. *Frontiers in Human Neuroscience* 13. https://doi.org/10.3389/fnhum.2019.00056.

Alba-Arbalat, Salut, Elisabeth Solana, Elisabet Lopez-Soley, et al. 2024. 'Predictive Value of Retinal Atrophy for Cognitive Decline across Disease Duration in Multiple Sclerosis'. *Journal of Neurology, Neurosurgery, and Psychiatry* 95 (5): 419–25. https://doi.org/10.1136/jnnp-2023-332332.

Altieri, Manuela, Francesco Cerciello, Antonio Gallo, and Gabriella Santangelo. 2024. 'The Relationship between Depression and Cognitive Performance in Multiple Sclerosis: A Meta-Analysis'. *The Clinical Neuropsychologist* 38 (1): 21–41. https://doi.org/10.1080/13854046.2023.2192963.

Amato, M. P., G. Ponziani, G. Siracusa, and S. Sorbi. 2001. 'Cognitive Dysfunction in Early-Onset Multiple Sclerosis: A Reappraisal after 10 Years'. *Archives of Neurology* 58 (10): 1602–6. https://doi.org/10.1001/archneur.58.10.1602.

Amato, Maria P., Benedetta Goretti, Angelo Ghezzi, et al. 2014. 'Neuropsychological Features in Childhood and Juvenile Multiple Sclerosis'. *Neurology* 83 (16): 1432–38. https://doi.org/10.1212/WNL.0000000000000885.

Amato, Maria Pia, Bahia Hakiki, Benedetta Goretti, et al. 2012. 'Association of MRI Metrics and Cognitive Impairment in Radiologically Isolated Syndromes'. *Neurology* 78 (5): 309–14. https://doi.org/10.1212/WNL.0b013e31824528c9.

Anagnostouli, Maria, Foteini Christidi, Ioannis Zalonis, et al. 2015. 'Clinical and Cognitive Implications of Cerebrospinal Fluid Oligoclonal Bands in Multiple Sclerosis Patients'. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 36 (11): 2053–60. https://doi.org/10.1007/s10072-015-2303-1.

Anhoque, C. F., L. Biccas-Neto, S. C. A. Domingues, A. L. Teixeira, and R. B. Domingues. 2013. 'Cognitive Impairment and Optic Nerve Axonal Loss in Patients with Clinically Isolated Syndrome'. *Clinical Neurology and Neurosurgery* 115 (7): 1032–35. https://doi.org/10.1016/j.clineuro.2012.10.025.

Arrondo, G., M. Alegre, J. Sepulcre, J. Iriarte, J. Artieda, and P. Villoslada. 2009. 'Abnormalities in Brain Synchronization Are Correlated with Cognitive Impairment in Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 15 (4): 509–16. https://doi.org/10.1177/1352458508101321.

Arthur, Karissa C., Andrea Calvo, T. Ryan Price, Joshua T. Geiger, Adriano Chiò, and Bryan J. Traynor. 2016. 'Projected Increase in Amyotrophic Lateral Sclerosis from 2015 to 2040'. *Nature Communications* 7 (1): 12408. https://doi.org/10.1038/ncomms12408.

Ascherio, A., K.L. Munger, R. White, et al. 2014. 'Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression'. *JAMA Neurology* 71 (3): 306–14. Scopus. https://doi.org/10.1001/jamaneurol.2013.5993.

Askari, Mozhde, Omid Mirmosayyeb, Fatemeh Fattahi, et al. 2024. 'Prevalence of Cognitive Impairment (CI) in Patients with Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis'. *Caspian Journal of Internal Medicine* 15 (3): 392–413. https://doi.org/10.22088/cjim.15.3.392.

Azcárraga-Guirola, Elisa, Yaneth Rodríguez-Agudelo, Julia Velázquez-Cardoso, Yamel Rito-García, and Rodolfo Solís-Vivanco. 2017. 'Electrophysiological Correlates of Decision Making Impairment in Multiple Sclerosis'. *The European Journal of Neuroscience* 45 (2): 321–29. https://doi.org/10.1111/ejn.13465.

Baetge, Sharon Jean, Michael Dietrich, Melanie Filser, et al. 2021. 'Association of Retinal Layer Thickness With Cognition in Patients With Multiple Sclerosis'. *Neurology® Neuroimmunology & Neuroinflammation* 8 (4): e1018. https://doi.org/10.1212/NXI.0000000000001018.

Balasooriya, Namal N., Thomas M. Elliott, Rachel E. Neale, Paola Vasquez, Tracy Comans, and Louisa G. Gordon. 2024. 'The Association between Vitamin D Deficiency and Multiple Sclerosis: An Updated Systematic Review and Meta-Analysis'. *Multiple Sclerosis and Related Disorders* 90 (August): 105804. https://doi.org/10.1016/j.msard.2024.105804.

Baldini, Sara, Maria Elisa Morelli, Arianna Sartori, et al. 2023. 'Microstates in Multiple Sclerosis: An Electrophysiological Signature of Altered Large-Scale Networks Functioning?' *Brain Communications* 5 (1): fcac255. https://doi.org/10.1093/braincomms/fcac255.

Baldini, Sara, Arianna Sartori, Lucrezia Rossi, et al. 2024. 'Fatigue in Multiple Sclerosis: A Resting-State EEG Microstate Study'. *Brain Topography*, ahead of print, June 7. https://doi.org/10.1007/s10548-024-01053-3.

Banwell, Brenda L., and Peter E. Anderson. 2005. 'The Cognitive Burden of Multiple Sclerosis in Children'. *Neurology* 64 (5): 891–94. https://doi.org/10.1212/01.WNL.0000152896.35341.51.

Baranzini, Sergio E., and Jorge R Oksenberg. 2017. 'The Genetics of Multiple Sclerosis: From 0 to 200 in 50 Years'. *Trends in Genetics : TIG* 33 (12): 960–70. https://doi.org/10.1016/j.tig.2017.09.004.

Barbey, Florentine M., Francesca R. Farina, Alison R. Buick, et al. 2022. 'Neuroscience from the Comfort of Your Home: Repeated, Self-Administered Wireless Dry EEG Measures Brain Function with High Fidelity'. *Frontiers in Digital Health* 4 (July). https://doi.org/10.3389/fdgth.2022.944753.

Barbu, Roxana M., Jason A. Berard, Louise M. Gresham, and Lisa A. S. Walker. 2018. 'Longitudinal Stability of Cognition in Early-Phase Relapsing-Remitting Multiple Sclerosis: Does Cognitive Reserve Play a Role?' *International Journal of MS Care* 20 (4): 173–79. https://doi.org/10.7224/1537-2073.2016-073.

Barkhof, F. 1999. 'MRI in Multiple Sclerosis: Correlation with Expanded Disability Status Scale (EDSS)'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 5 (4): 283–86. https://doi.org/10.1177/135245859900500415.

Barro, Christian, Brian C. Healy, Shrishti Saxena, et al. 2023. 'Serum NfL but Not GFAP Predicts Cognitive Decline in Active Progressive Multiple Sclerosis Patients'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 29 (2): 206–11. https://doi.org/10.1177/13524585221137697.

Barton, Joshua L., Justin Y. Garber, Alexander Klistorner, and Michael H. Barnett. 2019. 'The Electrophysiological Assessment of Visual Function in Multiple Sclerosis'. *Clinical Neurophysiology Practice* 4 (January): 90–96. https://doi.org/10.1016/j.cnp.2019.03.002.

Baudena, P., E. Halgren, G. Heit, and J. M. Clarke. 1995. 'Intracerebral Potentials to Rare Target and Distractor Auditory and Visual Stimuli. III. Frontal Cortex'. *Electroencephalography and Clinical Neurophysiology* 94 (4): 251–64. https://doi.org/10.1016/0013-4694(95)98476-o.

Bavato, Francesco, Christian Barro, Laura K. Schnider, et al. 2024. 'Introducing Neurofilament Light Chain Measure in Psychiatry: Current Evidence, Opportunities, and Pitfalls'. *Molecular Psychiatry*, March 19, 1–17. https://doi.org/10.1038/s41380-024-02524-6.

Beeldman, Emma, Joost Raaphorst, Michelle Klein Twennaar, Marianne de Visser, Ben A. Schmand, and Rob J. de Haan. 2016. 'The Cognitive Profile of ALS: A Systematic Review and Meta-Analysis Update'. *Journal of Neurology, Neurosurgery, and Psychiatry* 87 (6): 611–19. https://doi.org/10.1136/JNNP-2015-310734.

Benedict, Ralph H.B., Maria Pia Amato, John DeLuca, and Jeroen J G Geurts. 2020. 'Cognitive Impairment in Multiple Sclerosis: Clinical Management, MRI, and Therapeutic Avenues'. *The Lancet Neurology* 19 (10): 860–71. https://doi.org/10.1016/S1474-4422(20)30277-5.

Benedict, Ralph H.B., and Julie H. Bobholz. 2007. 'Multiple Sclerosis'. *Seminars in Neurology* 27 (1): 78–85. https://doi.org/10.1055/s-2006-956758.

Benedict, Ralph H.B., Jill S. Fischer, Cate J. Archibald, et al. 2002. 'Minimal Neuropsychological Assessment of MS Patients: A Consensus Approach'. *The Clinical Neuropsychologist* 16 (3): 381–97. https://doi.org/10.1076/clin.16.3.381.13859.

Benedict, Ralph H.B., Frederick Munschauer, R. Linn, et al. 2003. 'Screening for Multiple Sclerosis Cognitive Impairment Using a Self-Administered 15-Item Questionnaire'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 9 (1): 95–101. https://doi.org/10.1191/1352458503ms861oa.

Benedict, Ralph H.B., and Robert Zivadinov. 2007. 'Reliability and Validity of Neuropsychological Screening and Assessment Strategies in MS'. *Journal of Neurology* 254 Suppl 2 (May): II22–25. https://doi.org/10.1007/s00415-007-2007-4.

Benedict, Ralph H.B., Robert Zivadinov, Dominic A. Carone, et al. 2005. 'Regional Lobar Atrophy Predicts Memory Impairment in Multiple Sclerosis'. *AJNR: American Journal of Neuroradiology* 26 (7): 1824–31.

Benjamini, Yoav, and Yosef Hochberg. 1995. 'Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing'. *Journal of the Royal Statistical Society. Series B (Methodological)* 57 (1): 289–300.

Benjamini, Yoav, Abba M. Krieger, and Daniel Yekutieli. 2006. 'Adaptive Linear Step-up Procedures That Control the False Discovery Rate'. *Biometrika* 93 (3): 491–507. https://doi.org/10.1093/BIOMET/93.3.491.

Bergendal, G., S. Fredrikson, and O. Almkvist. 2007. 'Selective Decline in Information Processing in Subgroups of Multiple Sclerosis: An 8-Year Longitudinal Study'. *European Neurology* 57 (4): 193–202. https://doi.org/10.1159/000099158.

Bergmann, Catherine, Shenira Becker, Adreanna Watts, et al. 2023. 'Multiple Sclerosis and Quality of Life: The Role of Cognitive Impairment on Quality of Life in People with Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 79 (November): 104966. https://doi.org/10.1016/j.msard.2023.104966.

Bersano, Enrica, Maria Francesca Sarnelli, Valentina Solara, et al. 2020. 'Decline of Cognitive and Behavioral Functions in Amyotrophic Lateral Sclerosis: A Longitudinal Study'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 21 (5–6): 373–79. https://doi.org/10.1080/21678421.2020.1771732.

Beste, Christian, Carsten Saft, Onur Güntürkün, and Michael Falkenstein. 2008. 'Increased Cognitive Functioning in Symptomatic Huntington's Disease As Revealed by Behavioral and Event-Related Potential Indices of Auditory Sensory Memory and Attention'. *The Journal of Neuroscience* 28 (45): 11695–702. https://doi.org/10.1523/JNEUROSCI.2659-08.2008.

Bever, C. T., L. Grattan, H. S. Panitch, and K. P. Johnson. 1995. 'The Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis: A Preliminary Serial Study'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 1 (3): 165–69. https://doi.org/10.1177/135245859500100306.

Bhattarai, Jagriti Jackie, Krina S. Patel, Katherine M. Dunn, Aeysha Brown, Brett Opelt, and Abbey J. Hughes. 2023. 'Sleep Disturbance and Fatigue in Multiple Sclerosis: A Systematic Review and Meta-Analysis'. *Multiple Sclerosis Journal - Experimental, Translational and Clinical* 9 (3): 20552173231194352. https://doi.org/10.1177/20552173231194352.

Bielekova, B., P. A. Muraro, L. Golestaneh, J. Pascal, H. F. McFarland, and R. Martin. 1999. 'Preferential Expansion of Autoreactive T Lymphocytes from the Memory T-Cell Pool by IL-7'. *Journal of Neuroimmunology* 100 (1–2): 115–23. https://doi.org/10.1016/s0165-5728(99)00200-3.

Bigdely-Shamlo, Nima, Tim Mullen, Christian Kothe, Kyung-Min Su, and Kay A. Robbins. 2015. 'The PREP Pipeline: Standardized Preprocessing for Large-Scale EEG Analysis'. *Frontiers in Neuroinformatics* 9 (June). https://doi.org/10.3389/fninf.2015.00016.

Birkeldh, Ulrika, Ali Manouchehrinia, Max Albert Hietala, et al. 2019. 'Retinal Nerve Fiber Layer Thickness Associates with Cognitive Impairment and Physical Disability in Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 36 (November): 101414. https://doi.org/10.1016/j.msard.2019.101414.

Bissonnette, Jenna N., Laura Pimer, Ashley M. Francis, et al. 2023. 'An Investigation of Auditory Processing in Relapsing-Remitting Multiple Sclerosis'. *Experimental Brain Research* 241 (5): 1319–27. https://doi.org/10.1007/s00221-023-06594-w.

Bjornevik, Kjetil, Marianna Cortese, Brian C. Healy, et al. 2022. 'Longitudinal Analysis Reveals High Prevalence of Epstein-Barr Virus Associated with Multiple Sclerosis'. *Science* 375 (6578): 296–301. https://doi.org/10.1126/science.abj8222.

Blecher, Ronen, Michael A. Elliott, Emre Yilmaz, et al. 2019. 'Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review'. *Global Spine Journal* 9 (1): 104–18. https://doi.org/10.1177/2192568218813916.

Bonferroni, Carlo. 1936. 'Teoria Statistica Delle Classi e Calcolo Delle Probabilita'. *Pubblicazioni Del R Istituto Superiore Di Scienze Economiche e Commericiali Di Firenze* 8: 3–62.

Bora, Emre. 2017. 'Meta-Analysis of Social Cognition in Amyotrophic Lateral Sclerosis'. *Cortex* 88 (March): 1–7. https://doi.org/10.1016/j.cortex.2016.11.012.

Bora, Emre, Serkan Özakbaş, Dennis Velakoulis, and Mark Walterfang. 2016. 'Social Cognition in Multiple Sclerosis: A Meta-Analysis'. *Neuropsychology Review* 26 (2): 160–72. https://doi.org/10.1007/s11065-016-9320-6.

Boylan, Kevin. 2015. 'Familial ALS'. *Neurologic Clinics* 33 (4): 807–30. https://doi.org/10.1016/j.ncl.2015.07.001.

Braley, Tiffany J., Anna L. Kratz, Neeraj Kaplish, and Ronald D. Chervin. 2016. 'Sleep and Cognitive Function in Multiple Sclerosis'. *Sleep* 39 (8): 1525–33. https://doi.org/10.5665/sleep.6012.

Brasil-Neto, J. P., J. Valls-Solé, A. Pascual-Leone, et al. 1993. 'Rapid Modulation of Human Cortical Motor Outputs Following Ischaemic Nerve Block'. *Brain: A Journal of Neurology* 116 (Pt 3) (June): 511–25. https://doi.org/10.1093/brain/116.3.511.

Britz, Juliane, Dimitri Van De Ville, and Christoph M. Michel. 2010. 'BOLD Correlates of EEG Topography Reveal Rapid Resting-State Network Dynamics'. *NeuroImage* 52 (4): 1162–70. https://doi.org/10.1016/j.neuroimage.2010.02.052.

Brochet, Bruno, Pierre Clavelou, Gilles Defer, et al. 2022. 'Cognitive Impairment in Secondary Progressive Multiple Sclerosis: Effect of Disease Duration, Age, and Progressive Phenotype'. *Brain Sciences* 12 (2): 183. https://doi.org/10.3390/brainsci12020183.

Brønnick, Kolbjørn S., Helge Nordby, Jan Petter Larsen, and Dag Aarsland. 2010. 'Disturbance of Automatic Auditory Change Detection in Dementia Associated with Parkinson's Disease: A Mismatch Negativity Study'. *Neurobiology of Aging* 31 (1): 104–13. https://doi.org/10.1016/j.neurobiolaging.2008.02.021.

Brunner, Jan Ferenc, Tor Ivar Hansen, Alexander Olsen, Toril Skandsen, Asta Håberg, and Juri Kropotov. 2013. 'Long-Term Test-Retest Reliability of the P3 NoGo Wave and Two Independent Components Decomposed from the P3 NoGo Wave in a Visual Go/NoGo Task'. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology* 89 (1): 106–14. https://doi.org/10.1016/j.ijpsycho.2013.06.005.

Bsteh, Gabriel, Assunta Dal-Bianco, Nik Krajnc, and Thomas Berger. 2025. 'Biomarkers of Progression Independent of Relapse Activity—Can We Actually Measure It Yet?' *International Journal of Molecular Sciences* 26 (10): 4704. https://doi.org/10.3390/ijms26104704.

Bsteh, Gabriel, Harald Hegen, Barbara Teuchner, et al. 2019. 'Peripapillary Retinal Nerve Fibre Layer as Measured by Optical Coherence Tomography Is a Prognostic Biomarker Not Only for Physical but Also for Cognitive Disability Progression in Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 25 (2): 196–203. https://doi.org/10.1177/1352458517740216.

Burhan, Amer M., Priya Subramanian, Luljeta Pallaveshi, Brittany Barnes, and Manuel Montero-Odasso. 2015. 'Modulation of the Left Prefrontal Cortex with High Frequency Repetitive Transcranial Magnetic Stimulation Facilitates Gait in Multiple

Sclerosis'. *Case Reports in Neurological Medicine* 2015: 251829. https://doi.org/10.1155/2015/251829.

Burke, Tom, Marta Pinto-Grau, Katie Lonergan, et al. 2017. 'A Cross-Sectional Population-Based Investigation into Behavioral Change in Amyotrophic Lateral Sclerosis: Subphenotypes, Staging, Cognitive Predictors, and Survival'. *Annals of Clinical and Translational Neurology* 4 (5): 305–17. https://doi.org/10.1002/acn3.407.

Buron, Mathias Due, Thor Ameri Chalmer, Finn Sellebjerg, et al. 2020. 'Initial High-Efficacy Disease-Modifying Therapy in Multiple Sclerosis'. *Neurology* 95 (8): e1041–51. https://doi.org/10.1212/WNL.0000000000010135.

Buyukturkoglu, Korhan, Camillo Porcaro, Carlo Cottone, Andrea Cancelli, Matilde Inglese, and Franca Tecchio. 2017. 'Simple Index of Functional Connectivity at Rest in Multiple Sclerosis Fatigue'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 128 (5): 807–13. https://doi.org/10.1016/j.clinph.2017.02.010.

Calabrese, Massimiliano, Paolo Preziosa, Antonio Scalfari, et al. 2024. 'Determinants and Biomarkers of Progression Independent of Relapses in Multiple Sclerosis'. *Annals of Neurology* 96 (1): 1–20. https://doi.org/10.1002/ana.26913.

Candiri, Busra, Engin Ramazanoglu, Burcu Talu, and Mehmet Tecellioglu. 2024. 'The Relationship between Cognitive Function and Functional Capacity, and Cognitive Reserve and Reaction Time in Patients with Multiple Sclerosis'. *Arquivos De Neuro-Psiquiatria* 82 (9): 1–9. https://doi.org/10.1055/s-0044-1788273.

Candore, Giuseppina, Domenico Lio, Giuseppina Colonna Romano, and Calogero Caruso. 2002. 'Pathogenesis of Autoimmune Diseases Associated with 8.1 Ancestral Haplotype: Effect of Multiple Gene Interactions'. *Autoimmunity Reviews* 1 (1–2): 29–35. https://doi.org/10.1016/s1568-9972(01)00004-0.

Canosa, Antonio, Cristina Moglia, Umberto Manera, et al. 2020. 'Metabolic Brain Changes across Different Levels of Cognitive Impairment in ALS: A 18F-FDG-PET Study'. *Journal of Neurology, Neurosurgery, and Psychiatry*, November 23, jnnp-2020-323876. https://doi.org/10.1136/jnnp-2020-323876.

Caramia, M. Donatella, M. Giuseppina Palmieri, M. Teresa Desiato, et al. 2004. 'Brain Excitability Changes in the Relapsing and Remitting Phases of Multiple Sclerosis: A Study with Transcranial Magnetic Stimulation'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 115 (4): 956–65. https://doi.org/10.1016/j.clinph.2003.11.024.

Carone, D. A., R. H. B. Benedict, F. E. Munschauer, I. Fishman, and B. Weinstock-Guttman. 2005. 'Interpreting Patient/Informant Discrepancies of Reported Cognitive Symptoms in MS'. *Journal of the International Neuropsychological Society: JINS* 11 (5): 574–83. https://doi.org/10.1017/S135561770505068X.

Cerdá-Fuertes, Nuria, Marc Stoessel, Gintaras Mickeliunas, et al. 2023. 'Optical Coherence Tomography versus Other Biomarkers: Associations with Physical and Cognitive Disability in Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 29 (13): 1540–50. https://doi.org/10.1177/13524585231198760.

Chapelle, Anne-Catherine. 2025. 'Anterograde Degeneration along the Visual Pathway Following Optic Nerve Injury: A Review'. *Frontiers in Neurology* 16 (August). https://doi.org/10.3389/fneur.2025.1623798.

Chard, Declan, and S Anand Trip. 2017. 'Resolving the Clinico-Radiological Paradox in Multiple Sclerosis'. *F1000Research* 6 (October): 1828. https://doi.org/10.12688/f1000research.11932.1.

Charest, Kim, Alexandra Tremblay, Roxane Langlois, Élaine Roger, Pierre Duquette, and Isabelle Rouleau. 2020. 'Detecting Subtle Cognitive Impairment in Multiple Sclerosis with the Montreal Cognitive Assessment'. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques* 47 (5): 620–26. https://doi.org/10.1017/cjn.2020.97.

Cheng, Chia-Hsiung, Bing-Wen Soong, Wan-Yu Hsu, and Yung-Yang Lin. 2014. 'Reduced Automatic Frontal Response to Auditory Deviance in Huntington's Disease as Indexed by Magnetic Mismatch Negativity'. *Journal of Clinical Neuroscience* 21 (10): 1773–78. https://doi.org/10.1016/j.jocn.2014.01.019.

Chiaravalloti, Nancy D., and John DeLuca. 2008. 'Cognitive Impairment in Multiple Sclerosis'. *The Lancet Neurology* 7 (12): 1139–51. https://doi.org/10.1016/S1474-4422(08)70259-X.

Chiò, Adriano, G Logroscino, BJ Traynor, et al. 2013. 'Global Epidemiology of Amyotrophic Lateral Sclerosis: A Systematic Review of the Published Literature'. *Neuroepidemiology* 41 (2): 118–30. https://doi.org/10.1159/000351153.

Chiò, Adriano, Giancarlo Logroscino, Orla Hardiman, et al. 2009. 'Prognostic Factors in ALS: A Critical Review'. *Amyotrophic Lateral Sclerosis: Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases* 10 (5–6): 310–23. https://doi.org/10.3109/17482960802566824.

Cho, Eun Bin, Se Young Jung, Jin-Hyung Jung, et al. 2023. 'The Risk of Dementia in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder'. *Frontiers in Neuroscience* 17 (June): 1214652. https://doi.org/10.3389/fnins.2023.1214652.

Ciubotaru, Alin, Emilian Bogdan Ignat, Daniel Alexa, et al. 2024. 'Influence of Education, Cognition, and Physical Disability on Quality of Life of Romanian Patients with Multiple Sclerosis-A Cohort Study'. *Medicina (Kaunas, Lithuania)* 60 (3): 386. https://doi.org/10.3390/medicina60030386.

Clough, Meaghan, Lynette Millist, Nathaniel Lizak, et al. 2015. 'Ocular Motor Measures of Cognitive Dysfunction in Multiple Sclerosis I: Inhibitory Control'. *Journal of Neurology* 262 (5): 1130–37. https://doi.org/10.1007/s00415-015-7645-3.

Cogliati Dezza, I., G. Zito, L. Tomasevic, et al. 2015. 'Functional and Structural Balances of Homologous Sensorimotor Regions in Multiple Sclerosis Fatigue'. *Journal of Neurology* 262 (3): 614–22. https://doi.org/10.1007/s00415-014-7590-6.

Collins, D. W. K., J. L. Black, and F. L. Mastaglia. 1978. 'Pattern-Reversal Visual Evoked Potential: Method of Analysis and Results in Multiple Sclerosis'. *Journal of the Neurological Sciences* 36 (1): 83–95. https://doi.org/10.1016/0022-510X(78)90163-6.

Comi, G., M. Filippi, V. Martinelli, et al. 1995. 'Brain MRI Correlates of Cognitive Impairment in Primary and Secondary Progressive Multiple Sclerosis'. *Journal of the Neurological Sciences* 132 (2): 222–27. https://doi.org/10.1016/0022-510x(95)00168-2.

Connick, Peter, Siddharthan Chandran, and Thomas H. Bak. 2013. 'Patterns of Cognitive Dysfunction in Progressive MS'. *Behavioural Neurology* 27 (3): 259–65. https://doi.org/10.3233/BEN-120286.

Conte, A., D. Lenzi, V. Frasca, et al. 2009. 'Intracortical Excitability in Patients with Relapsing-Remitting and Secondary Progressive Multiple Sclerosis'. *Journal of Neurology* 256 (6): 933–38. https://doi.org/10.1007/s00415-009-5047-0.

Coric, Danko, Lisanne J. Balk, Merike Verrijp, et al. 2018. 'Cognitive Impairment in Patients with Multiple Sclerosis Is Associated with Atrophy of the Inner Retinal Layers'.

Multiple Sclerosis (Houndmills, Basingstoke, England) 24 (2): 158–66. https://doi.org/10.1177/1352458517694090.

Cortese, Marianna, Kassandra L. Munger, Elena H. Martínez-Lapiscina, et al. 2020. 'Vitamin D, Smoking, EBV, and Long-Term Cognitive Performance in MS: 11-Year Follow-up of BENEFIT'. *Neurology* 94 (18): e1950–60. https://doi.org/10.1212/WNL.0000000000009371.

Covey, Thomas J., Daniel Golan, Robert Sergott, et al. 2024. 'Peering Further into the Mind's Eye: Combining Visual Evoked Potential and Optical Coherence Tomography Measures Enhances Insight into the Variance in Cognitive Functioning in Multiple Sclerosis'. *Journal of Neurology* 271 (2): 658–73. https://doi.org/10.1007/s00415-023-12075-5.

Covey, Thomas J., Janet L. Shucard, Ralph Hb Benedict, Bianca Weinstock-Guttman, and David W. Shucard. 2018. 'Improved Cognitive Performance and Event-Related Potential Changes Following Working Memory Training in Patients with Multiple Sclerosis'. *Multiple Sclerosis Journal - Experimental, Translational and Clinical* 4 (1): 2055217317747626. https://doi.org/10.1177/2055217317747626.

Cree, Bruce A.C., Douglas L. Arnold, Jeremy Chataway, et al. 2021. 'Secondary Progressive Multiple Sclerosis'. *Neurology* 97 (8): 378–88. https://doi.org/10.1212/WNL.0000000000012323.

Cruz-Gomez, Álvaro J., Lucía Forero, Elena Lozano-Soto, et al. 2021. 'Cortical Thickness and Serum NfL Explain Cognitive Dysfunction in Newly Diagnosed Patients With Multiple Sclerosis'. *Neurology(R) Neuroimmunology & Neuroinflammation* 8 (6): e1074. https://doi.org/10.1212/NXI.0000000000001074.

Cruz-Tapias, Paola, John Castiblanco, and Juan-Manuel Anaya. 2013. 'Major Histocompatibility Complex: Antigen Processing and Presentation'. In *Autoimmunity: From Bench to Bedside [Internet]*. El Rosario University Press. https://www.ncbi.nlm.nih.gov/books/NBK459467/.

Custo, Anna, Dimitri Van De Ville, William M. Wells, Miralena I. Tomescu, Denis Brunet, and Christoph M. Michel. 2017. 'Electroencephalographic Resting-State Networks: Source Localization of Microstates'. *Brain Connectivity* 7 (10): 671–82. https://doi.org/10.1089/brain.2016.0476.

Dagenais, Emmanuelle, Isabelle Rouleau, Mélanie Demers, et al. 2013. 'Value of the MoCA Test as a Screening Instrument in Multiple Sclerosis'. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques* 40 (3): 410–15. https://doi.org/10.1017/s0317167100014384.

Dam, Maureen van, Brigit A. de Jong, Eline A. J. Willemse, et al. 2023. 'A Multimodal Marker for Cognitive Functioning in Multiple Sclerosis: The Role of NfL, GFAP and Conventional MRI in Predicting Cognitive Functioning in a Prospective Clinical Cohort'. *Journal of Neurology* 270 (8): 3851–61. https://doi.org/10.1007/s00415-023-11676-4.

Dam, Maureen van, Eva A. Krijnen, Ilse M. Nauta, et al. 2024. 'Identifying and Understanding Cognitive Profiles in Multiple Sclerosis: A Role for Visuospatial Memory Functioning'. *Journal of Neurology* 271 (5): 2195–206. https://doi.org/10.1007/s00415-024-12227-1.

Darwish, Hala, Natali Farran, Salem Hannoun, et al. 2020. 'Serum Vitamin D Level Is Associated with Speed of Processing in Multiple Sclerosis Patients'. *The Journal of Steroid Biochemistry and Molecular Biology* 200 (June): 105628. https://doi.org/10.1016/j.jsbmb.2020.105628.

Darwish, Hala, Ribal Haddad, Sahar Osman, et al. 2017. 'Effect of Vitamin D Replacement on Cognition in Multiple Sclerosis Patients'. *Scientific Reports* 7 (April): 45926. https://doi.org/10.1038/srep45926.

Davion, Jean-Baptiste, Caroline Jougleux, Renaud Lopes, Xavier Leclerc, and Olivier Outteryck. 2023. 'Relation between Retina, Cognition and Brain Volumes in MS: A Consequence of Asymptomatic Optic Nerve Lesions'. *Journal of Neurology* 270 (1): 240–49. https://doi.org/10.1007/s00415-022-11348-9.

De Groote, Evelien, Annelies Bockstael, Dick Botteldooren, Patrick Santens, and Miet De Letter. 2021. 'Evaluation of Multi-Feature Auditory Deviance Detection in Parkinson's Disease: A Mismatch Negativity Study'. *Journal of Neural Transmission (Vienna, Austria: 1996)* 128 (5): 645–57. https://doi.org/10.1007/s00702-021-02341-z.

De Meo, Ermelinda, Emilio Portaccio, Antonio Giorgio, et al. 2021. 'Identifying the Distinct Cognitive Phenotypes in Multiple Sclerosis'. *JAMA Neurology* 78 (4): 414–25. https://doi.org/10.1001/jamaneurol.2020.4920.

Delgado-Álvarez, Alfonso, Jordi A. Matias-Guiu, Cristina Delgado-Alonso, et al. 2020. 'Cognitive Processes Underlying Verbal Fluency in Multiple Sclerosis'. *Frontiers in Neurology* 11: 629183. https://doi.org/10.3389/fneur.2020.629183.

Delorme, Arnaud, and Scott Makeig. 2004. 'EEGLAB: An Open Source Toolbox for Analysis of Single-Trial EEG Dynamics Including Independent Component Analysis'. *Journal of Neuroscience Methods* 134 (1): 9–21. https://doi.org/10.1016/J.JNEUMETH.2003.10.009.

Delussi, Marianna, Christian Valt, Adelchi Silvestri, et al. 2024. 'Auditory Mismatch Negativity in Pre-Manifest and Manifest Huntington's Disease'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 162 (June): 121–28. https://doi.org/10.1016/j.clinph.2024.03.020.

Denney, Douglas R., Lisa A. Sworowski, and Sharon G. Lynch. 2005. 'Cognitive Impairment in Three Subtypes of Multiple Sclerosis'. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists* 20 (8): 967–81. https://doi.org/10.1016/j.acn.2005.04.012.

D'haeseleer, Miguel, Stéphanie Hostenbach, Ilse Peeters, et al. 2015. 'Cerebral Hypoperfusion: A New Pathophysiologic Concept in Multiple Sclerosis?' *Journal of Cerebral Blood Flow & Metabolism* 35 (9): 1406–10. https://doi.org/10.1038/jcbfm.2015.131.

Didcote, Lyndsay, Silia Vitoratou, Ammar Al-Chalabi, and Laura H. Goldstein. 2024. 'What Is the Extent of Reliability and Validity Evidence for Screening Tools for Cognitive and Behavioral Change in People with ALS? A Systematic Review'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 25 (5–6): 437–51. https://doi.org/10.1080/21678421.2024.2314063.

Dreyer-Alster, Sapir, Aviva Gal, and Anat Achiron. 2022. 'Optical Coherence Tomography Is Associated With Cognitive Impairment in Multiple Sclerosis'. *Journal of Neuro-Ophthalmology: The Official Journal of the North American Neuro-Ophthalmology Society* 42 (1): e14–21. https://doi.org/10.1097/WNO.0000000000001326.

Duan, Qing-Qing, Zheng Jiang, Wei-Ming Su, et al. 2023. 'Risk Factors of Amyotrophic Lateral Sclerosis: A Global Meta-Summary'. *Frontiers in Neuroscience* 17: 1177431. https://doi.org/10.3389/fnins.2023.1177431.

Dukic, S., P. M. Iyer, K. Mohr, O. Hardiman, E. C. Lalor, and B. Nasseroleslami. 2017. 'Estimation of Coherence Using the Median Is Robust against EEG Artefacts'. *2017*

39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), July, 3949–52. https://doi.org/10.1109/EMBC.2017.8037720.

Dukic, Stefan, Roisin McMackin, Teresa Buxo, et al. 2019. 'Patterned Functional Network Disruption in Amyotrophic Lateral Sclerosis'. *Human Brain Mapping* 40 (16): 4827–42. https://doi.org/10.1002/hbm.24740.

Dukic, Stefan, Roisin McMackin, Emmet Costello, et al. 2022. 'Resting-State EEG Reveals Four Subphenotypes of Amyotrophic Lateral Sclerosis'. *Brain* 145 (2): 621–31. https://doi.org/10.1093/brain/awab322.

Ehtesham, Naeim, Maryam Zare Rafie, and Meysam Mosallaei. 2021. 'The Global Prevalence of Familial Multiple Sclerosis: An Updated Systematic Review and Meta-Analysis'. *BMC Neurology* 21 (1): 246. https://doi.org/10.1186/s12883-021-02267-9.

El Ayoubi, Nabil K., Stephanie Ghassan, Marianne Said, Joelle Allam, Hala Darwish, and Samia J. Khoury. 2016. 'Retinal Measures Correlate with Cognitive and Physical Disability in Early Multiple Sclerosis'. *Journal of Neurology* 263 (11): 2287–95. https://doi.org/10.1007/s00415-016-8271-4.

Elosúa, M. Rosa, and Noelia Villadangos. 2023. 'Executive Functions in Relapsing-Remitting Multiple Sclerosis'. *Applied Neuropsychology. Adult*, November 6, 1–9. https://doi.org/10.1080/23279095.2023.2252125.

Escal, Jean, Anthony Fourier, Maité Formaglio, et al. 2022. 'Comparative Diagnosis Interest of NfL and pNfH in CSF and Plasma in a Context of FTD–ALS Spectrum'. *Journal of Neurology* 269 (3): 1522–29. https://doi.org/10.1007/s00415-021-10714-3.

Escera, Carles, and Carles Grau. 1996. 'Short-Term Replicability of the Mismatch Negativity'. *Electroencephalography & Clinical Neurophysiology: Evoked Potentials* (Netherlands) 100 (6): 549–54. https://doi.org/10.1016/S0168-5597(96)95633-6.

Esmael, Ahmed, Mohamed Elsherif, Mohamed Abdelsalam, Dalia Sabry, Mohamed Mamdouh, and Tamer Belal. 2020. 'Retinal Thickness as a Potential Biomarker of Neurodegeneration and a Predictor of Early Cognitive Impairment in Patients with Multiple Sclerosis'. *Neurological Research* 42 (7): 564–74. https://doi.org/10.1080/01616412.2020.1761174.

Espiritu, Adrian I., Yasmin Soliman, Mervin Blair, et al. 2024. 'Self-Reported Cognitive Function Mediates the Relationship between Employment Status and Cognitive Functioning in Persons with Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 87 (July): 105645. https://doi.org/10.1016/j.msard.2024.105645.

Essa, Shimaa Abdelalim, Ahmed Elokda, Dalia Mosaad, et al. 2023. 'Efficacy of Ultraviolet B Radiation versus Vitamin D3 on Postural Control and Cognitive Functions in Relapsing-Remitting Multiple Sclerosis: A Randomized Controlled Study'. *Journal of Bodywork and Movement Therapies* 35 (July): 49–56. https://doi.org/10.1016/j.jbmt.2023.04.069.

Evstigneeva, Maria D., Alexander A. Alexandrov, Svend Erik Mathiassen, and Eugene Lyskov. 2010. 'Muscle Contraction Force and Fatigue: Effects on Mismatch Negativity'. *Neuroreport* 21 (18): 1152–56. https://doi.org/10.1097/WNR.0b013e328340cc66.

Faber, Pascal L., Patricia Milz, Eva Z. Reininghaus, et al. 2021. 'Fundamentally Altered Global- and Microstate EEG Characteristics in Huntington's Disease'. *Clinical Neurophysiology* 132 (1): 13–22. https://doi.org/10.1016/j.clinph.2020.10.006.

Falzone, Yuri Matteo, Teuta Domi, Alessandra Mandelli, et al. 2022. 'Integrated Evaluation of a Panel of Neurochemical Biomarkers to Optimize Diagnosis and Prognosis in Amyotrophic Lateral Sclerosis'. *European Journal of Neurology* 29 (7): 1930–39. https://doi.org/10.1111/ene.15321.

Farina, Gabriele, Roberta Magliozzi, Marco Pitteri, et al. 2017. 'Increased Cortical Lesion Load and Intrathecal Inflammation Is Associated with Oligoclonal Bands in Multiple Sclerosis Patients: A Combined CSF and MRI Study'. *Journal of Neuroinflammation* 14 (1): 40. https://doi.org/10.1186/s12974-017-0812-y.

Farrell, R., M. Summers, C. Doogan, et al. 2021. 'Evaluation of the Cognitive Benefits of Intrathecal Baclofen Pump Implantation in People with Intractable Multiple Sclerosis Related Spasticity'. *Multiple Sclerosis and Related Disorders* 50 (May): 102831. https://doi.org/10.1016/J.MSARD.2021.102831.

Feldman, Eva L, Stephen A Goutman, Susanne Petri, et al. 2022. 'Amyotrophic Lateral Sclerosis'. *The Lancet* 400 (10360): 1363–80. https://doi.org/10.1016/S0140-6736(22)01272-7.

Ferreira, Joana Almeida, Nuno Pinto, Tiago Maricoto, and Maria Vaz Pato. 2024. 'Relationship between Event-Related Potentials and Cognitive Dysfunction in Multiple Sclerosis: A Systematic Review'. *Clinical Neurophysiology* 163 (July): 174–84. https://doi.org/10.1016/j.clinph.2024.04.024.

Figved, Nanna, Kjell-Morten Myhr, Jan-Petter Larsen, and Dag Aarsland. 2007. 'Caregiver Burden in Multiple Sclerosis: The Impact of Neuropsychiatric Symptoms'. *Journal of Neurology, Neurosurgery, and Psychiatry* 78 (10): 1097–102. https://doi.org/10.1136/jnnp.2006.104216.

Filippi, Massimo, Amit Bar-Or, Fredrik Piehl, et al. 2018. 'Multiple Sclerosis'. *Nature Reviews Disease Primers* 4 (1): 1. https://doi.org/10.1038/s41572-018-0041-4.

Filippi, Massimo, Gianna Riccitelli, Flavia Mattioli, et al. 2012. 'Multiple Sclerosis: Effects of Cognitive Rehabilitation on Structural and Functional MR Imaging Measures--an Explorative Study'. *Radiology* 262 (3): 932–40. https://doi.org/10.1148/radiol.11111299.

Finegan, Eoin, Rangariroyashe H. Chipika, Stacey Li Hi Shing, Orla Hardiman, and Peter Bede. 2019. 'Pathological Crying and Laughing in Motor Neuron Disease: Pathobiology, Screening, Intervention'. *Frontiers in Neurology* 10: 260. https://doi.org/10.3389/fneur.2019.00260.

Fischer, J S, R A Rudick, G R Cutter, and S C Reingold. n.d. *The Multiple Sclerosis Functional Composite Measure (MSFC): An Integrated Approach to MS Clinical Outcome Assessment*.

Fisher, R. A. 1915. 'Frequency Distribution of the Values of the Correlation Coefficient in Samples from an Indefinitely Large Population'. *Biometrika* 10 (4): 507–21. https://doi.org/10.2307/2331838.

Foucher, Juliette, Linn Öijerstedt, Anikó Lovik, et al. 2024. 'ECAS Correlation with Metabolic Alterations on FDG-PET Imaging in ALS'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, June 5, 1–9. https://doi.org/10.1080/21678421.2024.2361695.

França, Márcia, Cláudia Sousa, Patricia Campos, et al. 2024. 'Assessment of Phonemic Verbal Fluency in Portuguese Patients with Multiple Sclerosis'. *Journal of Clinical and Experimental Neuropsychology*, July 9, 1–9. https://doi.org/10.1080/13803395.2024.2376295.

Frau, Jessica, Giuseppe Fenu, Alessio Signori, et al. 2018. 'A Cross-Sectional and Longitudinal Study Evaluating Brain Volumes, RNFL, and Cognitive Functions in MS

Patients and Healthy Controls'. *BMC Neurology* 18 (May): 67. https://doi.org/10.1186/s12883-018-1065-9.

Freedman, David E., Jiwon Oh, Alex Kiss, et al. 2024. 'The Influence of Depression and Anxiety on Cognition in People with Multiple Sclerosis: A Cross-Sectional Analysis'. *Journal of Neurology* 271 (8): 4885–96. https://doi.org/10.1007/s00415-024-12409-x.

Freeman, Léorah, Erin E. Longbrake, Patricia K. Coyle, Barry Hendin, and Timothy Vollmer. 2022. 'High-Efficacy Therapies for Treatment-Naïve Individuals with Relapsing-Remitting Multiple Sclerosis'. *CNS Drugs* 36 (12): 1285–99. https://doi.org/10.1007/s40263-022-00965-7.

Freunberger, R., W. Klimesch, M. Doppelmayr, and Y. Höller. 2007. 'Visual P2 Component Is Related to Theta Phase-Locking'. *Neuroscience Letters* 426 (3): 181–86. https://doi.org/10.1016/j.neulet.2007.08.062.

Friedova, Lucie, Jiri Motyl, Barbora Srpova, et al. 2020. 'The Weak Association between Neurofilament Levels at Multiple Sclerosis Onset and Cognitive Performance after 9 Years'. *Multiple Sclerosis and Related Disorders* 46 (November): 102534. https://doi.org/10.1016/j.msard.2020.102534.

Frodl-Bauch, Thomas, Norbert Kathmann, Hans-Jürgen Möller, and Ulrich Hegerl. 1997. 'Dipole Localization and Test-Retest Reliability of Frequency and Duration Mismatch Negativity Generator Processes'. *Brain Topography* 10 (1): 3–8. https://doi.org/10.1023/A:1022214905452.

Fuchs, Tom A., Menno M. Schoonheim, Robert Zivadinov, et al. 2024. 'Cognitive Progression Independent of Relapse in Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, August 28, 13524585241256540. https://doi.org/10.1177/13524585241256540.

Gaeta, Helen, David Friedman, Walter Ritter, and Jeff Cheng. 1999. 'Changes in Sensitivity to Stimulus Deviance in Alzheimer's Disease: An ERP Perspective'. *NeuroReport* 10 (2): 281.

Gaetani, Lorenzo, Nicola Salvadori, Viviana Lisetti, et al. 2019. 'Cerebrospinal Fluid Neurofilament Light Chain Tracks Cognitive Impairment in Multiple Sclerosis'. *Journal of Neurology* 266 (9): 2157–63. https://doi.org/10.1007/s00415-019-09398-7.

Gaudino, EA, Nancy Chiaravalloti, John Deluca, and B Diamond. 2001. 'A Comparison of Memory Performance in Relapsing-Remitting, Primary Progressive and Secondary Progressive, Multiple Sclerosis'. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 14 (February): 32–44.

Giard, Marie-Hélène, François Perrin, Jacques Pernier, and Patrick Bouchet. 1990. 'Brain Generators Implicated in the Processing of Auditory Stimulus Deviance: A Topographic Event-Related Potential Study'. *Psychophysiology* 27 (6): 627–40. https://doi.org/10.1111/j.1469-8986.1990.tb03184.x.

Gibbons, Zoe C., Anna Richardson, David Neary, and Julie S. Snowden. 2008. 'Behaviour in Amyotrophic Lateral Sclerosis'. *Amyotrophic Lateral Sclerosis: Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases* 9 (2): 67–74. https://doi.org/10.1080/17482960701642437.

Giedraitiene, Natasa, Egle Drukteiniene, Rasa Kizlaitiene, Andrius Cimbalas, Rimvydas Asoklis, and Gintaras Kaubrys. 2021. 'Cognitive Decline in Multiple Sclerosis Is Related to the Progression of Retinal Atrophy and Presence of Oligoclonal Bands: A 5-Year Follow-Up Study'. *Frontiers in Neurology* 12 (July). https://doi.org/10.3389/fneur.2021.678735.

Glover, Gary H. 2011. 'Overview of Functional Magnetic Resonance Imaging'. *Neurosurgery Clinics of North America* 22 (2): 133–39. https://doi.org/10.1016/j.nec.2010.11.001.

Gombash, Sara E., Priscilla W. Lee, Elizabeth Sawdai, and Amy E. Lovett-Racke. 2022. 'Vitamin D as a Risk Factor for Multiple Sclerosis: Immunoregulatory or Neuroprotective?' *Frontiers in Neurology* 13 (May): 796933. https://doi.org/10.3389/fneur.2022.796933.

Gómez-Melero, Sara, Javier Caballero-Villarraso, Begoña Mª Escribano, Alejandro Galvao-Carmona, Isaac Túnez, and Eduardo Agüera-Morales. 2024. 'Impact of Cognitive Impairment on Quality of Life in Multiple Sclerosis Patients-A Comprehensive Review'. *Journal of Clinical Medicine* 13 (11): 3321. https://doi.org/10.3390/jcm13113321.

Gonzalez-Rosa, Javier J, Manuel Vazquez-Marrufo, Encarnacion Vaquero, et al. 2006. 'Differential Cognitive Impairment for Diverse Forms of Multiple Sclerosis'. *BMC Neuroscience* 7 (May): 39. https://doi.org/10.1186/1471-2202-7-39.

Gonzalez-Rosa, Javier J., Manuel Vazquez-Marrufo, Encarnacion Vaquero, et al. 2011. 'Cluster Analysis of Behavioural and Event-Related Potentials during a Contingent Negative Variation Paradigm in Remitting-Relapsing and Benign Forms of Multiple Sclerosis'. *BMC Neurology* 11 (June): 64. https://doi.org/10.1186/1471-2377-11-64.

Gordon-Lipkin, Eliza, and Peter A. Calabresi. 2017. 'Optical Coherence Tomography: A Quantitative Tool to Measure Neurodegeneration and Facilitate Testing of Novel Treatments for Tissue Protection in Multiple Sclerosis'. *Journal of Neuroimmunology*, SI: 40 Years-Neuroimmunology, vol. 304 (March): 93–96. https://doi.org/10.1016/j.jneuroim.2016.12.003.

Gosselt, Isabel K., Tanja C. W. Nijboer, and Michael A. Van Es. 2020. 'An Overview of Screening Instruments for Cognition and Behavior in Patients with ALS: Selecting the Appropriate Tool for Clinical Practice'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 21 (5–6): 324–36. https://doi.org/10.1080/21678421.2020.1732424.

Gouider, Riadh, Amira Souissi, Saloua Mrabet, et al. 2024. 'Environmental Factors Related to Multiple Sclerosis Progression'. *Journal of the Neurological Sciences* 464 (September): 123161. https://doi.org/10.1016/j.jns.2024.123161.

Granberg, Tobias, Juha Martola, Maria Kristoffersen-Wiberg, Peter Aspelin, and Sten Fredrikson. 2013. 'Radiologically Isolated Syndrome--Incidental Magnetic Resonance Imaging Findings Suggestive of Multiple Sclerosis, a Systematic Review'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 19 (3): 271–80. https://doi.org/10.1177/1352458512451943.

Gschwind, Markus, Martin Hardmeier, Dimitri Van De Ville, et al. 2016. 'Fluctuations of Spontaneous EEG Topographies Predict Disease State in Relapsing-Remitting Multiple Sclerosis'. *NeuroImage. Clinical* 12: 466–77. https://doi.org/10.1016/j.nicl.2016.08.008.

Gu, Dongqing, Shan Ou, Mingshuang Tang, Zhiyong Yin, Zhengguo Wang, and Guodong Liu. 2021. 'Trauma and Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 22 (3–4): 170–85. https://doi.org/10.1080/21678421.2020.1861024.

Guillemin, C., E. Lommers, G. Delrue, E. Gester, P. Maquet, and F. Collette. 2022. 'The Complex Interplay Between Trait Fatigue and Cognition in Multiple Sclerosis'. *Psychologica Belgica* 62 (1): 108–22. https://doi.org/10.5334/pb.1125.

Gunnarsson, Lars-Gunnar, and Lennart Bodin. 2018. 'Amyotrophic Lateral Sclerosis and Occupational Exposures: A Systematic Literature Review and Meta-Analyses'. *International Journal of Environmental Research and Public Health* 15 (11): 2371. https://doi.org/10.3390/ijerph15112371.

Gür, Evrim, Ghada Binkhamis, and Karolina Kluk. 2022. 'Effects of Multiple Sclerosis on the Audio-Vestibular System: A Systematic Review'. *BMJ Open* 12 (8): e060540. https://doi.org/10.1136/bmjopen-2021-060540.

Hadriche, Abir, Nawel Jmail, Jean-Luc Blanc, and Laurent Pezard. 2019. 'Using Centrality Measures to Extract Core Pattern of Brain Dynamics during the Resting State'. *Computer Methods and Programs in Biomedicine* 179 (October): 104985. https://doi.org/10.1016/j.cmpb.2019.104985.

Halgren, E., P. Baudena, J. M. Clarke, et al. 1995. 'Intracerebral Potentials to Rare Target and Distractor Auditory and Visual Stimuli. II. Medial, Lateral and Posterior Temporal Lobe'. *Electroencephalography and Clinical Neurophysiology* 94 (4): 229–50. https://doi.org/10.1016/0013-4694(95)98475-n.

Hämäläinen, P., and E. Rosti-Otajärvi. 2016. 'Cognitive Impairment in MS: Rehabilitation Approaches'. *Acta Neurologica Scandinavica* 134 Suppl 200 (September): 8–13. https://doi.org/10.1111/ane.12650.

Hammer, Anke, Stefan Vielhaber, Antoni Rodriguez-Fornells, Bahram Mohammadi, and Thomas F. Münte. 2011. 'A Neurophysiological Analysis of Working Memory in Amyotrophic Lateral Sclerosis'. *Brain Research* 1421 (November): 90–99. https://doi.org/10.1016/j.brainres.2011.09.010.

Hämmerer, Dorothea, Shu-Chen Li, Manuel Völkle, Viktor Müller, and Ulman Lindenberger. 2013. 'A Lifespan Comparison of the Reliability, Test-Retest Stability, and Signal-to-Noise Ratio of Event-Related Potentials Assessed during Performance Monitoring'. *Psychophysiology* 50 (1): 111–23. https://doi.org/10.1111/j.1469-8986.2012.01476.x.

Hardiman, Orla, Ammar Al-Chalabi, Carol Brayne, et al. 2017. 'The Changing Picture of Amyotrophic Lateral Sclerosis: Lessons from European Registers'. Neurodegeneration. *Journal of Neurology, Neurosurgery & Psychiatry* 88 (7): 557–63. https://doi.org/10.1136/jnnp-2016-314495.

Hardiman, Orla, Ammar Al-Chalabi, Adriano Chio, et al. 2017. 'Amyotrophic Lateral Sclerosis'. *Nature Reviews. Disease Primers* 3 (October): 17071. https://doi.org/10.1038/nrdp.2017.71.

Hardmeier, Martin, Menno M. Schoonheim, Jeroen J. G. Geurts, et al. 2012. 'Cognitive Dysfunction in Early Multiple Sclerosis: Altered Centrality Derived from Resting-State Functional Connectivity Using Magneto-Encephalography'. *PloS One* 7 (7): e42087. https://doi.org/10.1371/journal.pone.0042087.

Hartmann, Ana, Fabio Noro, Paulo Roberto Valle Bahia, et al. 2023. 'The Clinical-Radiological Paradox in Multiple Sclerosis: Myth or Truth?' *Arquivos De Neuro-Psiquiatria* 81 (1): 55–61. https://doi.org/10.1055/s-0042-1758457.

Hazanavicius, Michel, dir. 2011. *The Artist*. La Petite Reine and ARP Sélection. 100 min.

Hedström, A. K., J. Hillert, T. Olsson, and L. Alfredsson. 2013. 'Nicotine Might Have a Protective Effect in the Etiology of Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 19 (8): 1009–13. https://doi.org/10.1177/1352458512471879.

Huijbregts, S. C.J., N. F. Kalkers, L. M.J. de Sonneville, V. de Groot, I. E.W. Reuling, and C. H. Polman. 2004. 'Differences in Cognitive Impairment of Relapsing Remitting,

Secondary, and Primary Progressive MS'. *Neurology* 63 (2): 335–39. https://doi.org/10.1212/01.WNL.0000129828.03714.90.

Hynes, Sinéad M., Fiadhnait O'Keeffe, Eimear Bane, et al. 2022. 'Assessment and Management of Cognitive and Psychosocial Difficulties for People with Multiple Sclerosis in Ireland: A National Survey of Clinical Practice'. *International Journal of Clinical Practice* 2022 (October): 3232076. https://doi.org/10.1155/2022/3232076.

Illán-Gala, Ignacio, Daniel Alcolea, Victor Montal, et al. 2018. 'CSF sAPPβ, YKL-40, and NfL along the ALS-FTD Spectrum'. *Neurology* 91 (17): e1619–28. https://doi.org/10.1212/WNL.0000000000006383.

International Multiple Sclerosis Genetics Consortium, David A. Hafler, Alastair Compston, et al. 2007. 'Risk Alleles for Multiple Sclerosis Identified by a Genomewide Study'. *The New England Journal of Medicine* 357 (9): 851–62. https://doi.org/10.1056/NEJMoa073493.

Iyer, Parameswaran Mahadeva, Kieran Mohr, Michael Broderick, et al. 2017. 'Mismatch Negativity as an Indicator of Cognitive Sub-Domain Dysfunction in Amyotrophic Lateral Sclerosis'. *Frontiers in Neurology* 0 (AUG): 395. https://doi.org/10.3389/FNEUR.2017.00395.

Jakimovski, Dejan, Ralph H. B. Benedict, Bianca Weinstock-Guttman, et al. 2021. 'Visual Deficits and Cognitive Assessment of Multiple Sclerosis: Confounder, Correlate, or Both?' *Journal of Neurology* 268 (7): 2578–88. https://doi.org/10.1007/s00415-021-10437-5.

Jakimovski, Dejan, Robert Zivadinov, Murali Ramanthan, et al. 2020. 'Serum Neurofilament Light Chain Level Associations with Clinical and Cognitive Performance in Multiple Sclerosis: A Longitudinal Retrospective 5-Year Study'. *Multiple Sclerosis Journal* 26 (13): 1670–81. https://doi.org/10.1177/1352458519881428.

Jellinger, Kurt A. 2023. 'The Spectrum of Cognitive Dysfunction in Amyotrophic Lateral Sclerosis: An Update'. *International Journal of Molecular Sciences* 24 (19): 14647. https://doi.org/10.3390/ijms241914647.

Jung, Julien, Dominique Morlet, Bernadette Mercier, Christian Confavreux, and Catherine Fischer. 2006. 'Mismatch Negativity (MMN) in Multiple Sclerosis: An Event-Related Potentials Study in 46 Patients'. *Clinical Neurophysiology* 117 (1): 85–93. https://doi.org/10.1016/J.CLINPH.2005.09.013.

Kalatha, Thaleia, Marianthi Arnaoutoglou, Theodoros Koukoulidis, et al. 2019. 'Does Cognitive Dysfunction Correlate with Neurofilament Light Polypeptide Levels in the CSF of Patients with Multiple Sclerosis?' *The Journal of International Medical Research* 47 (5): 2187–98. https://doi.org/10.1177/0300060519840550.

Kazmerski, V. A., D. Friedman, and W. Ritter. 1997. 'Mismatch Negativity during Attend and Ignore Conditions in Alzheimer's Disease'. *Biological Psychiatry* 42 (5): 382–402. https://doi.org/10.1016/S0006-3223(96)00344-7.

Keune, Philipp M., Sascha Hansen, Emily Weber, et al. 2017. 'Exploring Resting-State EEG Brain Oscillatory Activity in Relation to Cognitive Functioning in Multiple Sclerosis'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 128 (9): 1746–54. https://doi.org/10.1016/j.clinph.2017.06.253.

Khalil, Michael, Charlotte E. Teunissen, Sylvain Lehmann, et al. 2024. 'Neurofilaments as Biomarkers in Neurological Disorders — towards Clinical Application'. *Nature Reviews Neurology* 20 (5): 269–87. https://doi.org/10.1038/s41582-024-00955-x.

Kiiski, Hanni, Richard B. Reilly, R. Lonergan, et al. 2011. 'Change in PASAT Performance Correlates with Change in P3 ERP Amplitude over a 12-Month Period in Multiple

Sclerosis Patients'. *Journal of the Neurological Sciences* 305 (1–2): 45–52. https://doi.org/10.1016/j.jns.2011.03.018.

Kiiski, Hanni, Richard B. Reilly, Róisín Lonergan, et al. 2012. 'Only Low Frequency Event-Related EEG Activity Is Compromised in Multiple Sclerosis: Insights from an Independent Component Clustering Analysis'. *PloS One* 7 (9): e45536. https://doi.org/10.1371/journal.pone.0045536.

Kiiski, Hanni, Robert Whelan, Róisín Lonergan, et al. 2011. 'Preliminary Evidence for Correlation between PASAT Performance and P3a and P3b Amplitudes in Progressive Multiple Sclerosis'. *European Journal of Neurology* 18 (5): 792–95. https://doi.org/10.1111/J.1468-1331.2010.03172.X.

Kimiskidis, VK, Sotirakoglou K, Kouvatsou ZK, et al. 2016. 'Cognitive Event-Related Potentials in Multiple Sclerosis: Correlation with MRI and Neuropsychological Findings'. *Multiple Sclerosis and Related Disorders* 10 (November): 192–97. https://doi.org/10.1016/J.MSARD.2016.10.006.

Klein, Olga A., Roshan das Nair, Joanne Ablewhite, and Avril Drummond. 2019. 'Assessment and Management of Cognitive Problems in People with Multiple Sclerosis: A National Survey of Clinical Practice'. *International Journal of Clinical Practice* 73 (3): e13300. https://doi.org/10.1111/ijcp.13300.

Ko, Fang, Zaynah A. Muthy, John Gallacher, et al. 2018. 'Association of Retinal Nerve Fiber Layer Thinning With Current and Future Cognitive Decline'. *JAMA Neurology* 75 (10): 1198–205. https://doi.org/10.1001/jamaneurol.2018.1578.

Koenig, Thomas, Dietrich Lehmann, Marco C. G. Merlo, Kieko Kochi, Daniel Hell, and Martha Koukkou. 1999. 'A Deviant EEG Brain Microstate in Acute, Neuroleptic-Naive Schizophrenics at Rest'. *European Archives of Psychiatry and Clinical Neuroscience* 249 (4): 205–11. https://doi.org/10.1007/s004060050088.

Koenig, Thomas, Leslie Prichep, Dietrich Lehmann, et al. 2002. 'Millisecond by Millisecond, Year by Year: Normative EEG Microstates and Developmental Stages'. *NeuroImage* 16 (1): 41–48. https://doi.org/10.1006/nimg.2002.1070.

Kolčava, Jan, Jan Kočica, Monika Hulová, et al. 2020. 'Conversion of Clinically Isolated Syndrome to Multiple Sclerosis: A Prospective Study'. *Multiple Sclerosis and Related Disorders* 44 (September): 102262. https://doi.org/10.1016/j.msard.2020.102262.

Koo, Terry K, and Mae Y. Li. 2016. 'A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research'. *Journal of Chiropractic Medicine* 15 (2): 155–63. https://doi.org/10.1016/J.JCM.2016.02.012.

Kotterba, Sylvia, Maritta Orth, Esma Eren, Tanja Fangerau, and Eckhart Sindern. 2003. 'Assessment of Driving Performance in Patients with Relapsing-Remitting Multiple Sclerosis by a Driving Simulator'. *European Neurology* 50 (3): 160–64. https://doi.org/10.1159/000073057.

Kropotov, J. D., R. Näätänen, A. V. Sevostianov, K. Alho, K. Reinikainen, and O. V. Kropotova. 1995. 'Mismatch Negativity to Auditory Stimulus Change Recorded Directly from the Human Temporal Cortex'. *Psychophysiology* 32 (4): 418–22. https://doi.org/10.1111/j.1469-8986.1995.tb01226.x.

Kuhle, Jens, G Disanto, R Dobson, et al. 2015. 'Conversion from Clinically Isolated Syndrome to Multiple Sclerosis: A Large Multicentre Study'. *Multiple Sclerosis Journal* 21 (8): 1013–24. https://doi.org/10.1177/1352458514568827.

Kuhle, Jens, Harald Kropshofer, Dieter A. Haering, et al. 2019. 'Blood Neurofilament Light Chain as a Biomarker of MS Disease Activity and Treatment Response'. *Neurology* 92 (10). https://doi.org/10.1212/WNL.0000000000007032.

Kurtzke, J. F. 1983. 'Rating Neurologic Impairment in Multiple Sclerosis: An Expanded Disability Status Scale (EDSS)'. *Neurology* 33 (11): 1444–52. https://doi.org/10.1212/wnl.33.11.1444.

Lancia, Samantha, Ruth Ann Marrie, Gary Cutter, Robert J. Fox, and Amber Salter. 2024. 'Association of Patient-Reported Cognitive Impairment with Quality of Life and Employment in Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 87 (July): 105675. https://doi.org/10.1016/j.msard.2024.105675.

Langdon, D. W., M. P. Amato, J. Boringa, et al. 2012. 'Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 18 (6): 891–98. https://doi.org/10.1177/1352458511431076.

Lange, Florian, Maj-Britt Vogts, Caroline Seer, et al. 2016. 'Impaired Set-Shifting in Amyotrophic Lateral Sclerosis: An Event-Related Potential Study of Executive Function'. *Neuropsychology* 30 (1): 120–34. https://doi.org/10.1037/neu0000218.

Larsson, Susanna C., and Stephen Burgess. 2021. 'Causal Role of High Body Mass Index in Multiple Chronic Diseases: A Systematic Review and Meta-Analysis of Mendelian Randomization Studies'. *BMC Medicine* 19 (1): 320. https://doi.org/10.1186/s12916-021-02188-x.

Leavitt, Victoria M., Gabriella Tosto, and Claire S. Riley. 2018. 'Cognitive Phenotypes in Multiple Sclerosis'. *Journal of Neurology* 265 (3): 562–66. https://doi.org/10.1007/s00415-018-8747-5.

Lehmann, Pia, Paul Eling, Andreas Kastrup, Oliver Grothues, and Helmut Hildebrandt. 2013. 'Self-Reported Sleep Problems, but Not Fatigue, Lead to Decline in Sustained Attention in MS Patients'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 19 (4): 490–97. https://doi.org/10.1177/1352458512457719.

Lehto, Annaliis, Julia Schumacher, Elisabeth Kasper, et al. 2024. 'Cerebral Glucose Metabolic Correlates of Cognitive and Behavioural Impairments in Amyotrophic Lateral Sclerosis'. *Journal of Neurology* 271 (8): 5290–300. https://doi.org/10.1007/s00415-024-12388-z.

Lenne, Bruno, Jean-Luc Blanc, Jean-Louis Nandrino, Philippe Gallois, Patrick Hautecæur, and Laurent Pezard. 2013. 'Decrease of Mutual Information in Brain Electrical Activity of Patients with Relapsing-Remitting Multiple Sclerosis'. *Behavioural Neurology* 27 (2): 627529. https://doi.org/10.3233/BEN-120278.

Leocani, L. 2000. 'Electroencephalographic Coherence Analysis in Multiple Sclerosis: Correlation with Clinical, Neuropsychological, and MRI Findings'. *Journal of Neurology, Neurosurgery & Psychiatry* 69 (2): 192–98. https://doi.org/10.1136/jnnp.69.2.192.

Leocani, L., B. Colombo, G. Magnani, et al. 2001. 'Fatigue in Multiple Sclerosis Is Associated with Abnormal Cortical Activation to Voluntary Movement--EEG Evidence'. *NeuroImage* 13 (6 Pt 1): 1186–92. https://doi.org/10.1006/nimg.2001.0759.

Lester, Kristin, Lara Stepleman, and Mary Hughes. 2007. 'The Association of Illness Severity, Self-Reported Cognitive Impairment, and Perceived Illness Management with Depression and Anxiety in a Multiple Sclerosis Clinic Population'. *Journal of Behavioral Medicine* 30 (2): 177–86. https://doi.org/10.1007/s10865-007-9095-6.

Liepert, J., D. Mingers, C. Heesen, T. Bäumer, and C. Weiller. 2005. 'Motor Cortex Excitability and Fatigue in Multiple Sclerosis: A Transcranial Magnetic Stimulation Study'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 11 (3): 316–21. https://doi.org/10.1191/1352458505ms1163oa.

Lincoln, N. B., and K. A. Radford. 2008. 'Cognitive Abilities as Predictors of Safety to Drive in People with Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 14 (1): 123–28. https://doi.org/10.1177/1352458507080467.

Logroscino, Giancarlo, Bryan J. Traynor, Orla Hardiman, et al. 2010. 'Incidence of Amyotrophic Lateral Sclerosis in Europe'. Research Paper. *Journal of Neurology, Neurosurgery & Psychiatry* 81 (4): 385–90. https://doi.org/10.1136/jnnp.2009.183525.

Lomer, Nima Broomand, Kamal AmirAshjei Asalemi, Alia Saberi, and Kasra Sarlak. 2024. 'Predictors of Multiple Sclerosis Progression: A Systematic Review of Conventional Magnetic Resonance Imaging Studies'. *PloS One* 19 (4): e0300415. https://doi.org/10.1371/journal.pone.0300415.

Lopez-Calderon, Javier, and Steven J. Luck. 2014. 'ERPLAB: An Open-Source Toolbox for the Analysis of Event-Related Potentials'. *Frontiers in Human Neuroscience* 8 (April). https://doi.org/10.3389/fnhum.2014.00213.

López-Góngora, Mariana, Antonio Escartín, Saul Martínez-Horta, et al. 2015. 'Neurophysiological Evidence of Compensatory Brain Mechanisms in Early-Stage Multiple Sclerosis'. *PloS One* 10 (8): e0136786. https://doi.org/10.1371/journal.pone.0136786.

Lublin, Fred D., Stephen C. Reingold, Jeffrey A. Cohen, et al. 2014. 'Defining the Clinical Course of Multiple Sclerosis'. *Neurology* 83 (3): 278–86. https://doi.org/10.1212/WNL.0000000000000560.

Luck, S. J., and S. A. Hillyard. 1994. 'Electrophysiological Correlates of Feature Analysis during Visual Search'. *Psychophysiology* 31 (3): 291–308. https://doi.org/10.1111/j.1469-8986.1994.tb02218.x.

Lugosi, Katalin, Marie A. Engh, Zsolt Huszár, et al. 2024. 'Domain-Specific Cognitive Impairment in Multiple Sclerosis: A Systematic Review and Meta-Analysis'. *Annals of Clinical and Translational Neurology* 11 (3): 564–76. https://doi.org/10.1002/acn3.51976.

MacAllister, W. S., A. L. Belman, M. Milazzo, et al. 2005. 'Cognitive Functioning in Children and Adolescents with Multiple Sclerosis'. *Neurology* 64 (8): 1422–25. https://doi.org/10.1212/01.WNL.0000158474.24191.BC.

Macaron, G., L. E. Baldassari, K. Nakamura, et al. 2020. 'Cognitive Processing Speed in Multiple Sclerosis Clinical Practice: Association with Patient-Reported Outcomes, Employment and Magnetic Resonance Imaging Metrics'. *European Journal of Neurology* 27 (7): 1238–49. https://doi.org/10.1111/ene.14239.

Mackenzie, Ian Ra, Rosa Rademakers, and Manuela Neumann. 2010. 'TDP-43 and FUS in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia'. *The Lancet. Neurology* 9 (10): 995–1007. https://doi.org/10.1016/S1474-4422(10)70195-2.

Maghbooli, Zhila, Arash Shirvani, Abdorreza Naser Moghadasi, Tarlan Varzandi, Sara Hamtaei Ghashti, and Mohammad Ali Sahraian. 2024. 'Investigating the Effects of 25-Hydroxyvitamin D3 on Clinical Outcomes in Multiple Sclerosis Patients: A Randomized, Double-Blind Clinical Trial- a Pilot Study'. *Multiple Sclerosis and Related Disorders* 87 (July): 105673. https://doi.org/10.1016/j.msard.2024.105673.

Magliozzi, Roberta, Marco Pitteri, Stefano Ziccardi, et al. 2021. 'CSF Parvalbumin Levels Reflect Interneuron Loss Linked with Cortical Pathology in Multiple Sclerosis'. *Annals of Clinical and Translational Neurology* 8 (3): 534–47. https://doi.org/10.1002/acn3.51298.

Mahler, João Vitor, Marina Solti, Samira Luísa Apóstolos-Pereira, Tarso Adoni, Guilherme Diogo Silva, and Dagoberto Callegaro. 2024. 'Vitamin D3 as an Add-on Treatment for Multiple Sclerosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials'. *Multiple Sclerosis and Related Disorders* 82 (February): 105433. https://doi.org/10.1016/j.msard.2024.105433.

Mahmoudi, Elham, Shima Sadaghiyani, Paul Lin, et al. 2022. 'Diagnosis of Alzheimer's Disease and Related Dementia among People with Multiple Sclerosis: Large Cohort Study, USA'. *Multiple Sclerosis and Related Disorders* 57 (January): 103351. https://doi.org/10.1016/j.msard.2021.103351.

Maier, Smaranda, Laura Barcutean, Sebastian Andone, et al. 2023. 'Recent Progress in the Identification of Early Transition Biomarkers from Relapsing-Remitting to Progressive Multiple Sclerosis'. *International Journal of Molecular Sciences* 24 (5): 4375. https://doi.org/10.3390/ijms24054375.

Maltby, Vicki E., Rodney A. Lea, Penny Reeves, Bente Saugbjerg, and Jeannette Lechner-Scott. 2022. 'Reduced Cognitive Function Contributes to Economic Burden of Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 60 (April): 103707. https://doi.org/10.1016/j.msard.2022.103707.

Manjaly, Zita R., Kirsten M. Scott, Kumar Abhinav, et al. 2010. 'The Sex Ratio in Amyotrophic Lateral Sclerosis: A Population Based Study'. *Amyotrophic Lateral Sclerosis : Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases* 11 (5): 439–42. https://doi.org/10.3109/17482961003610853.

Mann, H. B., and D. R. Whitney. 1947a. 'On a Test of Whether One of Two Random Variables Is Stochastically Larger than the Other'. *The Annals of Mathematical Statistics* 18 (1): 50–60.

Mann, H. B., and D. R. Whitney. 1947b. 'On a Test of Whether One of Two Random Variables Is Stochastically Larger than the Other'. *The Annals of Mathematical Statistics* 18 (1): 50–60.

Mannarelli, Daniela, Caterina Pauletti, Nicoletta Locuratolo, et al. 2014. 'Attentional Processing in Bulbar- and Spinal-Onset Amyotrophic Lateral Sclerosis: Insights from Event-Related Potentials'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 15 (1–2): 30–38. https://doi.org/10.3109/21678421.2013.787628.

Mäntynen, Anu, Eija Rosti-Otajärvi, Keijo Koivisto, Arja Lilja, Heini Huhtala, and Päivi Hämäläinen. 2014. 'Neuropsychological Rehabilitation Does Not Improve Cognitive Performance but Reduces Perceived Cognitive Deficits in Patients with Multiple Sclerosis: A Randomised, Controlled, Multi-Centre Trial'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 20 (1): 99–107. https://doi.org/10.1177/1352458513494487.

Marafioti, Giulia, Davide Cardile, Laura Culicetto, Angelo Quartarone, and Viviana Lo Buono. 2024. 'The Impact of Social Cognition Deficits on Quality of Life in Multiple Sclerosis: A Scoping Review'. *Brain Sciences* 14 (7): 691. https://doi.org/10.3390/brainsci14070691.

Marin, Benoît, Andrea Fontana, Simona Arcuti, et al. 2018. 'Age-Specific ALS Incidence: A Dose-Response Meta-Analysis'. *European Journal of Epidemiology* 33 (7): 621–34. https://doi.org/10.1007/s10654-018-0392-x.

Marzullo, Aldo, Gabriel Kocevar, Claudio Stamile, et al. 2019. 'Classification of Multiple Sclerosis Clinical Profiles via Graph Convolutional Neural Networks'. *Frontiers in Neuroscience* 13: 594. https://doi.org/10.3389/fnins.2019.00594.

Mata, Sabrina, Matteo Bussotti, Monica Del Mastio, et al. 2023. 'Epidemiology of Amyotrophic Lateral Sclerosis in the North East Tuscany in the 2018–2021 Period'. *eNeurologicalSci* 31 (June): 100457. https://doi.org/10.1016/j.ensci.2023.100457.

Mattioli, Flavia, F. Bellomi, C. Stampatori, et al. 2020. 'Longitudinal Serum Neurofilament Light Chain (sNfL) Concentration Relates to Cognitive Function in Multiple Sclerosis Patients'. *Journal of Neurology* 267 (8): 2245–51. https://doi.org/10.1007/s00415-020-09832-1.

McCarthy, M., J. G. Beaumont, R. Thompson, and S. Peacock. 2005. 'Modality-Specific Aspects of Sustained and Divided Attentional Performance in Multiple Sclerosis'. *Archives of Clinical Neuropsychology* 20 (6): 705–18. https://doi.org/10.1016/j.acn.2005.04.007.

McClintock, Shawn M., Irving M. Reti, Linda L. Carpenter, et al. 2018. 'Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression'. *The Journal of Clinical Psychiatry* 79 (1): 16cs10905. https://doi.org/10.4088/JCP.16cs10905.

McGraw, Kenneth O., and S. P. Wong. 1996. 'Forming Inferences about Some Intraclass Correlation Coefficients'. *Psychological Methods* (US) 1 (1): 30–46. https://doi.org/10.1037/1082-989X.1.1.30.

McGuigan, Christopher. 2013. 'Evoked Potentials Are of Little Use in the Diagnosis or Monitoring of MS: Yes'. *Multiple Sclerosis Journal* 19 (14): 1820–21. https://doi.org/10.1177/1352458513505695.

McKay, Kyla A., Shayesteh Jahanfar, Tom Duggan, Stacey Tkachuk, and Helen Tremlett. 2017. 'Factors Associated with Onset, Relapses or Progression in Multiple Sclerosis: A Systematic Review'. *Neurotoxicology* 61 (July): 189–212. https://doi.org/10.1016/j.neuro.2016.03.020.

McMackin, Roisin. 2021. 'Human Neurodegeneration: A Spectral EEG and TMS Based Approach in Amyotrophic Lateral Sclerosis'. Thesis, Trinity College Dublin. School of Medicine. Discipline of Clinical Medicine. https://www.tara.tcd.ie/handle/2262/96213.

McMackin, Roisin, Stefan Dukic, Emmet Costello, et al. 2020. 'Localization of Brain Networks Engaged by the Sustained Attention to Response Task Provides Quantitative Markers of Executive Impairment in Amyotrophic Lateral Sclerosis'. *Cerebral Cortex (New York, NY)* 30 (9): 4834. https://doi.org/10.1093/CERCOR/BHAA076.

McMackin, Roisin, Stefan Dukic, Emmet Costello, Marta Pinto-Grau, Lara McManus, et al. 2021. 'Cognitive Network Hyperactivation and Motor Cortex Decline Correlate with ALS Prognosis'. *Neurobiology of Aging* 104 (August): 57–70. https://doi.org/10.1016/J.NEUROBIOLAGING.2021.03.002.

McMackin, Roisin, Stefan Dukic, Emmet Costello, Marta Pinto-Grau, Orla Keenan, et al. 2021. 'Sustained Attention to Response Task-Related Beta Oscillations Relate to Performance and Provide a Functional Biomarker in ALS'. *Journal of Neural Engineering* 18 (2). https://doi.org/10.1088/1741-2552/abd829.

McMackin, Roisin, Dukic S, Broderick M, et al. 2019. 'Dysfunction of Attention Switching Networks in Amyotrophic Lateral Sclerosis'. *NeuroImage. Clinical* 22 (January). https://doi.org/10.1016/J.NICL.2019.101707.

Metzger, Aude, Emmanuelle Le Bars, Jeremy Deverdun, et al. 2018. 'Is Impaired Cerebral Vasoreactivity an Early Marker of Cognitive Decline in Multiple Sclerosis Patients?' *European Radiology* 28 (3): 1204–14. https://doi.org/10.1007/s00330-017-5068-5.

Metzger, Marjorie, Stefan Dukic, Roisin McMackin, et al. 2023. 'Functional Network Dynamics Revealed by EEG Microstates Reflect Cognitive Decline in Amyotrophic Lateral Sclerosis'. *Human Brain Mapping* 45 (1): e26536. https://doi.org/10.1002/hbm.26536.

Metzger, Marjorie, Stefan Dukic, Roisin McMackin, et al. 2024. 'Functional Network Dynamics Revealed by EEG Microstates Reflect Cognitive Decline in Amyotrophic Lateral Sclerosis'. *Human Brain Mapping* 45 (1): e26536. https://doi.org/10.1002/hbm.26536.

Meyer-Moock, Sandra, You-Shan Feng, Mathias Maeurer, Franz-Werner Dippel, and Thomas Kohlmann. 2014. 'Systematic Literature Review and Validity Evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in Patients with Multiple Sclerosis'. *BMC Neurology* 14 (1): 58. https://doi.org/10.1186/1471-2377-14-58.

Michel, Christoph M., and Thomas Koenig. 2018. 'EEG Microstates as a Tool for Studying the Temporal Dynamics of Whole-Brain Neuronal Networks: A Review'. *NeuroImage*, Brain Connectivity Dynamics, vol. 180 (October): 577–93. https://doi.org/10.1016/j.neuroimage.2017.11.062.

Michielsen, Annebelle, Kevin van Veenhuijzen, Mark R. Janse van Mantgem, et al. 2024. 'Association Between Hypothalamic Volume and Metabolism, Cognition, and Behavior in Patients With Amyotrophic Lateral Sclerosis'. *Neurology* 103 (2): e209603. https://doi.org/10.1212/WNL.0000000000209603.

Migliore, Simone, Giuseppe Curcio, Alessandro Couyoumdjian, et al. 2018. 'Executive Functioning in Relapsing-Remitting Multiple Sclerosis Patients without Cognitive Impairment: A Task-Switching Protocol'. *Multiple Sclerosis Journal* 24 (10): 1328–36. https://doi.org/10.1177/1352458517719149.

Miller, Robert G., J. D. Mitchell[a], and Dan H. Moore. 2012. 'Riluzole for Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Disease (MND)'. *Cochrane Database of Systematic Reviews*, no. 3. https://doi.org/10.1002/14651858.CD001447.pub3.

Milz, P., P. L. Faber, D. Lehmann, T. Koenig, K. Kochi, and R. D. Pascual-Marqui. 2016. 'The Functional Significance of EEG Microstates--Associations with Modalities of Thinking'. *NeuroImage* 125 (January): 643–56. https://doi.org/10.1016/j.neuroimage.2015.08.023.

Mioshi, Eneida, Kate Dawson, Joanna Mitchell, Robert Arnold, and John R. Hodges. 2006. 'The Addenbrooke's Cognitive Examination Revised (ACE-R): A Brief Cognitive Test Battery for Dementia Screening'. *International Journal of Geriatric Psychiatry* 21 (11): 1078–85. https://doi.org/10.1002/gps.1610.

Mirmosayyeb, Omid, Fardin Nabizadeh, Elham Moases Ghaffary, et al. 2024. 'Cognitive Performance and Magnetic Resonance Imaging in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis'. *Multiple Sclerosis and Related Disorders* 88 (August): 105705. https://doi.org/10.1016/j.msard.2024.105705.

Mirmosayyeb, Omid, Robert Zivadinov, Bianca Weinstock-Guttman, Ralph H. B. Benedict, and Dejan Jakimovski. 2023. 'Optical Coherence Tomography (OCT) Measurements and Cognitive Performance in Multiple Sclerosis: A Systematic Review and Meta-Analysis'. *Journal of Neurology* 270 (3): 1266–85. https://doi.org/10.1007/s00415-022-11449-5.

Mistri, Damiano, Nicolò Tedone, Diana Biondi, et al. 2024. 'Cognitive Phenotypes in Multiple Sclerosis: Mapping the Spectrum of Impairment'. *Journal of Neurology* 271 (4): 1571–83. https://doi.org/10.1007/s00415-023-12102-5.

Mognon, Andrea, Jorge Jovicich, Lorenzo Bruzzone, and Marco Buiatti. 2010. *ADJUST: An Automatic EEG Artifact Detector Based on the Joint Use of Spatial and Temporal Features*. https://doi.org/10.1111/j.1469-8986.2010.01061.x.

Mohammadi, Sana, Sadegh Ghaderi, and Farzad Fatehi. 2024. 'MRI Biomarkers and Neuropsychological Assessments of Hippocampal and Parahippocampal Regions Affected by ALS: A Systematic Review'. *CNS Neuroscience & Therapeutics* 30 (2): e14578. https://doi.org/10.1111/cns.14578.

Mohammadi, Sana, Sadegh Ghaderi, Mahdi Mohammadi, et al. 2024. 'Thalamic Alterations in Motor Neuron Diseases: A Systematic Review of MRI Findings'. *Journal of Integrative Neuroscience* 23 (4): 77. https://doi.org/10.31083/j.jin2304077.

Mohr, Kieran, Bahman Nasseroleslami, Parameswaran Mahadeva Iyer, Orla Hardiman, and Edmund C. Lalor. 2017. 'EyeBallGUI: A Tool for Visual Inspection and Binary Marking of Multi-Channel Bio-Signals'. *bioRxiv*, May 6, 129437. https://doi.org/10.1101/129437.

Montuschi, Anna, Barbara Iazzolino, Andrea Calvo, et al. 2015. 'Cognitive Correlates in Amyotrophic Lateral Sclerosis: A Population-Based Study in Italy'. *Journal of Neurology, Neurosurgery, and Psychiatry* 86 (2): 168–73. https://doi.org/10.1136/jnnp-2013-307223.

Moreno-Torres, Irene, Virginia Meca Lallana, Lucienne Costa-Frossard, et al. 2021. 'Risk and Outcomes of COVID-19 in Patients with Multiple Sclerosis'. *European Journal of Neurology* 28 (11): 3712–21. https://doi.org/10.1111/ene.14990.

Mori, Francesco, Concetta Ljoka, Elisabetta Magni, et al. 2011. 'Transcranial Magnetic Stimulation Primes the Effects of Exercise Therapy in Multiple Sclerosis'. *Journal of Neurology* 258 (7): 1281–87. https://doi.org/10.1007/s00415-011-5924-1.

Mori, Franceso, C. Codecà, H. Kusayanagi, et al. 2010. 'Effects of Intermittent Theta Burst Stimulation on Spasticity in Patients with Multiple Sclerosis'. *European Journal of Neurology* 17 (2): 295–300. https://doi.org/10.1111/j.1468-1331.2009.02806.x.

Murphy, Michael, Jun Wang, Chenguang Jiang, et al. 2024. 'A Potential Source of Bias in Group-Level EEG Microstate Analysis'. *Brain Topography* 37 (2): 232–42. https://doi.org/10.1007/s10548-023-00992-7.

Näätänen, Risto, T. Kujala, C. Escera, et al. 2012. 'The Mismatch Negativity (MMN) – A Unique Window to Disturbed Central Auditory Processing in Ageing and Different Clinical Conditions'. *Clinical Neurophysiology* 123 (3): 424–58. https://doi.org/10.1016/J.CLINPH.2011.09.020.

Näätänen, Risto, and Patricia T. Michie. 1979. 'Early Selective-Attention Effects on the Evoked Potential: A Critical Review and Reinterpretation'. *Biological Psychology* 8 (2): 81–136. https://doi.org/10.1016/0301-0511(79)90053-X.

Näätänen, Risto, P. Paavilainen, T. Rinne, and K. Alho. 2007. 'The Mismatch Negativity (MMN) in Basic Research of Central Auditory Processing: A Review'. *Clinical Neurophysiology* 118 (12): 2544–90. https://doi.org/10.1016/j.clinph.2007.04.026.

Näätänen, Risto, Elyse S. Sussman, Dean Salisbury, and Valerie L. Shafer. 2014. 'Mismatch Negativity (MMN) as an Index of Cognitive Dysfunction'. *Brain Topography* 27 (4): 451–66. https://doi.org/10.1007/s10548-014-0374-6.

Nabizadeh, Fardin, Parya Valizadeh, Maryam Yazdani Tabrizi, Kimia Moayyed, Niousha Ghomashi, and Omid Mirmosayyeb. 2022. 'Seasonal and Monthly Variation in Multiple Sclerosis Relapses: A Systematic Review and Meta-Analysis'. *Acta Neurologica Belgica* 122 (6): 1447–56. https://doi.org/10.1007/s13760-022-02103-y.

Nasreddine, Ziad S., Natalie A. Phillips, Valérie Bédirian, et al. 2005. 'The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment'. *Journal of the American Geriatrics Society* 53 (4): 695–99. https://doi.org/10.1111/j.1532-5415.2005.53221.x.

Nasseroleslami, Bahman. 2018. 'An Implementation of Empirical Bayesian Inference and Non-Null Bootstrapping for Threshold Selection and Power Estimation in Multiple and Single Statistical Testing'. *bioRxiv*, June 8, 342964. https://doi.org/10.1101/342964.

Nasseroleslami, Bahman, Stefan Dukic, Michael Broderick, et al. 2019. 'Characteristic Increases in EEG Connectivity Correlate With Changes of Structural MRI in Amyotrophic Lateral Sclerosis'. *Cerebral Cortex* 29 (1): 27–41. https://doi.org/10.1093/cercor/bhx301.

Nauta, Ilse M., Maureen van Dam, Dirk Bertens, et al. 2024. 'Improved Quality of Life and Psychological Symptoms Following Mindfulness and Cognitive Rehabilitation in Multiple Sclerosis and Their Mediating Role for Cognition: A Randomized Controlled Trial'. *Journal of Neurology* 271 (7): 4361–72. https://doi.org/10.1007/s00415-024-12327-y.

Nova, Andrea, Giovanni Di Caprio, Giulia N. Baldrighi, Davide Galdiolo, Luisa Bernardinelli, and Teresa Fazia. 2024. 'Investigating the Influence of Oral Contraceptive Pill Use on Multiple Sclerosis Risk Using UK Biobank Data'. *Fertility and Sterility*, August 3, S0015-0282(24)01931-9. https://doi.org/10.1016/j.fertnstert.2024.07.999.

Nyári, Aliz, Zsófia Kokas, Szabolcs Szamosi, et al. 2024. 'The 7-Year Follow-up of the Hungarian BICAMS Validation Cohort Implies That Cognitive Performance May Improve in Multiple Sclerosis Patients'. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 45 (7): 3369–78. https://doi.org/10.1007/s10072-024-07347-5.

Nygaard, Gro O., Sigrid A. de Rodez Benavent, Hanne F. Harbo, et al. 2015. 'Eye and Hand Motor Interactions with the Symbol Digit Modalities Test in Early Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 4 (6): 585–89. https://doi.org/10.1016/j.msard.2015.08.003.

O'Brien, A, E Gaudinogoering, M Shawaryn, E Komaroff, N Moore, and J Deluca. 2007. 'Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to Functional, Emotional, and Neuropsychological Outcomes'. *Archives of Clinical Neuropsychology* 22 (8): 933–48. https://doi.org/10.1016/j.acn.2007.07.002.

O'Connell, K., N. Tubridy, M. Hutchinson, and C. McGuigan. 2017. 'Incidence of Multiple Sclerosis in the Republic of Ireland: A Prospective Population-Based Study'. *Multiple Sclerosis and Related Disorders* 13 (April): 75–80. https://doi.org/10.1016/j.msard.2017.02.010.

O'Connell, Redmond G., Paul M. Dockree, Mark A. Bellgrove, et al. 2009. 'Two Types of Action Error: Electrophysiological Evidence for Separable Inhibitory and Sustained Attention Neural Mechanisms Producing Error on Go/No-Go Tasks'. *Journal of Cognitive Neuroscience* 21 (1): 93–104. https://doi.org/10.1162/jocn.2009.21008.

Ogawa, Seiji, Tso-Ming Lee, Ray Stepnoski, Wei Chen, Xiao-Hong Zhu, and Kamil Ugurbil. 2000. 'An Approach to Probe Some Neural Systems Interaction by Functional MRI at Neural Time Scale down to Milliseconds'. *Proceedings of the National Academy of Sciences of the United States of America* 97 (20): 11026–31.

Oh, Seong-il, Aram Park, Hee-Jin Kim, et al. 2014. 'Spectrum of Cognitive Impairment in Korean ALS Patients without Known Genetic Mutations'. *PloS One* 9 (2): e87163. https://doi.org/10.1371/journal.pone.0087163.

Öijerstedt, Linn, Juliette Foucher, Anikó Lovik, et al. 2024. 'Repeated Cognitive Assessments Show Stable Function over Time in Patients with ALS'. *Journal of Neurology* 271 (8): 5267–74. https://doi.org/10.1007/s00415-024-12479-x.

Oksenberg, Jorge R., Sergio E. Baranzini, Stephen Sawcer, and Stephen L. Hauser. 2008. 'The Genetics of Multiple Sclerosis: SNPs to Pathways to Pathogenesis'. *Nature Reviews Genetics* 9 (7): 516–26. https://doi.org/10.1038/nrg2395.

Oliva Ramirez, Abril, Alexander Keenan, Olivia Kalau, Evelyn Worthington, Lucas Cohen, and Sumeet Singh. 2021. 'Prevalence and Burden of Multiple Sclerosis-Related Fatigue: A Systematic Literature Review'. *BMC Neurology* 21 (1): 468. https://doi.org/10.1186/s12883-021-02396-1.

Oliveira, Ana Inês, Isabel Rovisco Monteiro, Alexandre Roldão Alferes, et al. 2024. 'Cognitive Outcomes in Late-Onset versus Adult-Onset Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 90 (August): 105845. https://doi.org/10.1016/j.msard.2024.105845.

Oliveira, S.R., A.N.C. Simão, D.F. Alfieri, et al. 2017. 'Vitamin D Deficiency Is Associated with Disability and Disease Progression in Multiple Sclerosis Patients Independently of Oxidative and Nitrosative Stress'. *Journal of the Neurological Sciences* 381: 213–19. Scopus. https://doi.org/10.1016/j.jns.2017.07.046.

Olsson, Bob, Erik Portelius, Nicholas C. Cullen, et al. 2019. 'Association of Cerebrospinal Fluid Neurofilament Light Protein Levels With Cognition in Patients With Dementia, Motor Neuron Disease, and Movement Disorders'. *JAMA Neurology* 76 (3): 318–25. https://doi.org/10.1001/jamaneurol.2018.3746.

Olsson, Tomas, Lisa F. Barcellos, and Lars Alfredsson. 2017. 'Interactions between Genetic, Lifestyle and Environmental Risk Factors for Multiple Sclerosis'. *Nature Reviews. Neurology* 13 (1): 25–36. https://doi.org/10.1038/nrneurol.2016.187.

O'Meara, Etain. 2024. 'Determining the Impact of Medication on Cognition in Multiple Sclerosis: Insights from ERP Analysis'. Undergraduate thesis, University of Dublin, Trinity College Dublin.

Oostenveld, Robert, Pascal Fries, Eric Maris, and Jan Mathijs Schoffelen. 2011. 'FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data'. *Computational Intelligence and Neuroscience* 2011. https://doi.org/10.1155/2011/156869.

Oranje, Bob, Kristian Jensen, Malene Wienberg, and Birte Y. Glenthøj. 2008. 'Divergent Effects of Increased Serotonergic Activity on Psychophysiological Parameters of Human Attention'. *The International Journal of Neuropsychopharmacology* 11 (4): 453–63. https://doi.org/10.1017/S1461145707008176.

O'Reilly, Éilis J., Hao Wang, Marc G. Weisskopf, et al. 2013. 'Premorbid Body Mass Index and Risk of Amyotrophic Lateral Sclerosis'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 14 (3): 205–11. https://doi.org/10.3109/21678421.2012.735240.

Ortega-Hernandez, Oscar-Danilo, Eva M. Martínez-Cáceres, Silvia Presas-Rodríguez, and Cristina Ramo-Tello. 2023. 'Epstein-Barr Virus and Multiple Sclerosis: A Convoluted Interaction and the Opportunity to Unravel Predictive Biomarkers'. *International Journal of Molecular Sciences* 24 (8): 7407. https://doi.org/10.3390/ijms24087407.

Ortiz, Genaro Gabriel, Fermín Paul Pacheco-Moisés, Miguel Ángel Macías-Islas, et al. 2014. 'Role of the Blood-Brain Barrier in Multiple Sclerosis'. *Archives of Medical Research* 45 (8): 687–97. https://doi.org/10.1016/j.arcmed.2014.11.013.

Oset, Magdalena, Małgorzata Domowicz, Paula Wildner, et al. 2023. 'Predictive Value of Brain Atrophy, Serum Biomarkers and Information Processing Speed for Early

Disease Progression in Multiple Sclerosis'. *Frontiers in Neurology* 14 (July). https://doi.org/10.3389/fneur.2023.1223220.

Oudejans, Ellen, Antonio Luchicchi, Eva M.M. Strijbis, Jeroen J.G. Geurts, and Anne-Marie van Dam. 2021. 'Is MS Affecting the CNS Only?' *Neurology Neuroimmunology & Neuroinflammation* 8 (1): e914. https://doi.org/10.1212/NXI.0000000000000914.

Pantavou, Katerina G., and Pantelis G. Bagos. 2020. 'Season of Birth and Multiple Sclerosis: A Systematic Review and Multivariate Meta-Analysis'. *Journal of Neurology* 267 (10): 2815–22. https://doi.org/10.1007/s00415-019-09346-5.

Papadaniil, Chrysa D., Vasiliki E. Kosmidou, Anthoula Tsolaki, Magda Tsolaki, Ioannis (Yiannis) Kompatsiaris, and Leontios J. Hadjileontiadis. 2016. 'Cognitive MMN and P300 in Mild Cognitive Impairment and Alzheimer's Disease: A High Density EEG-3D Vector Field Tomography Approach'. *Brain Research* 1648 (October): 425–33. https://doi.org/10.1016/j.brainres.2016.07.043.

Parisi, Laura, Maria A. Rocca, Paola Valsasina, Letizia Panicari, Flavia Mattioli, and Massimo Filippi. 2014. 'Cognitive Rehabilitation Correlates with the Functional Connectivity of the Anterior Cingulate Cortex in Patients with Multiple Sclerosis'. *Brain Imaging and Behavior* 8 (3): 387–93. https://doi.org/10.1007/s11682-012-9160-9.

Pascual-Marqui, R.D., C.M. Michel, and D. Lehmann. 1995. 'Segmentation of Brain Electrical Activity into Microstates: Model Estimation and Validation'. *IEEE Transactions on Biomedical Engineering* 42 (7): 658–65. https://doi.org/10.1109/10.391164.

Patten, Scott B., Ruth Ann Marrie, and Mauro G. Carta. 2017. 'Depression in Multiple Sclerosis'. *International Review of Psychiatry (Abingdon, England)* 29 (5): 463–72. https://doi.org/10.1080/09540261.2017.1322555.

Pekkonen, E., V. Jousmäki, M. Könönen, K. Reinikainen, and J. Partanen. 1994. 'Auditory Sensory Memory Impairment in Alzheimer's Disease: An Event-Related Potential Study'. *Neuroreport* 5 (18): 2537–40. https://doi.org/10.1097/00001756-199412000-00033.

Pekkonen, Eero, Veikko Jousmäki, Kalevi Reinikainen, and Juhani Partanen. 1995. 'Automatic Auditory Discrimination Is Impaired in Parkinson's Disease'. *Electroencephalography and Clinical Neurophysiology* 95 (1): 47–52. https://doi.org/10.1016/0013-4694(94)00304-4.

Pender, Niall, Marta Pinto-Grau, and Orla Hardiman. 2020. 'Cognitive and Behavioural Impairment in Amyotrophic Lateral Sclerosis'. *Current Opinion in Neurology* 33 (5): 649–54. https://doi.org/10.1097/WCO.0000000000000862.

Perretti, A., P. Balbi, G. Orefice, et al. 2004. 'Post-Exercise Facilitation and Depression of Motor Evoked Potentials to Transcranial Magnetic Stimulation: A Study in Multiple Sclerosis'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 115 (9): 2128–33. https://doi.org/10.1016/j.clinph.2004.03.028.

Petracca, M., J. Sumowski, M. Fabian, A. Miller, F. Lublin, and M. Inglese. 2018. 'Looking into Cognitive Impairment in Primary-Progressive Multiple Sclerosis'. *European Journal of Neurology* 25 (1): 192–95. https://doi.org/10.1111/ene.13489.

Phukan, Julie, Marwa Elamin, Peter Bede, et al. 2012. 'The Syndrome of Cognitive Impairment in Amyotrophic Lateral Sclerosis: A Population-Based Study'. *Journal of Neurology, Neurosurgery, and Psychiatry* 83 (1): 102–8. https://doi.org/10.1136/jnnp-2011-300188.

Pinkhardt, E. H., R. Jürgens, W. Becker, et al. 2008. 'Signs of Impaired Selective Attention in Patients with Amyotrophic Lateral Sclerosis'. *Journal of Neurology* 255 (4): 532–38. https://doi.org/10.1007/s00415-008-0734-9.

Piras, M. R., I. Magnano, E. D. G. Canu, et al. 2003. 'Longitudinal Study of Cognitive Dysfunction in Multiple Sclerosis: Neuropsychological, Neuroradiological, and Neurophysiological Findings'. *Journal of Neurology, Neurosurgery, and Psychiatry* 74 (7): 878–85. https://doi.org/10.1136/jnnp.74.7.878.

Planche, V., M. Gibelin, D. Cregut, B. Pereira, and P. Clavelou. 2016. 'Cognitive Impairment in a Population-Based Study of Patients with Multiple Sclerosis: Differences between Late Relapsing-Remitting, Secondary Progressive and Primary Progressive Multiple Sclerosis'. *European Journal of Neurology* 23 (2): 282–89. https://doi.org/10.1111/ene.12715.

Pokryszko-Dragan, Anna, Mieszko Zagrajek, Krzysztof Slotwinski, Malgorzata Bilinska, Ewa Gruszka, and Ryszard Podemski. 2016. 'Event-Related Potentials and Cognitive Performance in Multiple Sclerosis Patients with Fatigue'. *Neurological Sciences* 37 (9): 1545–56. https://doi.org/10.1007/s10072-016-2622-x.

Polich, John. 2007. 'Updating P300: An Integrative Theory of P3a and P3b'. *Clinical Neurophysiology* 118 (10): 2128–48. https://doi.org/10.1016/j.clinph.2007.04.019.

Poulsen, Andreas Trier, Andreas Pedroni, Nicolas Langer, and Lars Kai Hansen. 2018. 'Microstate EEGlab Toolbox: An Introductory Guide'. Preprint, bioRxiv, March 27. https://doi.org/10.1101/289850.

Quintana, E., C. Coll, J. Salavedra-Pont, et al. 2018. 'Cognitive Impairment in Early Stages of Multiple Sclerosis Is Associated with High Cerebrospinal Fluid Levels of Chitinase 3-like 1 and Neurofilament Light Chain'. *European Journal of Neurology* 25 (9): 1189–91. https://doi.org/10.1111/ene.13687.

Rademacher, Tom-D., Sven G. Meuth, Heinz Wiendl, Andreas Johnen, and Nils C. Landmeyer. 2023. 'Molecular Biomarkers and Cognitive Impairment in Multiple Sclerosis: State of the Field, Limitations, and Future Direction – A Systematic Review and Meta-Analysis'. *Neuroscience & Biobehavioral Reviews* 146 (March): 105035. https://doi.org/10.1016/j.neubiorev.2023.105035.

Raggi, Alberto, Monica Consonni, Sandro Iannaccone, et al. 2008. 'Auditory Event-Related Potentials in Non-Demented Patients with Sporadic Amyotrophic Lateral Sclerosis'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 119 (2): 342–50. https://doi.org/10.1016/j.clinph.2007.10.010.

Rao, Stephen M. 1990. *Neurobehavioral Aspects of Multiple Sclerosis*. Oxford University Press.

Rao, Stephen M., G. J. Leo, L. Ellington, T. Nauertz, L. Bernardin, and F. Unverzagt. 1991. 'Cognitive Dysfunction in Multiple Sclerosis. II. Impact on Employment and Social Functioning'. *Neurology* 41 (5): 692–96. https://doi.org/10.1212/wnl.41.5.692.

Redero, Daniel, Esther Lázaro, Natalia Vázquez, and Cristina Soria. 2023. 'Neuropsychological Rehabilitation in Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review'. *Applied Neuropsychology. Adult*, August 28, 1–9. https://doi.org/10.1080/23279095.2023.2248642.

Renner, Alina, Sharon Jean Baetge, Melanie Filser, and Iris-Katharina Penner. 2020. 'Working Ability in Individuals with Different Disease Courses of Multiple Sclerosis: Factors beyond Physical Impairment'. *Multiple Sclerosis and Related Disorders* 46 (November): 102559. https://doi.org/10.1016/j.msard.2020.102559.

Reuter, Françoise, Wafaa Zaaraoui, Lydie Crespy, et al. 2011. 'Cognitive Impairment at the Onset of Multiple Sclerosis: Relationship to Lesion Location'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 17 (6): 755–58. https://doi.org/10.1177/1352458511398265.

Robertson, Ian H, Tom Manly, Jackie Andrade, Bart T Baddeley, and Jenny Yiend. 1997. '`Oops!': Performance Correlates of Everyday Attentional Failures in Traumatic Brain Injured and Normal Subjects'. *Neuropsychologia* 35 (6): 747–58. https://doi.org/10.1016/S0028-3932(97)00015-8.

Rocca, M. A., E. De Meo, and M. Filippi. 2016. 'Functional MRI in Investigating Cognitive Impairment in Multiple Sclerosis'. *Acta Neurologica Scandinavica* 134 (S200): 39–46. https://doi.org/10.1111/ane.12654.

Rocca, Maria A., Paolo Preziosa, Frederik Barkhof, et al. 2024. 'Current and Future Role of MRI in the Diagnosis and Prognosis of Multiple Sclerosis'. *The Lancet Regional Health – Europe* 44 (September). https://doi.org/10.1016/j.lanepe.2024.100978.

Roche, Richard A. P., Hugh Garavan, John J. Foxe, and Shane M. O'Mara. 2005. 'Individual Differences Discriminate Event-Related Potentials but Not Performance during Response Inhibition'. *Experimental Brain Research* 160 (1): 60–70. https://doi.org/10.1007/s00221-004-1985-z.

Rosca, Elena Cecilia, and Mihaela Simu. 2020. 'Montreal Cognitive Assessment for Evaluating Cognitive Impairment in Multiple Sclerosis: A Systematic Review'. *Acta Neurologica Belgica* 120 (6): 1307–21. https://doi.org/10.1007/s13760-020-01509-w.

Rosti-Otajärvi, Eija M., and Päivi I. Hämäläinen. 2014. 'Neuropsychological Rehabilitation for Multiple Sclerosis'. *The Cochrane Database of Systematic Reviews* 2014 (2): CD009131. https://doi.org/10.1002/14651858.CD009131.pub3.

Rovaris, Marco, Christian Confavreux, Roberto Furlan, Ludwig Kappos, Giancarlo Comi, and Massimo Filippi. 2006. 'Secondary Progressive Multiple Sclerosis: Current Knowledge and Future Challenges'. *The Lancet Neurology* 5 (4): 343–54. https://doi.org/10.1016/S1474-4422(06)70410-0.

Rupert, Deborah D., and Stephen D. Shea. 2022. 'Parvalbumin-Positive Interneurons Regulate Cortical Sensory Plasticity in Adulthood and Development Through Shared Mechanisms'. *Frontiers in Neural Circuits* 16 (May). https://doi.org/10.3389/fncir.2022.886629.

Russo, Margherita, Domenica Crupi, Antonino Naro, et al. 2015. 'Fatigue in Patients with Multiple Sclerosis: From Movement Preparation to Motor Execution'. *Journal of the Neurological Sciences* 351 (1–2): 52–57. https://doi.org/10.1016/j.jns.2015.02.031.

Sacco, Rosaria, Simona Bonavita, Fabrizio Esposito, Gioacchino Tedeschi, and Antonio Gallo. 2013. 'The Contribution of Resting State Networks to the Study of Cortical Reorganization in MS'. *Multiple Sclerosis International* 2013: 857807. https://doi.org/10.1155/2013/857807.

Sailer, M., H. J. Heinze, I. Tendolkar, et al. 2001. 'Influence of Cerebral Lesion Volume and Lesion Distribution on Event-Related Brain Potentials in Multiple Sclerosis'. *Journal of Neurology* 248 (12): 1049–55. https://doi.org/10.1007/s004150170024.

Salamone, Paula C., Sol Esteves, Vladimiro J. Sinay, et al. 2018. 'Altered Neural Signatures of Interoception in Multiple Sclerosis'. *Human Brain Mapping* 39 (12): 4743–54. https://doi.org/10.1002/hbm.24319.

Salarian, Arash. 2021. 'Intraclass Correlation Coefficient (ICC) - File Exchange - MATLAB Central'. https://uk.mathworks.com/matlabcentral/fileexchange/22099-intraclass-correlation-coefficient-icc.

Santiago, O, J Guardia, V Casado, O Carmona, and T Arbizu. 2007. 'Specificity of Frontal Dysfunctions in Relapsing–Remitting Multiple Sclerosis'. *Archives of Clinical Neuropsychology* 22 (5): 623–29. https://doi.org/10.1016/j.acn.2007.04.003.

Santos, Marco Aurélio Rocha, Mário Sérgio Lei Munhoz, Marco Aurélio L. Peixoto, Vitor Geraldi Haase, Jussara L. Rodrigues, and Luciana Macedo Resende. 2006. 'Mismatch Negativity Contribution in Multiple Sclerosis Patients'. *Brazilian Journal of Otorhinolaryngology* 72 (6): 800–807. https://doi.org/10.1016/S1808-8694(15)31047-8.

Sarhan, Abdallah A., Khaled A. El-Sharkawy, Ahmed M. Mahmoudy, and Noha A. Hashim. 2022. 'Burden of Multiple Sclerosis: Impact on the Patient, Family and Society'. *Multiple Sclerosis and Related Disorders* 63 (July): 103864. https://doi.org/10.1016/j.msard.2022.103864.

Scherg, Michael, Jiri Vajsar, and Terence W. Picton. 1989. 'A Source Analysis of the Late Human Auditory Evoked Potentials'. *Journal of Cognitive Neuroscience* 1 (4): 336–55. https://doi.org/10.1162/jocn.1989.1.4.336.

Schlindwein, Marco Antônio Machado, Marcelo Henrique de Moura Campos, Leticia Caroline Breis, et al. 2024. 'Impacts of Environmental Tobacco Smoke on the Onset and Progression of Multiple Sclerosis: A Systematic Review'. *Arquivos de Neuro-Psiquiatria* 82 (3): 1–10. https://doi.org/10.1055/s-0044-1779271.

Schloegl, Alois. 2017. *Biosig - A Free and Open Source Software Library for Biomedical Signal Processing*. Version 3.3.0. The BioSig Project, released.

Schoonheim, Menno M., Jeroen J. G. Geurts, Doriana Landi, et al. 2013. 'Functional Connectivity Changes in Multiple Sclerosis Patients: A Graph Analytical Study of MEG Resting State Data'. *Human Brain Mapping* 34 (1): 52–61. https://doi.org/10.1002/hbm.21424.

Schwarz, Karin, and Frank Schmitz. 2023. 'Synapse Dysfunctions in Multiple Sclerosis'. *International Journal of Molecular Sciences* 24 (2): 1639. https://doi.org/10.3390/ijms24021639.

Seer, Caroline, Max Joop, Florian Lange, et al. 2017. 'Attenuated Error-Related Potentials in Amyotrophic Lateral Sclerosis with Executive Dysfunctions'. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 128 (8): 1496–503. https://doi.org/10.1016/j.clinph.2017.05.007.

Selmaj, Krzysztof, Bruce A. C. Cree, Michael Barnett, Alan Thompson, and Hans-Peter Hartung. 2024. 'Multiple Sclerosis: Time for Early Treatment with High-Efficacy Drugs'. *Journal of Neurology* 271 (1): 105–15. https://doi.org/10.1007/s00415-023-11969-8.

Shefner, Jeremy M., Ammar Al-Chalabi, Mark R. Baker, et al. 2020. 'A Proposal for New Diagnostic Criteria for ALS'. *Clinical Neurophysiology* 131 (8): 1975–78. https://doi.org/10.1016/j.clinph.2020.04.005.

Shefner, Jeremy M., G. A. Mackin, and D. M. Dawson. 1992. 'Lower Motor Neuron Dysfunction in Patients with Multiple Sclerosis'. *Muscle & Nerve* 15 (11): 1265–70. https://doi.org/10.1002/mus.880151108.

Shirani, Sepehr, and Maryam Mohebbi. 2022. 'Brain Functional Connectivity Analysis in Patients with Relapsing-Remitting Multiple Sclerosis: A Graph Theory Approach of EEG Resting State'. *Frontiers in Neuroscience* 16 (September): 801774. https://doi.org/10.3389/fnins.2022.801774.

Silva, Renata, Pedro Coelho, Mafalda Seabra, et al. 2022. 'Cognitive Impairment and Markers of Optical Neurodegeneration in Early Multiple Sclerosis'. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 43 (7): 4381–86. https://doi.org/10.1007/s10072-022-05945-9.

Simani, Leila, Mahrooz Roozbeh, Maziyar Shojaei, Mohammad Rostami, Mehrdad Roozbeh, and Mohammad Ali Sahraian. 2023. 'Cognitive Deficits in Multiple Sclerosis: Auditory and Visual Attention and Inhibitory Control'. *Applied Neuropsychology: Adult* 0 (0): 1–8. https://doi.org/10.1080/23279095.2023.2192408.

Simon, Natalie, and Laura H. Goldstein. 2019. 'Screening for Cognitive and Behavioral Change in Amyotrophic Lateral Sclerosis/Motor Neuron Disease: A Systematic Review of Validated Screening Methods'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 20 (1–2): 1–11. https://doi.org/10.1080/21678421.2018.1530264.

Simpson, Steve, Wendy Wang, Peter Otahal, Leigh Blizzard, Ingrid A. F. van der Mei, and Bruce V. Taylor. 2019. 'Latitude Continues to Be Significantly Associated with the Prevalence of Multiple Sclerosis: An Updated Meta-Analysis'. *Journal of Neurology, Neurosurgery, and Psychiatry* 90 (11): 1193–200. https://doi.org/10.1136/jnnp-2018-320189.

Šoda, Joško, Sanda Pavelin, Igor Vujović, and Maja Rogić Vidaković. 2023. 'Assessment of Motor Evoked Potentials in Multiple Sclerosis'. *Sensors* 23 (1): 497. https://doi.org/10.3390/s23010497.

Solís-Vivanco, Rodolfo, Josefina Ricardo-Garcell, Mario Rodríguez-Camacho, et al. 2011. 'Involuntary Attention Impairment in Early Parkinson's Disease: An Event-Related Potential Study'. *Neuroscience Letters* 495 (2): 144–49. https://doi.org/10.1016/j.neulet.2011.03.058.

Spearman, C. 1904. 'The Proof and Measurement of Association between Two Things'. *The American Journal of Psychology* 15 (1): 72–101. https://doi.org/10.2307/1412159.

Spiezia, Antonio Luca, Fabrizia Falco, Andrea Manganelli, et al. 2023. 'Low Serum 25-hydroxy-Vitamin D Levels Are Associated with Cognitive Impairment in Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 79 (November): 105044. https://doi.org/10.1016/j.msard.2023.105044.

Spinelli, Edoardo G., Alma Ghirelli, Silvia Basaia, et al. 2024. 'Structural and Functional Brain Network Connectivity at Different King's Stages in Patients With Amyotrophic Lateral Sclerosis'. *Neurology* 102 (2): e207946. https://doi.org/10.1212/WNL.0000000000207946.

Sporns, Olaf, Giulio Tononi, and Rolf Kötter. 2005. 'The Human Connectome: A Structural Description of the Human Brain'. *PLoS Computational Biology* 1 (4): e42. https://doi.org/10.1371/journal.pcbi.0010042.

Srpova, Barbora, Lukas Sobisek, Klara Novotna, et al. 2022. 'The Clinical and Paraclinical Correlates of Employment Status in Multiple Sclerosis'. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 43 (3): 1911–20. https://doi.org/10.1007/s10072-021-05553-z.

Stellmann, Jan-Patrick, Hanife Cetin, Kim Lea Young, et al. 2017. 'Pattern of Gray Matter Volumes Related to Retinal Thickness and Its Association with Cognitive Function

in Relapsing–Remitting MS'. *Brain and Behavior* 7 (2): e00614. https://doi.org/10.1002/brb3.614.

Strimbu, Kyle, and Jorge A. Tavel. 2010. 'What Are Biomarkers?' *Current Opinion in HIV and AIDS* 5 (6): 463–66. https://doi.org/10.1097/COH.0b013e32833ed177.

Strong, Michael J., Sharon Abrahams, Laura H. Goldstein, et al. 2017. 'Amyotrophic Lateral Sclerosis - Frontotemporal Spectrum Disorder (ALS-FTSD): Revised Diagnostic Criteria'. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration* 18 (3–4): 153–74. https://doi.org/10.1080/21678421.2016.1267768.

Sundgren, Mathias, Nikulin VV, Maurex L, Wahlin Å, Piehl F, and Brismar T. 2015. 'P300 Amplitude and Response Speed Relate to Preserved Cognitive Function in Relapsing-Remitting Multiple Sclerosis'. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology* 126 (4): 689–97. https://doi.org/10.1016/J.CLINPH.2014.07.024.

Sundgren, Mathias, Åke Wahlin, Liselotte Maurex, and Tom Brismar. 2015. 'Event Related Potential and Response Time Give Evidence for a Physiological Reserve in Cognitive Functioning in Relapsing-Remitting Multiple Sclerosis'. *Journal of the Neurological Sciences* 356 (1–2): 107–12. https://doi.org/10.1016/J.JNS.2015.06.025.

Tarailis, Povilas, Thomas Koenig, Christoph M. Michel, and Inga Griškova-Bulanova. 2024. 'The Functional Aspects of Resting EEG Microstates: A Systematic Review'. *Brain Topography* 37 (2): 181–217. https://doi.org/10.1007/s10548-023-00958-9.

Taylor, Lauren A, Jacqueline R Mhizha-Murira, Laura Smith, et al. 2021. 'Memory Rehabilitation for People with Multiple Sclerosis'. *The Cochrane Database of Systematic Reviews* 2021 (10): CD008754. https://doi.org/10.1002/14651858.CD008754.pub4.

Tedeholm, H., F. Piehl, J. Lycke, et al. 2022. 'Effectiveness of First Generation Disease-Modifying Therapy to Prevent Conversion to Secondary Progressive Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 68 (December): 104220. https://doi.org/10.1016/j.msard.2022.104220.

Tempest, Adelaide, Sajesh K. Veettil, Mari Kannan Maharajan, Jacob Craig Earl, Surachat Ngorsuraches, and Nathorn Chaiyakunapruk. 2022. 'Genetic Biomarkers in Multiple Sclerosis: An Umbrella Review of Meta-Analyses of Observational Studies'. *Multiple Sclerosis and Related Disorders* 63 (July): 103834. https://doi.org/10.1016/j.msard.2022.103834.

Tena-Cucala, Raquel, Pablo Naval-Baudin, Antonio Martínez-Yélamos, et al. 2025. 'The 2024 McDonald Criteria Show Comparable Sensitivity to Previous Criteria for Late-Onset Multiple Sclerosis'. *Multiple Sclerosis and Related Disorders* 103 (November). https://doi.org/10.1016/j.msard.2025.106658.

Ternes, Anne-Marie, Meaghan Clough, Paige Foletta, Owen White, and Joanne Fielding. 2019. 'Characterization of Inhibitory Failure in Multiple Sclerosis: Evidence of Impaired Conflict Resolution'. *Journal of Clinical and Experimental Neuropsychology* 41 (3): 320–29. https://doi.org/10.1080/13803395.2018.1552756.

Tervaniemi, Mari. 2022. 'Mismatch Negativity–Stimulation Paradigms in Past and in Future'. *Frontiers in Neuroscience* 16 (November). https://doi.org/10.3389/fnins.2022.1025763.

Tervaniemi, Mari, A. Lehtokoski, J. Sinkkonen, J. Virtanen, R. J. Ilmoniemi, and R. Näätänen. 1999. 'Test–Retest Reliability of Mismatch Negativity for Duration,

Frequency and Intensity Changes'. *Clinical Neurophysiology* 110 (8): 1388–93. https://doi.org/10.1016/S1388-2457(99)00108-X.

Tewarie, Prejaas, A. Hillebrand, M. M. Schoonheim, et al. 2014. 'Functional Brain Network Analysis Using Minimum Spanning Trees in Multiple Sclerosis: An MEG Source-Space Study'. *NeuroImage* 88 (March): 308–18. https://doi.org/10.1016/j.neuroimage.2013.10.022.

Tewarie, Prejaas, Menno M. Schoonheim, Daphne I. Schouten, et al. 2015. 'Functional Brain Networks: Linking Thalamic Atrophy to Clinical Disability in Multiple Sclerosis, a Multimodal fMRI and MEG Study'. *Human Brain Mapping* 36 (2): 603–18. https://doi.org/10.1002/hbm.22650.

The MathWorks Inc. 2020. *MATLAB Version 9.8.0.1396136 (R2020a)*. MATLAB. Released.

Thompson, Alan J., Brenda L. Banwell, Frederik Barkhof, et al. 2018. 'Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria'. *The Lancet. Neurology* 17 (2): 162–73. https://doi.org/10.1016/S1474-4422(17)30470-2.

Tiu, Vlad Eugen, Bogdan Ovidiu Popescu, Iulian Ion Enache, Cristina Tiu, Elena Terecoasa, and Cristina Aura Panea. 2022. 'Serum and CSF Biomarkers Predict Active Early Cognitive Decline Rather Than Established Cognitive Impairment at the Moment of RRMS Diagnosis'. *Diagnostics* 12 (11): 2571. https://doi.org/10.3390/diagnostics12112571.

Toledo, J., J. Sepulcre, A. Salinas-Alaman, et al. 2008. 'Retinal Nerve Fiber Layer Atrophy Is Associated with Physical and Cognitive Disability in Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 14 (7): 906–12. https://doi.org/10.1177/1352458508090221.

Tombaugh, Tom N. 2006. 'A Comprehensive Review of the Paced Auditory Serial Addition Test (PASAT)'. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists* 21 (1): 53–76. https://doi.org/10.1016/j.acn.2005.07.006.

Tortorella, C., V. Direnzo, P. Taurisano, et al. 2015. 'Cerebrospinal Fluid Neurofilament Tracks fMRI Correlates of Attention at the First Attack of Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 21 (4): 396–401. https://doi.org/10.1177/1352458514546789.

Traboulsee, Anthony L., Cecily Q. Bernales, Jay P. Ross, Joshua D. Lee, A. Dessa Sadovnick, and Carles Vilariño-Güell. 2014. 'Genetic Variants in IL2RA and IL7R Affect Multiple Sclerosis Disease Risk and Progression'. *Neurogenetics* 15 (3): 165–69. https://doi.org/10.1007/s10048-014-0403-3.

Turtola, Zachary P., and Thomas J. Covey. 2021. 'Working Memory Training Impacts Neural Activity during Untrained Cognitive Tasks in People with Multiple Sclerosis'. *Experimental Neurology* 335 (January): 113487. https://doi.org/10.1016/j.expneurol.2020.113487.

Vacchi, Laura, Maria A. Rocca, Alessandro Meani, et al. 2017. 'Working Memory Network Dysfunction in Relapse-Onset Multiple Sclerosis Phenotypes: A Clinical-Imaging Evaluation'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 23 (4): 577–87. https://doi.org/10.1177/1352458516656809.

Vandebergh, Marijne, Nicolas Degryse, Bénédicte Dubois, and An Goris. 2022. 'Environmental Risk Factors in Multiple Sclerosis: Bridging Mendelian Randomization and Observational Studies'. *Journal of Neurology* 269 (8): 4565–74. https://doi.org/10.1007/s00415-022-11072-4.

Vázquez-Marrufo, M, González-Rosa JJ, Vaquero E, et al. 2008. 'Abnormal ERPs and High Frequency Bands Power in Multiple Sclerosis'. *The International Journal of Neuroscience* 118 (1): 27–38. https://doi.org/10.1080/00207450601041906.

Vecchio, Fabrizio, Francesca Miraglia, Camillo Porcaro, et al. 2017. 'Electroencephalography-Derived Sensory and Motor Network Topology in Multiple Sclerosis Fatigue'. *Neurorehabilitation and Neural Repair* 31 (1): 56–64. https://doi.org/10.1177/1545968316656055.

Verde, Federico, Sara Licaj, Davide Soranna, Nicola Ticozzi, Vincenzo Silani, and Antonella Zambon. 2024. 'Cerebrospinal Fluid and Blood Neurofilament Light Chain Levels in Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration: A Meta-Analysis'. *European Journal of Neurology* 31 (9): e16371. https://doi.org/10.1111/ene.16371.

Verde, Federico, Ilaria Milone, Eleonora Colombo, et al. 2023. 'Phenotypic Correlates of Serum Neurofilament Light Chain Levels in Amyotrophic Lateral Sclerosis'. *Frontiers in Aging Neuroscience* 15: 1132808. https://doi.org/10.3389/fnagi.2023.1132808.

Verde, Federico, Ilaria Milone, Alessio Maranzano, et al. 2023. 'Serum Levels of Glial Fibrillary Acidic Protein in Patients with Amyotrophic Lateral Sclerosis'. *Annals of Clinical and Translational Neurology* 10 (1): 118–29. https://doi.org/10.1002/acn3.51708.

Virgilio, Eleonora, Domizia Vecchio, Ilaria Crespi, et al. 2021. 'Serum Vitamin D as a Marker of Impaired Information Processing Speed and Early Disability in Multiple Sclerosis Patients'. *Brain Sciences* 11 (11): 1521. https://doi.org/10.3390/brainsci11111521.

Virgilio, Eleonora, Domizia Vecchio, Ilaria Crespi, et al. 2022. 'Cerebrospinal Fluid Biomarkers and Cognitive Functions at Multiple Sclerosis Diagnosis'. *Journal of Neurology* 269 (6): 3249–57. https://doi.org/10.1007/s00415-021-10945-4.

Vogt, Johannes, Friedemann Paul, Orhan Aktas, et al. 2009. 'Lower Motor Neuron Loss in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis'. *Annals of Neurology* 66 (3): 310–22. https://doi.org/10.1002/ana.21719.

Vucic, Steve, Therese Burke, Kerry Lenton, et al. 2012. 'Cortical Dysfunction Underlies Disability in Multiple Sclerosis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 18 (4): 425–32. https://doi.org/10.1177/1352458511424308.

Vucic, Steve, Toby A. Ferguson, Catherine Cummings, et al. 2021. 'Gold Coast Diagnostic Criteria: Implications for ALS Diagnosis and Clinical Trial Enrollment'. *Muscle & Nerve* 64 (5): 532–37. https://doi.org/10.1002/mus.27392.

Vucic, Steve, Nathan Pavey, Mouna Haidar, Bradley J. Turner, and Matthew C. Kiernan. 2021. 'Cortical Hyperexcitability: Diagnostic and Pathogenic Biomarker of ALS'. *Neuroscience Letters* 759 (August): 136039. https://doi.org/10.1016/j.neulet.2021.136039.

Walton, Clare, Rachel King, Lindsay Rechtman, et al. 2020. 'Rising Prevalence of Multiple Sclerosis Worldwide: Insights from the Atlas of MS, Third Edition'. *Multiple Sclerosis Journal* 26 (14): 1816–21. https://doi.org/10.1177/1352458520970841.

Wang, Jingyi, Tingting Chen, Xiong Jiao, Kai Liu, Shanbao Tong, and Junfeng Sun. 2021. 'Test-Retest Reliability of Duration-Related and Frequency-Related Mismatch Negativity'. *Neurophysiologie Clinique* 51 (6): 541–48. https://doi.org/10.1016/j.neucli.2021.10.004.

Wang, Ming-Dong, Julian Little, James Gomes, Neil R. Cashman, and Daniel Krewski. 2017. 'Identification of Risk Factors Associated with Onset and Progression of

Amyotrophic Lateral Sclerosis Using Systematic Review and Meta-Analysis'. *Neurotoxicology* 61 (July): 101–30. https://doi.org/10.1016/j.neuro.2016.06.015.

Wannarong, Thapat, and Patompong Ungprasert. 2020. 'Diabetes Mellitus Is Associated with a Lower Risk of Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis'. *Clinical Neurology and Neurosurgery* 199 (December): 106248. https://doi.org/10.1016/j.clineuro.2020.106248.

Wegen, J. van, E. E. A. van Egmond, R. H. B. Benedict, et al. 2022. 'Subjective Cognitive Impairment Is Related to Work Status in People with Multiple Sclerosis'. *IBRO Neuroscience Reports* 13 (December): 513–22. https://doi.org/10.1016/j.ibneur.2022.10.016.

Weisbrot, Deborah, Leigh Charvet, Dana Serafin, et al. 2014. 'Psychiatric Diagnoses and Cognitive Impairment in Pediatric Multiple Sclerosis'. *Multiple Sclerosis Journal* 20 (5): 588–93. https://doi.org/10.1177/1352458513504249.

Westervelt, Holly James. 2015. 'Dementia in Multiple Sclerosis: Why Is It Rarely Discussed?' *Archives of Clinical Neuropsychology* 30 (2): 174–77. https://doi.org/10.1093/arclin/acu095.

Whelan, Robert, Róisín Lonergan, Hanni Kiiski, Hugh Nolan, Katie Kinsella, Jessica Bramham, et al. 2010. 'A High-Density ERP Study Reveals Latency, Amplitude, and Topographical Differences in Multiple Sclerosis Patients versus Controls'. *Clinical Neurophysiology* 121 (9): 1420–26. https://doi.org/10.1016/J.CLINPH.2010.03.019.

Whelan, Robert, Róisín Lonergan, Hanni Kiiski, Hugh Nolan, Katie Kinsella, Michael Hutchinson, et al. 2010. 'Impaired Information Processing Speed and Attention Allocation in Multiple Sclerosis Patients versus Controls: A High-Density EEG Study'. *Journal of the Neurological Sciences* 293 (1–2): 45–50. https://doi.org/10.1016/j.jns.2010.03.010.

Wienberg, M., B. Y. Glenthoj, K. S. Jensen, and B. Oranje. 2010. 'A Single High Dose of Escitalopram Increases Mismatch Negativity without Affecting Processing Negativity or P300 Amplitude in Healthy Volunteers'. *Journal of Psychopharmacology (Oxford, England)* 24 (8): 1183–92. https://doi.org/10.1177/0269881109102606.

Wilkinson, Mark D., Michel Dumontier, IJsbrand Jan Aalbersberg, et al. 2016. 'The FAIR Guiding Principles for Scientific Data Management and Stewardship'. *Scientific Data* 3 (1): 160018. https://doi.org/10.1038/sdata.2016.18.

Williams, Lynne J, and Herve Abdi. 2010. 'Fisher's Least Significant Difference (LSD) Test'. *Encyclopedia of Research Design*, January 1.

Wilson, Barbara A. 2008. 'Neuropsychological Rehabilitation'. *Annual Review of Clinical Psychology* 4 (1): 141–62. https://doi.org/10.1146/annurev.clinpsy.4.022007.141212.

Wolfson, Christina, Danielle E. Gauvin, Foluso Ishola, and Maryam Oskoui. 2023. 'Global Prevalence and Incidence of Amyotrophic Lateral Sclerosis'. *Neurology* 101 (6): e613–23. https://doi.org/10.1212/WNL.0000000000207474.

Wood, B, IAF van der Mei, A-L Ponsonby, et al. 2013. 'Prevalence and Concurrence of Anxiety, Depression and Fatigue over Time in Multiple Sclerosis'. *Multiple Sclerosis Journal* 19 (2): 217–24. https://doi.org/10.1177/1352458512450351.

Wu, Jing, Tomas Olsson, Jan Hillert, Lars Alfredsson, and Anna Karin Hedström. 2023. 'Influence of Oral Tobacco versus Smoking on Multiple Sclerosis Disease Activity and Progression'. *Journal of Neurology, Neurosurgery, and Psychiatry* 94 (8): 589–96. https://doi.org/10.1136/jnnp-2022-330848.

Wu, Wendy, Heather Francis, Abbie Lucien, Tyler-Ann Wheeler, and Milena Gandy. 2024. 'The Prevalence of Cognitive Impairment in Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis'. *Neuropsychology Review*, ahead of print, April 8. https://doi.org/10.1007/s11065-024-09640-8.

Wunderlich, Julia L., and Barbara K. Cone-Wesson. 2001. 'Effects of Stimulus Frequency and Complexity on the Mismatch Negativity and Other Components of the Cortical Auditory-Evoked Potential'. *The Journal of the Acoustical Society of America* 109 (4): 1526–37. https://doi.org/10.1121/1.1349184.

Xu, Lu, Tanxin Liu, Lili Liu, et al. 2020. 'Global Variation in Prevalence and Incidence of Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis'. *Journal of Neurology* 267 (4): 944–53. https://doi.org/10.1007/s00415-019-09652-y.

Yang, Bo, Wei Xiao, Xufeng Liu, Shengjun Wu, and Danmin Miao. 2013. 'Mental Fatigue Impairs Pre-Attentive Processing: A MMN Study'. *Neuroscience Letters* 532 (January): 12–16. https://doi.org/10.1016/j.neulet.2012.08.080.

Yang, Runze, and Jeff F Dunn. 2019. 'Multiple Sclerosis Disease Progression: Contributions from a Hypoxia–Inflammation Cycle'. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 25 (13): 1715–18. https://doi.org/10.1177/1352458518791683.

Yap, Siew Mei, Mark S. Etzelmueller, Clodagh O'Keeffe, et al. 2021. 'Postural Stability Is a Valid and Meaningful Disability Metric in Progressive MS with Potential for Use in Neuroprotective Therapy Trials'. *Multiple Sclerosis and Related Disorders* 52 (July): 102946. https://doi.org/10.1016/j.msard.2021.102946.

Yeshokumar, Anusha K., Sona Narula, and Brenda Banwell. 2017. 'Pediatric Multiple Sclerosis'. *Current Opinion in Neurology* 30 (3): 216–21. https://doi.org/10.1097/WCO.0000000000000452.

Zerouali, Younes, Boutheina Jemel, and Roger Godbout. 2010. 'The Effects of Early and Late Night Partial Sleep Deprivation on Automatic and Selective Attention: An ERP Study'. *Brain Research* 1308 (January): 87–99. https://doi.org/10.1016/j.brainres.2009.09.090.

Zhang, Guoqiang, Meng E, and Xin Zhou. 2023. 'Environmental and Occupational Solvents Exposure and Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis'. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 44 (8): 2803–9. https://doi.org/10.1007/s10072-023-06718-8.

Zhang, Jiongliang, Minmin Wu, Jinting Li, Wenjing Song, Xiaoguang Lin, and Luwen Zhu. 2024. 'Effects of Virtual Reality-Based Rehabilitation on Cognitive Function and Mood in Multiple Sclerosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials'. *Multiple Sclerosis and Related Disorders* 87 (July): 105643. https://doi.org/10.1016/j.msard.2024.105643.

Zhu, Qiaochu, Jing Zhou, Yijie Zhang, et al. 2023. 'Risk Factors Associated with Amyotrophic Lateral Sclerosis Based on the Observational Study: A Systematic Review and Meta-Analysis'. *Frontiers in Neuroscience* 17: 1196722. https://doi.org/10.3389/fnins.2023.1196722.

Ziccardi, Stefano, Agnese Tamanti, Claudia Ruggieri, et al. 2024. 'CSF Parvalbumin Levels at Multiple Sclerosis Diagnosis Predict Future Worse Cognition, Physical Disability, Fatigue, and Gray Matter Damage'. *Neurology(R) Neuroimmunology & Neuroinflammation* 11 (6): e200301. https://doi.org/10.1212/NXI.0000000000200301.

Zigmond, A. S., and R. P. Snaith. 1983. 'The Hospital Anxiety and Depression Scale'. *Acta Psychiatrica Scandinavica* 67 (6): 361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

Zipser, Carl M., Isabella Premoli, Paolo Belardinelli, et al. 2018. 'Cortical Excitability and Interhemispheric Connectivity in Early Relapsing-Remitting Multiple Sclerosis Studied With TMS-EEG'. *Frontiers in Neuroscience* 12: 393. https://doi.org/10.3389/fnins.2018.00393.

Zivadinov, R., J. Sepcic, D. Nasuelli, et al. 2001. 'A Longitudinal Study of Brain Atrophy and Cognitive Disturbances in the Early Phase of Relapsing-Remitting Multiple Sclerosis'. *Journal of Neurology, Neurosurgery, and Psychiatry* 70 (6): 773–80. https://doi.org/10.1136/jnnp.70.6.773.

Zordan, Lara, Michela Sarlo, and Franca Stablum. 2008. 'ERP Components Activated by the "GO!" And "WITHHOLD!" Conflict in the Random Sustained Attention to Response Task'. *Brain and Cognition* 66 (1): 57–64. https://doi.org/10.1016/j.bandc.2007.05.005.

Zürrer, Wolfgang Emanuel, Amelia Elaine Cannon, Dariya Ilchenko, et al. 2024. 'Misdiagnosis and Underdiagnosis of Multiple Sclerosis: A Systematic Review and Meta-Analysis'. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, September 8, 13524585241274527. https://doi.org/10.1177/13524585241274527.

Appendix A: Inclusion and Exclusion

The inclusion and exclusion criteria for participants with MS and controls are shown below. The criteria for participants with ALS were the same as the criteria for controls, with the addition of a diagnosis of ALS. Participants with ALS and MS were excluded, but no potential participants had both ALS and MS.

Inclusion/Exclusion Criteria- MS

Inclusion

- Diagnosed multiple sclerosis:
  - Stable Relapsing Remitting MS (RRMS): use of a disease modifying drug (DMD) for at least 3 months or DMD free for at least 3 months
  - Secondary Progressive MS: DMD free for at least 3 months
  - Primary Progressive MS
- Neuroimaging (MRI) within the past 6 months
- Capable of participation and of providing informed consent
- ≥ 18 years old
- PHASE 2 ONLY: patients prescribed cladribine (RRMS)

Exclusion

- Relapse within past 3 months
- Active psychiatric disease
- Use of medications that will interfere with EEG recordings or cognitive functioning (e.g. antidepressants, antipsychotics, anxiolytics, anticonvulsants) or illicit drugs
- ADDITIONAL EXCLUSIONS FOR EEG PORTION OF STUDY:
  - Medical condition (other than MS) that affects the nervous or muscular systems (e.g. diabetes, seizure disorders).
  - Current or previous seizures
  - Currently pregnant or breastfeeding
  - Head trauma causing diagnosed concussion/loss of consciousness
  - Metallic implants in the head (e.g. cochlear implants)

Inclusion/Exclusion Criteria- Controls

Inclusion

- Capable of participation and of providing informed consent
- ≥ 18 years old

Exclusion

- Active psychiatric disease
- Use of medications that will interfere with EEG recordings or cognitive functioning (e.g. antidepressants, antipsychotics, anxiolytics, anticonvulsants) or illicit drugs
- Any medical condition that affects the nervous or muscular systems (e.g. MS, MND, diabetes, seizure disorders).
- Current or previous seizures
- Currently pregnant or breastfeeding
- Head trauma causing diagnosed concussion/loss of consciousness
- Metallic implants in the head (e.g. cochlear implants)

Appendix B: Detailed Protocol

Recruitment and participants

Ethical approval

All studies were carried out with prior ethical approval from the relevant bodies[22] and in accordance with the Declaration of Helsinki. Information leaflets (Appendix D) and procedural information were provided to all study participants before the study visit. Informed, voluntary consent was obtained from all study participants prior to data collection.

Recruitment process and sources

Participants were recruited to the study through a combination of in-person interactions in neurology clinics and outreach events, online advertisements, and word-of-mouth.

MS participant recruitment

Initially, potential participants with MS receiving routine neurological care at Beaumont Hospital were approached by study team members in waiting areas and asked about their interest in hearing about ongoing research projects. People who expressed interest were given a brief overview of the study, and if happy to proceed, were provided with an information packet consisting of an information leaflet, consent form, data capture form, and neuropsychological questionnaires. Participants were given the option to read the information leaflet on their own time or to have each section read or explained by the study team member. After reading the information leaflet, participants were given an opportunity to ask any questions and to decline to proceed. Participants were then asked to sign the consent form (Appendix D), which was then signed by the study team member. Participants were free to take the information packet with them if they wished to take more time before deciding to participate and were provided with contact information for study team members to ask questions. After completing the informed consent process, participants were asked to fill out a data capture form with their contact

[22] Beaumont Hospital Ethics (Medical Research) Committee –reference: 18/63
St. Vincent's University Hospital Research Ethics Committee –reference: RS19-054
St. James's Hospital/Tallaght University Hospital Joint Research Ethics Committee –reference: 2017-02, Chairman's Action 18

details, relevant medical details confirming eligibility, and interest in completing each of the study arms. Participants indicating an interest and eligibility for the EEG visit were contacted to confirm interest and schedule a study visit via phone call, email, or discussion during the neuropsychological battery visit.

Potential participants who were not attending Beaumont Hospital for their medical care were approached by research nurses and consultants in the MS and general neurology clinics at St. Vincent's Hospital and St. James' Hospital. Consent was obtained to share participant contact information with the TCD research team, who confirmed eligibility and interest via phone call or email.

During the COVID-19 pandemic, these paper information packets and intake questionnaires were moved to a Qualtrics survey that could be shared with participants via email. Participants were approached by their neurologists during telehealth visits, and participants who gave consent to be contacted were contacted to explain the study and share the link. This process was managed by the MS research study neuropsychologist in Beaumont Hospital. Respondents expressing an interest in the EEG study were followed up via phone call or email to provide more information and schedule a visit.

Additional participants were recruited through online advertisements on MS Society Ireland's research webpage, which directed potential participants to the Beaumont MS study research neuropsychologist's email. Prospective participants were then sent the Qualtrics survey to check eligibility before scheduling study visits.

ALS participant recruitment

Recruitment of participants with ALS was managed by other research teams within the Academic Unit of Neurology. Some of these data were collected over the course of this research project. Other datasets were recorded prior to the start of this project and were made available in a pseudo anonymized format. Participants were recruited in a similar manner to the process described above. Prospective participants were approached during multi-disciplinary ALS clinics at Beaumont Hospital to ascertain interest in research and consent for future contact. Those interested, willing, and able to participate were given more information in a follow-up phone call and were scheduled for an EEG visit if suitable.

Control recruitment

Neurologically healthy control participants were recruited through in-person outreach events, online advertisements, and word-of-mouth. Controls were recruited directly through this thesis project and via previous projects. Datasets from prior projects were shared in pseudo anonymized form. Control data collected prior to this project was intended to be age-matched to participants with ALS (which generally has an older age of onset than does MS) and therefore was not appropriately age-matched to our participants with MS. To combat this problem, an effort was made to recruit younger controls through word-of-mouth and online advertisements.

Wherever possible, inclusion and exclusion criteria were provided with study calls to allow prospective controls to self-assess eligibility before contacting the study team. This minimized our processing of personal data and reduced administrative burden on the research team.

i-Vol

One major source of recruitment for healthy controls (and some participants with neurological disease) was Volunteer Ireland's National Volunteering Database "i-Vol" (https://www.i-vol.ie/). The website is designed to match community members with volunteer opportunities, including research projects. A description of our research and eligibility criteria was published on the website, and interested volunteers could express interest and consent for contact through the website. Interested parties were contacted by email to provide further information and schedule study visits where appropriate.

Inclusion and exclusion criteria

Complete eligibility criteria are provided in Appendix A. Briefly, all participants were subject to the group's general EEG eligibility criteria, which involve exclusions for active psychiatric disease, metallic implants in the head, medications that could affect EEG signals, history of head trauma, history of seizures, and current pregnancy or breastfeeding.

Controls were additionally excluded if they had any neurological or muscular condition or if they had first-degree (parent, sibling, child) relative with ALS or MS.

Participants with ALS or MS were excluded for any diagnosis of neurological or muscular conditions other than ALS or MS. No participants with both ALS and MS were recruited.

Participants with MS were subject to additional recruitment criteria. Participants needed a diagnosis of RRMS, SPMS, or PPMS with no disease-modifying therapy (DMT) changes or relapses within the previous 3 months. People with MS taking SSRIs and SNRIs were eligible for recruitment, though severe active psychiatric disease remained an exclusion criterion for this group. This was allowed due to the expected high rate of participants with MS taking these medications. An unpublished undergraduate thesis found no effect of SSRI or SNRI medications on the ERP measures used in this thesis (O'Meara 2024).

Experimental paradigms

Data for this thesis were collected as part of a three-arm study of cognition in multiple sclerosis consisting of 1) questionnaires, 2) a full-battery neuropsychological visit, and 3) the EEG visit. All participants completed phase one (questionnaires) and could choose whether to then complete only phase two, only phase three, or both phase two and phase three. The thesis focuses on the EEG arm of the study, with inclusion of some data from the questionnaire phase.

Questionnaire collection and neuropsychological visit

Participants with MS completed the multiple sclerosis neuropsychological questionnaire (MSNQ) (Benedict et al. 2003) and hospital anxiety and depression scale (HADS) during in-person recruitment, online Qualtrics recruitment, or during the EEG visit if recruited directly. Some participants' carers or family members also completed the MSNQ informant-report, though there was insufficient data to include these scores in the studies reported here.

The neuropsychological visit phase consisted of a 2-3hr in-person or video call visit with a trained neuropsychologist researcher[23] at Beaumont Hospital. Participants completed a full battery of clinical neuropsychological tests. The tests included in this visit are listed in Appendix F.

Participants with ALS and controls did not complete these questionnaires or neuropsychological visit. However, some participants with ALS and controls completed

[23] Dr. Marta Pinto-Grau; Dr. Orla Strahan; Tara Boyle, Lorna O'Sullivan, Letícia Händel

similar neuropsychological batteries through other studies. This data may be available for future examination of the relationship between EEG and neuropsychological measures.

Equipment and set-up

All EEG recordings were carried out in the Wellcome-HRB Clinical Research Facility at St. James's Hospital[24]. Recording procedures were the same for each participant group. Experimenters were not blinded due to overlap between the recruitment, consenting, and study visit personnel. Upon arrival, participants were given time to review the information leaflet again and to ask any remaining questions. After signing a consent form for the visit, participants were led to an electrically shielded room and asked to sit in a comfortable, high-backed chair approximately 1m in front of a standard computer monitor. Ambulatory wheelchair users were given the option to sit in their own wheelchair or to transfer to the facility chair. Non-ambulatory wheelchair users remained in their wheelchair for safety purposes.

Flat Ag-Ag/Cl active EMG electrodes (BioSemi) with a small amount of conductive gel (Signagel, Parker Labs) were placed on cleaned right and left earlobes, right and left mastoids, right and left outer canthi, and above and below the left eye as alternate references or to aid in the detection of blink artefacts. EMG electrodes were secured with tape as needed. Participant head circumference was measured using a standard soft measuring tape placed around the widest circumference of the head (on most participants, across the supraorbital arch and inion). A 128-channel EASYCAP (GmbH) mesh cap was selected based on this measurement and placed on the participant's head to check for fit. Caps that were uncomfortably tight or did not make good contact with the participant's head were exchanged for the next largest or next smallest size. A small amount of conductive gel (Signagel, Parker Labs) was applied to each electrode holder with a plastic syringe. Active pin Ag-Ag/Cl electrodes bundled into 32-electrode "ribbons" were attached to the electrode holders in the cap, and the ribbons were taped to the back of the chair reduce weight on the participant's head and neck and to minimize electrode movement. EEG signals were recorded at 512Hz using a BioSemi ActiveTwo EEG

[24] https://www.sjhcrf.ie/

system in Actiview software. Signal offsets (electrode voltage-CMS reference voltage) were kept between ± 25mV throughout.

Experimental blocks

All EEG tasks were recorded in short blocks (2-7min, depending on the task) to help ensure that participants would be able to sit as still as possible for the duration of the recording block. Breaks between blocks allowed participants to stretch and have water or a small snack. Experimenters used these breaks to monitor participant well-being, check equipment, and explain task instructions.

Auditory oddball

Three blocks of a passive auditory frequency oddball task (Iyer et al. 2017) were recorded. Each block was approximately seven minutes long. Participants watched a silent movie (*The Artist* (Hazanavicius 2011)) while unattended auditory stimuli played through Sennheiser HD650 headphones (Wedemark, Germany). Recording room lights were turned off during these blocks. Auditory stimuli were 150ms pure tones of standard (720Hz) or deviant (800Hz) frequencies with 833ms inter-stimulus intervals. Deviant tones were presented at random and accounted for around 10% of the total stimuli.

SART

Four, five-minute blocks of the sustained attention to response task (SART) (Robertson et al. 1997) were delivered as described in McMackin et al. (McMackin et al. 2020). Participants were presented with a series of random single digits and asked to click a standard computer mouse in response to each digit except the digit “3”. Digits were presented in light grey (RGB: 250,250,250) on a black background with randomly varied font sizes of 100, 120, 140, 160, or 180pt. The inter-stimulus interval was randomly varied between 1120-1220ms. Participants were instructed to respond as quickly and as accurately as possible, prioritizing speed and accuracy equally. Participants were also reminded to stay as still as possible apart from their responding finger and to keep their finger in contact with the mouse.

After the task was explained, participants were given the opportunity to ask questions and complete an unrecorded practice block of up to 45 trials with experimenter feedback on the nature of task performance (e.g. “remember to keep the rest of your body still”, “click every time you see a number except for the number three”). No feedback was given

on the quality of task performance (e.g. “go faster”, “you got all of those right”). After the practice block, the recording room lights were turned off and participants completed four blocks of 252 trials each (approximately 5 minutes). Breaks between blocks for visual comfort and mental rest were given as appropriate.

Resting state

Six two-minute blocks of resting state EEG were recorded: three with eyes open and three with eyes closed. Eyes open recordings were conducted with the recording booth lights on, and eyes closed recordings were conducted with the recording booth lights off. Participants were instructed to relax their body and let their mind wander. The EEG signal was monitored for wakefulness and movement throughout.

Appendix C: Data protection

All individuals' personal data were pseudo anonymized and stored either physically in a locked room in the Academic Unit of Neurology or digitally on a password protected server in the Academic Unit of Neurology for access only by team members. All data were pseudo-anonymized from the point of collection and will be stored until five years after the end of the study, after which time it will be fully anonymized. The data has not been deposited in a repository, but nonetheless several steps have been taken to make the data abide by F.A.I.R. principles (Wilkinson et al. 2016).

Some essential non-anonymized information (e.g. contact information) is also stored as part of the research. This information is stored in password-protected files on TCD password-protected computers and servers and is only accessed by an approved subset of the research team (myself, the neuropsychologist, the supervising consultant Psychologist, and the research manager). This subset of the research team is approved to handle this identifiable data per the approved data ethics application. All data is backed-up regularly.

During processing, data is stored in commonly used file types and saved at intermediate analysis steps to facilitate the future use of unprocessed, partially processed, or fully processed data by our group or others. All data collected from the same participant are saved under the same subject identifier. Processing codes have been edited where applicable to be more generalizable to other protocols or research groups. No requests to access this data have been made by outside groups to date.

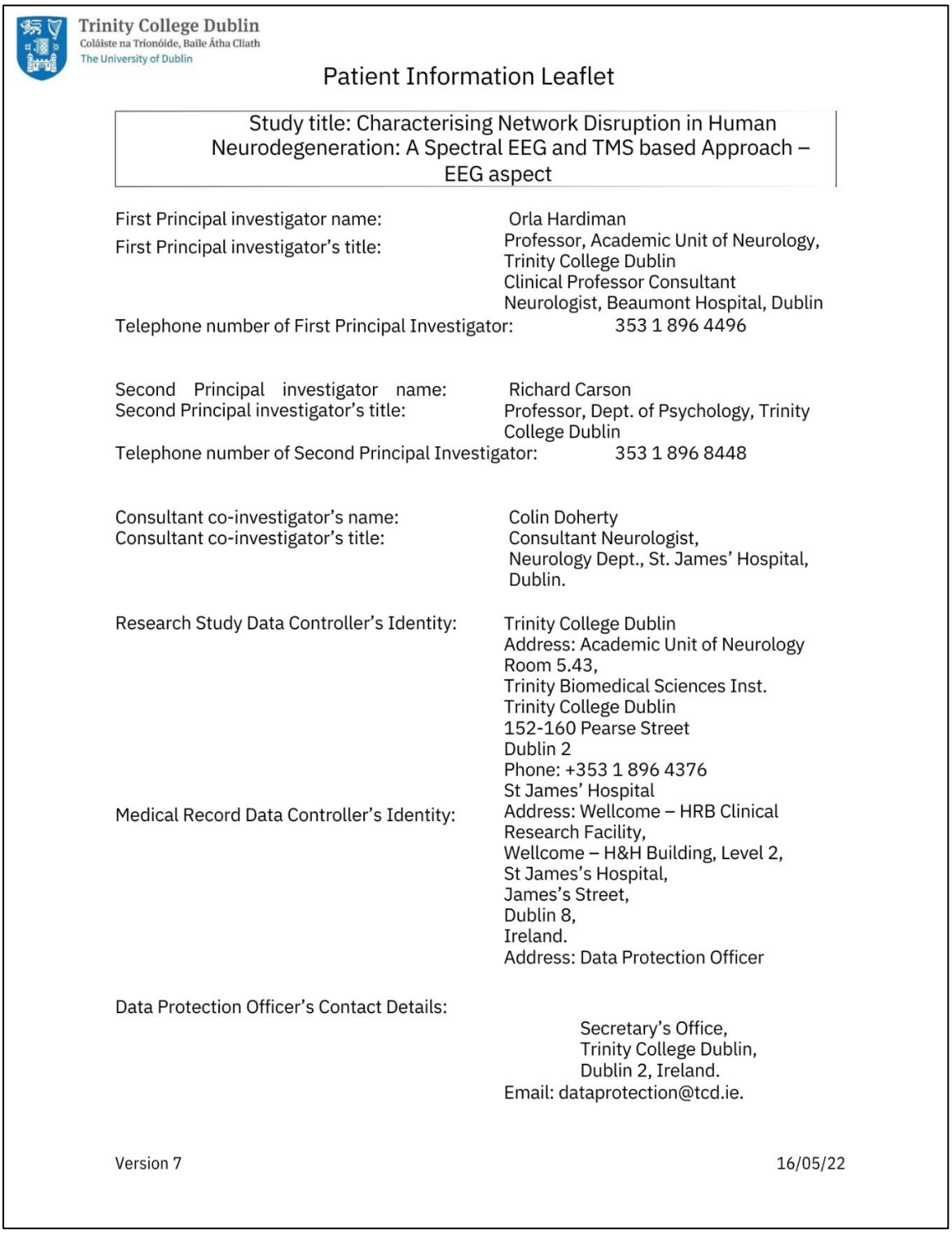
Fully anonymized individual or pooled data may be made available to other research teams upon request except in cases where data sharing would present a risk to participant privacy. All reasonable requests for data access will be fulfilled on a timely basis. To date, no data access requests have been made.

Participant data collected as a part of this project is subject to the protections laid out in the General Data Protection Regulations (GDPR). All participants were informed of their rights under GDPR during the informed consent process. All data collection, handling, and storage procedures were carried out in compliance with GDPR. A data protection impact assessment was performed for all research in the Academic Unit of Neurology and was approved by the Data Protection Officer of TCD.

Appendix D: Information leaflets and consent forms

Information leaflets

Patient information leaflet (TCD/SJH)



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Patient Information Leaflet

Study title: Characterising Network Disruption in Human Neurodegeneration: A Spectral EEG and TMS based Approach – EEG aspect

First Principal investigator name: Orla Hardiman
First Principal investigator's title: Professor, Academic Unit of Neurology, Trinity College Dublin
Clinical Professor Consultant Neurologist, Beaumont Hospital, Dublin
Telephone number of First Principal Investigator: 353 1 896 4496

Second Principal investigator name: Richard Carson
Second Principal investigator's title: Professor, Dept. of Psychology, Trinity College Dublin
Telephone number of Second Principal Investigator: 353 1 896 8448

Consultant co-investigator's name: Colin Doherty
Consultant co-investigator's title: Consultant Neurologist, Neurology Dept., St. James' Hospital, Dublin.

Research Study Data Controller's Identity: Trinity College Dublin
Address: Academic Unit of Neurology
Room 5.43,
Trinity Biomedical Sciences Inst.
Trinity College Dublin
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Dublin 2
Phone: +353 1 896 4376

Medical Record Data Controller's Identity: St James' Hospital
Address: Wellcome – HRB Clinical Research Facility,
Wellcome – H&H Building, Level 2,
St James's Hospital,
James's Street,
Dublin 8,
Ireland.
Address: Data Protection Officer

Data Protection Officer's Contact Details:
Secretary's Office,
Trinity College Dublin,
Dublin 2, Ireland.
Email: dataprotection@tcd.ie.

Version 7 16/05/22

You are being invited to take part in a research study to be carried out at The Wellcome Trust Clinical Research Facility, St. James' Hospital by The Academic Unit of Neurology, Trinity College Dublin.

Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP (doctor). Take time to ask questions – don't feel rushed and don't feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

You don't have to take part in this study. If you decide not to take part it won't affect your future medical care.

Why is this study being done?

The purpose of this study is to investigate if brain activity patterns predict how individuals will be affected by neurodegenerative diseases, including Motor Neurone Disease (MND) or Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), Multiple Sclerosis (MS), Frontotemporal Dementia (FTD) and post-polio syndrome (PPS). In this study we look at what parts of the brain are acting unusually with these diseases to:

1. Study if these patterns relate to how each individual is/will be affected by the disease in terms of symptoms and severity – If so, they may help to identify subtypes of these diseases which should be treated differently, and they may help us test if drugs work in clinical trials.
2. Study if these patterns could be used to objectively identify the presence of the disease – If so, they may help doctors to test for, and diagnose, these diseases earlier than is currently possible.
3. Learn more about how these diseases affect the brain and what we should try to target when developing new potential therapies.

We will measure brain activity using a procedure called Electroencephalography (EEG). This is described under 'What will happen to me if I agree to take part?'

Why am I being asked to take part?

You have been invited to take part in this study because you are over the age of 18 years and have requested to be provided with information about volunteering as a subject in research of those with/those who are genetic relatives of, someone with ALS, MS, FTD, HD or PPS.
We will be recruiting 90 participants per disease diagnosis group (ALS, MS, FTD, HD, PPS), 120 first-degree relatives of those with ALS, MS, FTD or HD and 90 participants without these conditions as controls.

Who should NOT attend the study (exclusion criteria)?
If any of the following apply to you, you will not be able to participate in this study:

1. Psychiatric disease (for example, clinically diagnosed major depressive disorder, anxiety disorders, bipolar disorder, schizophrenia)
2. Psychiatric medications (e.g. antidepressants, antipsychotics, anxiolytic medication), illicit drugs or other medications which modulate the central nervous system (e.g. anti-seizure medication)
3. Medical condition that affect the nervous system (e.g. diabetes, seizure disorders) or muscular system, other than HD, ALS, MS, FTD or PPS
4. Previous (allergic) reactions in similar recording environments, e.g. to recording gels
5. Pregnant or breastfeeding women.
6. Consumed alcohol on the previous evening, slept abnormally poorly or eaten very little in the previous 6 hours should not participate as it may affect performance.

The research team will ask if any of these apply to you prior to your recruitment to this study. Please answer as accurately as possible. If you are unsure if any of these criteria apply to you, the research team can answer your query.

What will happen to me if I agree to take part?

You will be asked to attend the Clinical Research Facility in St James's Hospital for a recording session. Each session will last approximately 2.5 hours. You may withdraw from the study at any time, including before, during and between sessions. We will ask you to attend up to 5 sessions at 4 month intervals, to monitor changes in the brain over time. However participation in all 5 sessions is not required to contribute to this study.

When you arrive, a member of the research team will bring you through this information leaflet including what you will be asked to do and what you will experience and you will be offered the chance to ask any questions or address any concerns you may have before agreeing to participate.

If you agree to participate, we will first ask you to sign a consent form. We will also ask you 10 questions to help us determine your "handedness" (i.e. whether your left or right hand is dominant). We will also ask you to tell us of any medications you are currently taking or if you have/have had any serious medical problems, so we can maximise your care should you require medical attention for any reason. This information will be destroyed at the end of the session.

In each EEG recording session, we will place a cap on your head. Electrodes will be placed into holes in the cap over your scalp to record the activity of your brain. 8 electrodes will be placed around the ears and eyes to record background activity. We will place some conductive gel between the electrodes and your skin. We will then do the recording while you are at rest, watching a movie or carrying out a mental test. This is called electroencephalography (EEG). The experimenter will tell you the details and instructions of the tasks in advance. Please let a member of the research team know if you have any questions or are uncertain about how to act or perform during these tasks, to ensure they are completed correctly.

You may need to wash your head after the experiment to remove the conductive gels. Showering facilities are available on site. You may also use a towel to wipe away the gel and subsequently wash it completely away after you leave if you prefer to do so.
These techniques are non-invasive, i.e. there are no needles involved and all electrodes are placed on the surface of the skin. You may feel bored, stiff or restless from sitting in a chair for 2-2.5 hours. You may move while seated in the chair between recording sessions, however due to the number of cables which connect the electrodes to the recording device, we will ask you to stay seated for the duration of the session once we begin applying the equipment. If you wish to withdraw from the study at any time this equipment can be quickly removed by a member of the research team so that you can leave the chair.
Your responsibilities as a participant:
If you agree to take part in this study, we request that you cooperate to the best of your ability. We also request that you answer the prescreening questions before attending and on the day of the session, as you believe to be accurate, to ensure we are aware of any potential biological factors which may affect your results.
Our responsibilities to you as investigators:
Alleviating any discomfort is important to us during this recording, both to ensure your own comfort is maximised and to improve the quality of the data we collect, which is best when the muscles are relaxed. Therefore please alert one of the research team during the session if at any time you feel uncomfortable or tense, if you wish to change
All data
will be maintained in a strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the study team.

position in the chair of if you would like a pillow to support your arm or back.

What are the benefits?

There is no direct benefit to you for taking part in this study. Your participation may, however, benefit those with HD, FTD, ALS, MS and/or PPS in future. Your participation also helps scientific and clinical research and postgraduate researchers undertaking this research as part of a higher degree.

What are the risks?

There is no risk involved in taking part in this study, as the procedure and devices are safe and commonly used. In the unlikely event that you show allergic reactions to the gels, the experiment will stop and we will provide medical advice to treat the reaction. There may be discomforts for you while taking part in the experiment. The experiment may be boring, tiring and fatiguing as it includes sitting in a chair for 2 to 2.5 hours. The conductive gel used to attach the electrodes to your skin may feel cold or warm, cause wet or mild itching sensation, and will need washing to remove after the experiment. The removal of medicine tape around the face and eyes may be slightly painful or uncomfortable for some patients. If at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive.

The experiments may be boring or tiring for some patients as you need to remain in a sitting position for more than an hour. The experimenter will minimise such discomforts by allowing limited mobility to the patient between the recording sessions. Please notify a member of the research team if you are feeling tense, uncomfortable or are unable to relax and they will help you to establish a more comfortable position. Pillows can be provided to support your posture and the chair may be adjusted in height/tilt to improve your comfort. If at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive. There is no intention to look for diseases using the recorded data. In case of incidental findings in the EEG recordings that may be an indirect sign of a previously unknown disease, you will be asked for permission to discuss the findings with a neurologist, your GP or other appropriate doctors.

What if something goes wrong when I'm taking part?

If for any reason you feel unwell, please alert a member of the research team and the study can be halted immediately. If you require medical attention there are nurses on site at the Wellcome Trust Clinical Research Facility who are on hand to provide any necessary care/assistance. Any leads/cables connecting the electrodes can be easily removed by the experimenter. Once these are removed you can stand, leave the room, go to the bathroom or elsewhere.
If you feel uncomfortable or for any reason wish to pause/stop the session, alert a member of the research team and we will do so immediately. You do not need to provide an explanation to the study team.

Who is organising and funding this study?

This research is being conducted by The Academic Unit of Neurology, Trinity College Dublin. The research is funded by academic grants provided by The Irish Research Council, Thierry Latran Foundation, The Health Research Board and Science Foundation Ireland in addition to charities such as Research Motor Neurone and Motor Neurone Disease Association (UK).
Members of the research team are undertaking postgraduate research at The Academic Unit of Neurology, including PhD candidates and postdoctoral fellows.

Is the study confidential?

Yes, all the information obtained from participating individuals will be treated in a strictly confidential manner. Your participation in this study will only be known to restricted members of the Academic Unit of Neurology, Trinity College Dublin. Some of those members may provide/have provided medical care to you separate from this study, (such as Prof. Orla Hardiman), Your participation will not be disclosed to anyone else. We will not contact your GP to inform them of your participation in this study, unless you request us to do so.

All digital personal and clinical information will be stored on a secure password-protected computer which only the study team can access.

Each individual participant will be assigned a unique numeric (code). This code will be used instead of your name on all research data.

The link between your name and this code will be maintained in a separate password-protected encrypted database with access limited to named researchers from the study team. We need to keep this link to connect information that you have provided in different sessions of this study and information you have shared with the Academic Unit of Neurology, Trinity College Dublin.

All paper records, including your consent form, certain task performance measures and your handedness information will be stored in a limited-access, secure storage space.

In order to ensure that the study has been conducted carefully national or international agencies (e.g. Department of Health, Irish Research Council, Health Research Board, American ALS Association, Motor Neurone Disease Association UK etc.) may require access to the data we collect for this study: you hereby give permission to the investigators to provide information obtained as a result of your participation in this study (biological signals and task performance measures) to such bodies. Your name or personal contact details will not be provided, only coded research data.

Data Protection

This section addresses the protection of your Personal Data. Personal Data means any information which can identify you.

What Personal Data will be collected?

To help answer the research questions, the study team will collect Personal Data about you so that they can understand your medical history and your brain activity responses. The following are examples of Personal Data that may be collected during this session:

- Name
- Date of birth
- ALS, PPS, HD, FTD or MS diagnosis
- Handedness (using a test called the Edinburgh Handedness Scale)
- Signals from your brain
- Information on what you did during tasks (verbal or button pressing or written responses)

To help us understand how the signals we measure relate to other aspects of the brain's activity or structure, we may also investigate the relationship between the signals we collect and data you have provided to the Academic Unit of Neurology, Trinity College Dublin during other research studies the Unit performs. The following are examples of Personal Data that may be collected from other studies performed by the Academic Unit of Neurology:

- Neuropsychological test scores
- MRI scans of your brain
- Transcranial Magnetic Stimulation (TMS) data

Your participation in other such studies is voluntary, you do not need to provide this information to us during this session or participate in these other studies to complete participation in this study.

If you have a diagnosis of ALS, we may also gather information relating to your diagnosis from the National ALS Register, to investigate how these signals relate to different symptoms or subgroups of the disease. The following are examples of Personal Data that may be collected from the National ALS Register:

- Symptoms you experience
- Genetic risk factors you do/do not have

Contribution of your data to the National ALS Register is voluntary, you do not need to provide this information to us during this session or contribute data to the National ALS Register to complete participation in this study. Such information about your disease will only be obtained from the National ALS Register upon approval of a justifiable request to a manager of the ALS register. We will not collect or store unnecessary information about your disease from the Register, only that which is used to help us better understand the signals we measure in this study.

How will my Personal Data be used?

If you agree to take part in this study, your Personal Data will be used:

- To determine if you can take part in the study
- To measure how your brain responds during the study and compare this to other study participants
- To learn more about the disease and to help develop new diagnostic and prognostic test protocol.
- To provide you with treatment in the event of a study related injury
- To develop new analysis methods to improve the study of neurological diseases.

What is the legal basis under which we are processing your data?

The research team at St James's Hospital and Trinity College Dublin will only use your personal data *for this* research to help us study how neurodegenerative diseases (ALS, PPS, HD, FTD and MS) affect the brain's function and how any changes in brain function relate to different symptoms or subtypes of these diseases.
This may improve our ability to diagnose these diseases or their subtypes, predict how the disease will progress in different individuals with these diseases, and test new

medications for these diseases.
This is in line with Article 6(1)e and Article 9(2)j of the General Data Protection Regulation.

We will also request your consent to the use of your Coded Data in continued medical research projects investigating ALS, HD, FTD, MS and PS and the development of new research methods that can be used to study these diseases. This is optional.

The results of this study and optional future research may be published in study reports, scientific presentations and publications. Information that could reasonably identify you will not be included in such publications. Your results will not be sent to you or your GP, consultant or other healthcare providers, unless you request us to do so.

How long will your data be stored for?

We will store the coded research data and a separate document which relates your name to your study code for up to 5 years after the study of brain function in ALS, PPS, HD, FTD and MS by the Academic Unit of Neurology has been completed.

After this, the *data will be fully anonymised, by destroying the link between your name and the study code, so that the data can no longer be attributed to/associated with you. This fully anonymised data may be used for future research and may be provided to other research teams or made available online to maximise the information learned from it.*

Is there any risks which might arise from processing your data?

There are low risks of your identity being revealed, but we take many measures to keep the information confidential such as coding the data, storing the data on secure password protected computers, and ensuring all staff are trained in data protection and have a duty of confidentiality.

Any future backup/archiving of your data with a third party vendor will be subject to a binding Agreement in compliance with GDPR.

What rights do you have regarding your data? Under the General Data Protection Regulation you have the following rights unless it would seriously affect the outcomes of the research study itself (for example – the right to removal of the data might lead to insufficient information for performing the analysis required for this research, and as such that right could be limited.

- Right to access (Article 15): You have a right to request access to your data and a copy of it.
- Right to rectification (Article 16): You have a right to have any inaccurate information about you corrected or deleted.
- Right to erasure (removal of your data) (Article 17): You have a right to have your personal data deleted.
- Right to restriction of processing (Article 18): You have a right to restrict or object to processing of your personal data.
- Right to object automated processing (Article 21-22): We will be applying automated methods on the collected data to sub-categorize patients into groups that might be used to facilitate more patient-specific future clinical trials. You have a right to object this.

How can you withdraw from this study?

You have a right to withdraw consent at any time. This can be done before, during or after the recording session in person by telling a member of the research team or using the contact details provided at the end of this leaflet.

How can you file a complaint?

If you would like to raise a concern regarding how we have used your personal data, you may do so by contacting Data Protection Officer in Trinity College Dublin (contact details are on the first page of this leaflet)

Consent to Future Uses

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Will your personal data be processed further after this study? If so, could your data leave the EU?
We would like to maximise the amount of information that can be learned from your data, by utilising it in future research of neurological diseases. Consenting to the future use of your data beyond this project is optional and will be restricted to use for specific aims, with GDPR compliant data sharing agreements in place to safeguard your rights.

Such further research is for the purposes of one or more of the following:

1. Improving understanding of neurological disorders
2. Improving the ability to diagnose neurological disorders
3. Improving the prediction of how neurological disorders will progress.
4. Developing new analysis methods, measurements or tools which can be used for purposes 1-3.

This research may be performed by research groups or commercial entities other than The Academic Unit of Neurology, Trinity College Dublin, and may be within or outside the EU/EEA. Commercial entities such as pharmaceutical companies may wish to investigate the data we collect in order to develop new tools for use in medical practice or drug testing. Any research/commercial groups will only be provided with coded information. The key which links your name to this data to make it identifiable will not be accessible to anyone other than a limited number of individuals within the research team.

Where can I get further information?

If you have any further questions about the study or if you want to opt out of the study, you can rest assured it won't affect the quality of treatment you get in the future.
If you need any further information now or at any time in the future, please contact:

Dr Roisin McMackin

Address:
Room 5.43,
Trinity Biomedical Sciences Institute,
152-160 Pearse St.,
Trinity College Dublin,
Dublin 2,
Ireland.

Phone No: +353 1 896 4497
Email: mcmackr@tcd.ie

Control information leaflet (TCD/SJH)

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Control Information Leaflet

Study title: Characterising Network Disruption in Human Neurodegeneration: A Spectral EEG and TMS based Approach – EEG aspect

First Principal investigator name:	Orla Hardiman
First Principal investigator's title:	Professor, Academic Unit of Neurology, Trinity College Dublin Clinical Professor Consultant Neurologist, Beaumont Hospital, Dublin
Telephone number of First Principal Investigator:	353 1 896 4496
Second Principal investigator name:	Richard Carson
Second Principal investigator's title:	Professor, Dept. of Psychology, Trinity College Dublin
Telephone number of Second Principal Investigator:	353 1 896 8448
Consultant co-investigator's name:	Colin Doherty
Consultant co-investigator's title:	Consultant Neurologist, Neurology Dept., St. James' Hospital, Dublin.
Research Study Data Controller's Identity:	Trinity College Dublin Address: Academic Unit of Neurology Room 5.43, Trinity Biomedical Sciences Inst. Trinity College Dublin 152-160 Pearse Street Dublin 2 Phone: +353 1 896 4376
Medical Record Data Controller's Identity:	St James' Hospital Address: Wellcome – HRB Clinical Research Facility, Wellcome – H&H Building, Level 2, St James's Hospital, James's Street, Dublin 8, Ireland.
Data Protection Officer's Contact Details:	Address: Data Protection Officer Secretary's Office, Trinity College Dublin, Dublin 2, Ireland. Email: dataprotection@tcd.ie.

Version 7 16/05/22

You are being invited to take part in a research study to be carried out at The Wellcome Trust Clinical Research Facility, St. James' Hospital by The Academic Unit of Neurology, Trinity College Dublin.

Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP (doctor). Take time to ask questions – don't feel rushed and don't feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

You don't have to take part in this study. If you decide not to take part it won't affect your future medical care.

Why is this study being done?

The purpose of this study is to investigate if brain activity patterns predict how individuals will be affected by neurodegenerative diseases, including Motor Neurone Disease (MND) or Amyotrophic Lateral Sclerosis (ALS), Huntington's Disease (HD), Multiple Sclerosis (MS), Frontotemporal Dementia (FTD) and post-polio syndrome (PPS). In this study we look at what parts of the brain are acting unusually with these diseases to:

1. Study if these patterns relate to how each individual is/will be affected by the disease in terms of symptoms and severity – If so, they may help to identify subtypes of these diseases which should be treated differently, and they may help us test if drugs work in clinical trials.
2. Study if these patterns could be used to objectively identify the presence of the disease – If so, they may help doctors to test for, and diagnose, these diseases earlier than is currently possible.
3. Learn more about how these diseases affect the brain and what we should try to target when developing new potential therapies.

We will measure brain activity using a procedure called Electroencephalography (EEG). This is described under 'What will happen to me if I agree to take part?'

Why am I being asked to take part?

You have been invited to take part in this study because you are over the age of 18 years and have requested to be provided with information about volunteering as a "healthy control" subject in research of those with/those who are genetic relatives of, someone with ALS, MS, FTD, HD or PPS.
We will be recruiting 90 participants per disease diagnosis group (ALS, MS, FTD, HD, PPS), 120 first-degree relatives of those with ALS, MS, FTD or HD and 90 participants without these conditions as controls.

Who should NOT attend the study (exclusion criteria)?

If any of the following apply to you, you will not be able to participate in this study:

1. Psychiatric disease (for example, clinically diagnosed major depressive disorder, anxiety disorders, bipolar disorder, schizophrenia)
2. Psychiatric medications (e.g. antidepressants, antipsychotics, anxiolytic medication), illicit drugs or other medications which modulate the central nervous system (e.g. anti-seizure medication)
3. Medical condition that affect the nervous system (e.g. diabetes, seizure disorders) or muscular system, other than HD, ALS, MS, FTD or PPS
4. Previous (allergic) reactions in similar recording environments, e.g. to recording gels
5. Pregnant or breastfeeding women.
6. Consumed alcohol on the previous evening, slept abnormally poorly or eaten very little in the previous 6 hours should not participate as it may affect performance.

The research team will ask if any of these apply to you prior to your recruitment to this study. Please answer as accurately as possible. If you are unsure if any of these criteria apply to you, the research team can answer your query.

What will happen to me if I agree to take part?

You will be asked to attend the Clinical Research Facility in St James's Hospital for a recording session. Each session will last approximately 2.5 hours. You may withdraw from the study at any time, including before, during and between sessions. We will ask you to attend up to 5 sessions at 4 month intervals, to monitor changes in the brain over time. However participation in all 5 sessions is not required to contribute to this study.

When you arrive, a member of the research team will bring you through this information leaflet including what you will be asked to do and what you will experience and you will be offered the chance to ask any questions or address any concerns you may have before agreeing to participate.

If you agree to participate, we will first ask you to sign a consent form. We will also ask you 10 questions to help us determine your "handedness" (i.e. whether your left or right hand is dominant). We will also ask you to tell us of any medications you are currently taking or if you have/have had any serious medical problems, so we can maximise your care should you require medical attention for any reason. This information will be destroyed at the end of the session.

In each EEG recording session, we will place a cap on your head. Electrodes will be placed into holes in the cap over your scalp to record the activity of your brain. 8 electrodes will be placed around the ears and eyes to record background activity. We will place some conductive gel between the electrodes and your skin. We will then do the recording while you are at rest, watching a movie or carrying out a mental test. This is called electroencephalography (EEG). The experimenter will tell you the details and instructions of the tasks in advance. Please let a member of the research team know if you have any questions or are uncertain about how to act or perform during these tasks, to ensure they are completed correctly.

You may need to wash your head after the experiment to remove the conductive gels. Showering facilities are available on site. You may also use a towel to wipe away the gel and subsequently wash it completely away after you leave if you prefer to do so. These techniques are non-invasive, i.e. there are no needles involved and all electrodes are placed on the surface of the skin. You may feel bored, stiff or restless from sitting in a chair for 2-2.5 hours. You may move while seated in the chair between recording sessions, however due to the number of cables which connect the electrodes to the recording device, we will ask you to stay seated for the duration of the session once we begin applying the equipment. If you wish to withdraw from the study at any time this equipment can be quickly removed by a member of the research team so that you can leave the chair. Your responsibilities as a participant: If you agree to take part in this study, we request that you cooperate to the best of your ability. We also request that you answer the prescreening questions before attending and on the day of the session, as you believe to be accurate, to ensure we are aware of any potential biological factors which may affect your results. Our responsibilities to you as investigators: Alleviating any discomfort is important to us during this recording, both to ensure your own comfort is maximised and to improve the quality of the data we collect, which is best when the muscles are relaxed. Therefore please alert one of the research team during the session if at any time you feel uncomfortable or tense, if you wish to change

position in the chair or if you would like a pillow to support your arm or back.

All data will be maintained in strictly confidential manner. The information that you provide will be stored in a way that it cannot be accessed except by the study team.

What are the benefits?

There is no direct benefit to you for taking part in this study. Your participation may, however, benefit those with HD, FTD, ALS, MS and/or PPS in future. Your participation also helps scientific and clinical research and postgraduate researchers undertaking this research as part of a higher degree.

What are the risks?

There is no risk involved in taking part in this study, as the procedure and devices are safe and commonly used. In the unlikely event that you show allergic reactions to the gels, the experiment will stop and we will provide medical advice to treat the reaction. There may be discomforts for you while taking part in the experiment. The experiment may be boring, tiring and fatiguing as it includes sitting in a chair for 2 to 2.5 hours. The conductive gel used to attach the electrodes to your skin may feel cold or warm, cause wet or mild itching sensation, and will need washing to remove after the experiment. The removal of medicine tape around the face and eyes may be slightly painful or uncomfortable for some patients. If at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive.

Page 4

The experiments may be boring or tiring for some patients as you need to remain in a sitting position for more than an hour. The experimenter will minimise such discomforts by allowing limited mobility to the patient between the recording sessions. Please notify a member of the research team if you are feeling tense, uncomfortable or are unable to relax and they will help you to establish a more comfortable position. Pillows can be provided to support your posture and the chair may be adjusted in height/tilt to improve your comfort. If at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive. There is no intention to look for diseases using the recorded data. In case of incidental findings in the EEG recordings that may be an indirect sign of a previously unknown disease, you will be asked for permission to discuss the findings with a neurologist, your GP or other appropriate doctors.

What if something goes wrong when I'm taking part?

If for any reason you feel unwell, please alert a member of the research team and the study can be halted immediately. If you require medical attention there are nurses on site at the Wellcome Trust Clinical Research Facility who are on hand to provide any necessary care/assistance. Any leads/cables connecting the electrodes can be easily removed by the experimenter. Once these are removed you can stand, leave the room, go to the bathroom or elsewhere.
If you feel uncomfortable or for any reason wish to pause/stop the session, alert a member of the research team and we will do so immediately. You do not need to provide an explanation to the study team.

Who is organising and funding this study?

This research is being conducted by The Academic Unit of Neurology, Trinity College Dublin. The research is funded by academic grants provided by The Irish Research Council, Thierry Latran Foundation, The Health Research Board and Science Foundation Ireland in addition to charities such as Research Motor Neurone and Motor Neurone Disease Association (UK).
Members of the research team are undertaking postgraduate research at The Academic Unit of Neurology, including PhD candidates and postdoctoral fellows.

Is the study confidential?

Yes, all the information obtained from participating individuals will be treated in a strictly confidential manner. Your participation in this study will only be known to restricted members of the Academic Unit of Neurology, Trinity College Dublin. Some of those members may provide/have provided medical care to you separate from this study, (such as Prof. Orla Hardiman), Your participation will not be disclosed to anyone else. We will not contact your GP to inform them of your participation in this study, unless you request us to do so.

All digital personal and clinical information will be stored on a secure password-protected computer which only the study team can access.

Each individual participant will be assigned a unique numeric (code). This code will be used instead of your name on all research data.

The link between your name and this code will be maintained in a separate password-protected encrypted database with access limited to named researchers from the study team. We need to keep this link to connect information that you have provided in different sessions of this study and information you have shared with the Academic Unit of Neurology, Trinity College Dublin.

All paper records, including your consent form, certain task performance measures and your handedness information will be stored in a limited-access, secure storage space.

In order to ensure that the study has been conducted carefully national or international agencies (e.g. Department of Health, Irish Research Council, Health Research Board, American ALS Association, Motor Neurone Disease Association UK etc.) may require access to the data we collect for this study: you hereby give permission to the investigators to provide information obtained as a result of your participation in this study (biological signals and task performance measures) to such bodies. Your name or personal contact details will not be provided, only coded research data.

Data Protection

This section addresses the protection of your Personal Data. Personal Data means any information which can identify you.

What Personal Data will be collected?

To help answer the research questions, the study team will collect Personal Data about you so that they can understand your medical history and your brain activity responses. The following are examples of Personal Data that may be collected during this session:

- Name
- Date of birth
- Lack of ALS, PPS, HD, FTD or MS diagnosis
- Handedness (using a test called the Edinburgh Handedness Scale)
- Signals from your brain
- Information on what you did during tasks (verbal or button pressing or written responses)

To help us understand how the signals we measure relate to other aspects of the brain's activity or structure, we may also investigate the relationship between the signals we collect and data you have provided to the Academic Unit of Neurology, Trinity College Dublin during other research studies the Unit performs. The following are examples of Personal Data that may be collected from other studies performed by the Academic Unit of Neurology:

- Neuropsychological test scores
- MRI scans of your brain
- Transcranial Magnetic Stimulation (TMS) data

Your participation in other such studies is voluntary, you do not need to provide this information to us during this session or participate in these other studies to complete participation in this study.

How will my Personal Data be used?

If you agree to take part in this study, your Personal Data will be used:

- To determine if you can take part in the study
- To measure how your brain responds during the study and compare this to other study participants

- To learn more about the disease and to help develop new diagnostic and prognostic test protocol.
- To provide you with treatment in the event of a study related injury
- To develop new analysis methods to improve the study of neurological diseases.

What is the legal basis under which we are processing your data?

The research team at St James's Hospital and Trinity College Dublin will only use your personal data *for this* research to help us study how neurodegenerative diseases (ALS, PPS, HD, FTD and MS) affect the brain's function and how any changes in brain function relate to different symptoms or subtypes of these diseases.
This may improve our ability to diagnose these diseases or their subtypes, predict how the disease will progress in different individuals with these diseases, and test new

medications for these diseases.
This is in line with Article 6(1)e and Article 9(2)j of the General Data Protection Regulation.

We will also request your consent to the use of your Coded Data in continued medical research projects investigating ALS, HD, FTD, MS and PS and the development of new research methods that can be used to study these diseases. This is optional. The results of this study and optional future research may be published in study reports, scientific presentations and publications. Information that could reasonably identify you will not be included in such publications. Your results will not be sent to you or your GP, consultant or other healthcare providers, unless you request us to do so.

How long will your data be stored for? We will store the coded research data and a separate document which relates your name to your study code for up to 5 years after the study of brain function in ALS, PPS, HD, FTD and MS by the Academic Unit of Neurology has been completed.

After this, the *data will be fully anonymised, by destroying the link between your name and the study code, so that the data can no longer be attributed to/associated with you. This fully anonymised data may be used for future research and may be provided to other research teams or made available online to maximise the information learned from it.*

Is there any risks which might arise from processing your data?

There are low risks of your identity being revealed, but we take many measures to keep the information confidential such as coding the data, storing the data on secure password protected computers, and ensuring all staff are trained in data protection and have a duty of confidentiality.

Any future backup/archiving of your data with a third party vendor will be subject to a binding Agreement in compliance with GDPR.

What rights do you have regarding your data?
Under the General Data Protection Regulation you have the following rights unless it would seriously affect the outcomes of the research study itself (for example – the right to removal of the data might lead to insufficient information for performing the analysis required for this research, and as such that right could be limited.

- Right to access (Article 15): You have a right to request access to your data and a copy of it.
- Right to rectification (Article 16): You have a right to have any inaccurate information about you corrected or deleted.
- Right to erasure (removal of your data) (Article 17): You have a right to have your personal data deleted.
- Right to restriction of processing (Article 18): You have a right to restrict or object to processing of your personal data.
- Right to object automated processing (Article 21-22): We will be applying automated methods on the collected data to sub-categorize patients into groups that might be used to facilitate more patient-specific future clinical trials. You have a right to object this.

How can you withdraw from this study?

You have a right to withdraw consent at any time. This can be done before, during or after the recording session in person by telling a member of the research team or using the contact details provided at the end of this leaflet.

How can you file a complaint?

If you would like to raise a concern regarding how we have used your personal data, you may do so by contacting Data Protection Officer in Trinity College Dublin (contact details are on the first page of this leaflet)

Consent to Future Uses

Will your personal data be processed further after this study? If so, could your data leave the EU?
We would like to maximise the amount of information that can be learned from your data, by utilising it in future research of neurological diseases. Consenting to the future use of your data beyond this project is optional and will be restricted to use for specific aims, with GDPR compliant data sharing agreements in place to safeguard your rights. Such further research is for the purposes of one or more of the following:

1. Improving understanding of neurological disorders
2. Improving the ability to diagnose neurological disorders
3. Improving the prediction of how neurological disorders will progress.
4. Developing new analysis methods, measurements or tools which can be used for purposes 1-3.

This research may be performed by research groups or commercial entities other than The Academic Unit of Neurology, Trinity College Dublin, and may be within or outside

the EU/EEA. Commercial entities such as pharmaceutical companies may wish to investigate the data we collect in order to develop new tools for use in medical practice or drug testing. Any research/commercial groups will only be provided with coded information. The key which links your name to this data to make it identifiable will not be accessible to anyone other than a limited number of individuals within the research team.

Where can I get further information?

If you have any further questions about the study or if you want to opt out of the study, you can rest assured it won't affect the quality of treatment you get in the future.
If you need any further information now or at any time in the future, please contact:

Dr Roisin McMackin

Address:
Room 5.43,
Trinity Biomedical Sciences Institute,
152-160 Pearse St.,
Trinity College Dublin,
Dublin 2,
Ireland.

Phone No: +353 1 896 4497

Email: mcmackr@tcd.ie

Patient information leaflet (BH)

Patient Information Leaflet

Study title: A Multidisciplinary Study of Cognition in Multiple Sclerosis

Principal investigator's name:	Prof. Orla Hardiman
Principal investigator's title:	Consultant Neurologist
Telephone number of principal investigator:	01 896-4497
Data Controller's/joint Controller's Identity:	Beaumont Hospital (Prof. Orla Hardiman)
Data Controller's/joint Controller's Contact Details:	01 896-4497
Data Protection Officer's Identity:	Mr. Mark Graham
Data Protection Officer's Contact Details:	dpo@beaumont.ie

You are being invited to take part in a research study to be carried out at Beaumont Hospital, under the supervision of Prof. Orla Hardiman, Principal Investigator and Consultant Neurologist. Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP (doctor). Take time to ask questions – do not feel rushed and do not feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

You don't have to take part in this study. If you decide not to take part it will not affect your future medical care.

You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You do not have to give us a reason. If you do opt out, rest assured it will not affect the quality of treatment you receive in the future.

Why is this study being done?

Changes in cognition (thinking and memory) are common in people with multiple sclerosis (MS) and can interfere with daily functioning and quality of life. However, these changes remain poorly understood. There is also a need for better and more reliable measurements of cognitive processing in people with MS. Because of this, it is difficult to design treatments that can improve cognitive performance in those affected.

This study aims to improve our understanding of the cognitive changes in MS to better understand the needs of patients.

Who is organising and funding this study?

This research is being conducted by Prof. Orla Hardiman, Consultant Neurologist in Beaumont Hospital, along with Prof. Niall Pender from Beaumont Hospital, Prof. Christopher McGuigan from St Vincent's Hospital and Dr. Siobhán Hutchinson from St. James's Hospital. This research is funded by Merck Pharmaceuticals and Science Foundation Ireland.

Why am I being asked to take part?

We are asking individuals 18 years or older with a diagnosis of MS to take part in this study.

How will the study be carried out?

If you agree to take part in the study, we will invite you to meet a researcher to complete a cognitive screening test to assess your thinking. We might also ask you to complete additional neuropsychological tests that assess your thinking in more detail, and/or take part in EEG recording sessions which will take place in St. James's Hospital.

What will happen to me if I agree to take part?

If you agree to take part in this study, we will firstly explain the study in greater detail and, if you are willing to participate, you will be invited to sign the consent form. By consenting to take part in this research, you are providing permission for the clinical research team to access your Hospital medical records.

This study involves completing a brief cognitive screening test which will assess your thinking. You will meet with a member of the research team who will complete this paper and pencil test with you.

You may also be invited to complete additional cognitive tests that will assess your thinking in greater detail. These paper and pencil tests will take approximately 2 hours to complete and you will able to take breaks whenever you would like to. We will arrange a suitable

appointment time to undergo these tests and will do our best to facilitate you with a suitable time and place.

As part of this study, you may also be invited to take part in EEG recording sessions. Each recording session lasts approximately 2 and a half hours and will be carried out at St. James's Hospital – Clinical Research Facility. In each EEG recording session, we will place a cap on your head. Electrodes will be placed into holes in the cap over your scalp to record the activity of your brain. 8 electrodes will be placed around the ears and eyes to record background activity. We will place some conductive gel between the electrodes and your skin. We will then do the recording while you are at rest, watching a movie or carrying out a mental test. The experimenter will tell you the details of the instructions in advance. You may need to wash your head after the experiment to remove the conductive gels. Showering facilities are available on site. There is no drug, intervention or stimulation involved in this study.

We would like to repeat these tests 3 times at 4-6 month intervals to gain a better understanding of MS as the disease changes over time. However, you are free to withdraw from the study at any stage or reduce your involvement, without reason, and this will not affect your medical care.

What other treatments are available to me?

The proposed study does not involve any change to your existing treatment plan. You may decide to withdraw consent from the study at any time without giving a reason and your future treatment will not be affected.

What happens if I do not agree to take part?

There is no consequence to you or your medical treatment if you do not agree to participate. Your decision to participate is entirely up to you. This study does not involve any treatment and your decision to take part or not will not impact your health condition, disease progression or your previous, current or future treatments. You may decide to withdraw consent from the study at any time without justifying your decision and your future treatment and care will not be affected.

Video/and or Audio recordings?

Assessments will not be video or audio recorded for this research study.

What are the benefits?

While there is no direct and immediate benefit to you in participating, this study is hoping to benefit people with MS by increasing our understanding of the cognitive changes that take place over the course of the disease.

What are the risks?

There are minimal risks anticipated from taking part in this research study, as the procedure and devices are safe and commonly used. If you do become fatigued while completing the cognitive tests and questionnaires you will be offered to take refreshment breaks at any time. In terms of the EEG recordings, in the unlikely event that you show allergic reactions to the gels, the experiment will stop and we will provide medical advice to treat the reaction. However, there may be discomforts for you during the recordings. You may find the recordings to be boring, tiring and fatiguing as it includes sitting in a chair for 1-2 hours. The conductive gel used to attach the electrodes to your skin may feel cold or warm, cause wet and mild itching sensation, and will need washing to remove after the experiment. The removal of medicine tapes around the face and eyes may be slightly painful or uncomfortable for some patients. If at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive.

There is no intention to look for diseases using the recorded data. In the unlikely case of incidental findings in the EEG recordings that may be an indirect sign of a previously unknown disease, you will be asked for permission to discuss the findings with a neurologist, your GP or other appropriate doctor.

Participants are also free to not participate or to withdraw from the study at any time if they choose to do so without giving a reason and without risking loss of present or future care you would otherwise expect to receive.

What if something goes wrong when I'm taking part in this study?

We do not anticipate anything will go wrong. However, if you begin to feel distressed or unwell during the study and feel you would like to discontinue your participation, you are free to do so at any time without any penalty and without giving a reason. If you have any other concerns you would like to raise, either during or after the study, participants will also be provided with contact details of the Principal Investigator Prof. Orla Hardiman, Consultant Neurologist.

Will it cost me anything to take part?

We will reimburse you for any reasonable and vouched travel expenses up to a value of €50. There will be no other costs associated with your participation in this study.

Is the study confidential?

All information which is collected about you during the course of the research will be kept strictly confidential.

During testing, your data will be "coded" by the researcher, meaning that you will be allocated a unique identification code which will be used in place of your name on our testing materials and computer databases. The 'key' that matches your name and unique identification code will be retained by the Research Manager (Mr. Mark Heverin, Academic Unit of Neurology), on behalf of the Principal Investigator, and will be stored on a password-protected, encrypted database in the Academic Unit of Neurology, Trinity College Dublin.

Paper files will be securely transported from the site of testing and will be stored in a locked cabinet in a dedicated office in the Academic Unit of Neurology, Trinity College Dublin. A log book will be retained by the Data Manager and those accessing the data will be required to sign to access the files. Electronic data will be securely transported from the site of testing and will be encrypted, password protected and held on a dedicated computer in a locked office in the Academic Unit of Neurology, Trinity College Dublin. Only staff members with login credentials will be able to access the computer. The login credentials will change every 6 months, and those accessing the computer will be tracked.

By consenting to take part in this study, you are also providing permission for the members of this research team to access your Hospital medical records to obtain information relevant to your history of MS for the purposes of the study. Only members of the research team working directly on the project and approved by Prof. Orla Hardiman will have access to this data.

Your GP will not receive any of the details of the information that you provide unless you request that it be sent to him/her.

You will not be given direct feedback on the results of your individual assessments. Any participant who wishes to find out about the results of the study will be provided with a report on the publication of results. If participants express concern as to their cognitive functioning, contact details for the Principal Investigator, Prof. Orla Hardiman, will be provided. There is no intention to look for diseases using the recorded data. In the unlikely case of incidental findings in the EEG recordings that may be an indirect sign of a previously unknown disease, you will be asked for permission to discuss the findings with a neurologist, your GP or other appropriate doctor. Results of this study will be communicated to other scientists through peer-reviewed academic journals and conference presentations. In all cases, data will be anonymous and your name and personal details will not be included.

Information gathered from this study will be stored for 10 years to allow us to perform additional analyses with other scientists interested in understanding and finding treatments for thinking problems in MS. If you agree, we will also use information we have gathered from this study to in future studies with scientists interested in Multiple Sclerosis, subject to appropriate future approval by the relevant Research Ethics committees.

Data Protection

1. We will be using your personal information in our research study to help us understand cognitive changes in MS.

2. We will be processing your data for legitimate interest and for scientific research purposes under Article 6 and 9 of the General Data Protection Regulation 2016.

3. Only members of the research team, under the approval and supervision of Prof. Orla Hardiman, Principal Investigator will have access to research participants' information.

4. Hard-copy data will be retained for a period of time after the study has completed to comply with publishing guidelines. The length of time is dependent on the specific journal in which the data is published, but will likely be 10 years. Electronic data will be retained in Trinity College Dublin.

5. As your hard-copy data will be coded at the time of testing we do not envisage any situation where a data breach could cause harm. The data contained on any computers will also be coded and the key to link your name with the number will be kept separate. In the unlikely event of a data breach, it will only be possible for someone to see your raw test scores which will not be meaningful to an untrained third party.

6. You have a right to withdraw your consent at any stage during the research study without giving a reason and without penalty. You can inform any member of the research team of your decision to withdraw at any time and they will accommodate your request.

7. You have the right to lodge a complaint about the research study with the Data Protection Commissioner.

8. You have a right to request access to your data and a copy of it, unless your request would make it impossible or make it very difficult to conduct the research.

9. You have a right to restrict or object to processing, unless your request would make it impossible or make it very difficult to conduct the research.

10. You have a right to have any inaccurate information about you corrected or deleted, unless your request would make it impossible or make it very difficult to conduct the research.

11. You have a right to have your personal data deleted, unless your request would make it impossible or make it very difficult to conduct the research

12. You have a right to data portability, meaning they you have the right to move your data from one controller to another in a readable format.

13. There will be no automated decision making or profiling using your data.

14. If automated decision making or profiling were to occur, you have the right to object to this if you wish.

15. You will be informed if we intend to further process your personal data and you will be provided with information on that other purpose.

16. You will be informed if we wish to transfer your data to a country outside of the EU or an international organisation and will be advised on the safeguards you have in place to protect your data. We do not foresee any situation where we will be transferring data outside the EU.

Consent to Further Contact

In addition to seeking consent for your data to be used for the purposes of the current research study, we are also seeking your permission to contact you about possible future research related and unrelated to the current study for which you may be eligible.

Consent to Future Uses

If you choose to take part, we are also seeking your permission for your data to be used in future research projects, either related or unrelated to the current study. This would involve giving permission for these research projects, as yet unknown, to use your data in an anonymised format without future consent being required. The use of this data in future research projects is subject to appropriate future approval by the relevant Research Ethics committees.

Where can I get further information?

If you have any questions about the study now, or in the future, please contact the Principal Investigator, Prof. Orla Hardiman via the Research Manager Mr. Mark Heverin.

Name: Mr. Mark Heverin
Position: Research Manager
Address: Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin
Email: mark.heverin@tcd.ie
Phone: +353 1896 4376

Control information leaflet (BH)

Healthy Control Information Leaflet

Study title: A Multidisciplinary Study of Cognition in Multiple Sclerosis

Principal investigator's name:	Prof. Orla Hardiman
Principal investigator's title:	Consultant Neurologist
Telephone number of principal investigator:	01 896-4497
Data Controller's/joint Controller's Identity:	Beaumont Hospital (Prof. Orla Hardiman)
Data Controller's/joint Controller's Contact Details:	01 896-4497
Data Protection Officer's Identity:	Mr. Mark Graham
Data Protection Officer's Contact Details:	dpo@beaumont.ie

You are being invited to take part in a research study to be carried out at Beaumont Hospital under the supervision of Prof. Orla Hardiman, Principal Investigator and Consultant Neurologist. Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP (doctor). Take time to ask questions – do not feel rushed and do not feel under pressure to make a quick decision.

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed Consent'.

You don't have to take part in this study. If you decide not to take part it will not affect your future medical care.

You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You do not have to give us a reason. If you do opt out, rest assured it will not affect the quality of treatment you receive in the future.

Why is this study being done?

You are being asked to participate in this research study on multiple sclerosis (MS), although you are not affected by MS.

Changes in cognition (thinking and memory) are common in people with multiple sclerosis (MS) and can interfere with daily functioning and quality of life. However, these changes remain poorly understood. There is also a need for better and more reliable measurements of cognitive processing in people with MS. Because of this, it is difficult to design treatments that can improve cognitive performance in those affected.

This study aims to improve our understanding of the cognitive changes in MS in order to better understand the needs of patients.

Who is organising and funding this study?

This research is being conducted by Prof. Orla Hardiman, Consultant Neurologist in Beaumont Hospital, along with Prof. Niall Pender from Beaumont Hospital, Prof. Christopher McGuigan from St Vincent's Hospital and Dr. Siobhán Hutchinson from St. James's Hospital. This research is funded by Merck Pharmaceuticals and Science Foundation Ireland.

Why am I being asked to take part?

We are asking you to participate in this study because you are a healthy individual who does not have a diagnosis of MS. This research focuses on the effects of MS on cognition over time, and we need to recruit healthy participants to measure thinking over time in unaffected people.

How will the study be carried out?

If you agree to take part in the study, we will invite you to meet a researcher to complete a cognitive screening test to assess your thinking. We might also ask you to complete additional neuropsychological tests that assess your thinking in more detail, and/or take part in EEG recording sessions which will take place in St. James's Hospital.

What will happen to me if I agree to take part?

If you agree to take part in this study, we will firstly explain the study in greater detail and, if you are willing to participate, you will be invited to sign the consent form. By consenting to take part in this research, you are providing permission for the clinical research team to access your Hospital medical records.

This study involves completing a brief cognitive screening test which will assess your thinking. You will meet with a member of the research team who will complete this paper and pencil test with you.

You may also be invited to complete additional cognitive tests that will assess your thinking in greater detail. These paper and pencil tests will take approximately 2 hours to complete and you will able to take breaks whenever you would like to. We will arrange a suitable appointment time to undergo these tests and will do our best to facilitate you with a suitable time and place.

As part of this study, you may also be invited to take part in EEG recording sessions. Each recording session lasts approximately 2 and a half hours and will be carried out at St. James's Hospital – Clinical Research Facility. In each EEG recording session, we will place a cap on your head. Electrodes will be placed into holes in the cap over your scalp to record the activity of your brain. 8 electrodes will be placed around the ears and eyes to record background activity. We will place some conductive gel between the electrodes and your skin. We will then do the recording while you are at rest, watching a movie or carrying out a mental test. The experimenter will tell you the details of the instructions in advance. You may need to wash your head after the experiment to remove the conductive gels. Showering facilities are available on site. There is no drug, intervention or stimulation involved in this study.

We would like to repeat these tests 3 times at 4-6 month intervals to gain a better understanding of MS as the disease changes over time. However, you are free to withdraw from the study at any stage or reduce your involvement, without reason, and this will not affect your medical care.

What happens if I do not agree to take part?

Your decision to participate is entirely up to you. Participants are free to not participate in the study without giving a reason and without risking loss of present or future care you would otherwise expect to receive.

Video/and or Audio recordings?

Assessments will not be video or audio recorded for this research study.

What are the benefits?

While there is no direct and immediate benefit to you in participating, this study is hoping to benefit patients with MS by increasing our understanding of the cognitive changes that take place over the course of MS and thus identify their needs.

What are the risks?

There are minimal risks anticipated from taking part in this research study, as the procedure and devices are safe and commonly used. If you do become fatigued while completing the neuropsychological tests and questionnaires you will be offered to take refreshment breaks at any time. In terms of the EEG recordings, in the unlikely event that you show allergic reactions to the gels, the experiment will stop and we will provide medical advice to treat the reaction. However, there may be discomforts for you during the recordings. You may find the recordings to be boring, tiring and fatiguing as it includes sitting in a chair for 1-2 hours. The conductive gel used to attach the electrodes to your skin may feel cold or warm, cause wet and mild itching sensation, and will need washing to remove after the experiment. The removal of medicine tapes around the face and eyes may be slightly painful or uncomfortable for some patients. If at any time you feel that your participation in this study has become unduly stressful, you are free to discontinue. This will not affect in any way the quality of care that you receive.

There is no intention to look for diseases using the recorded data. In the unlikely case of incidental findings in the EEG recordings that may be an indirect sign of a previously unknown disease, you will be asked for permission to discuss the findings with a neurologist, your GP or other appropriate doctor.

Participants are also free to not participate or to withdraw from the study at any time if they choose to do so without giving a reason and without risking loss of present or future care you would otherwise expect to receive.

What if something goes wrong when I'm taking part in this study?

We do not anticipate anything will go wrong. However, if you begin to feel distressed or unwell during the study and feel you would like to discontinue your participation, you are free to do so at any time without any penalty and without giving a reason. If you have any other concerns you would like to raise, either during or after the study, participants will also be provided with contact details of the Principal Investigator, Prof. Orla Hardiman, Consultant Neurologist.

Will it cost me anything to take part?

We will reimburse you for any reasonable and vouched travel expenses, usually up to a value of €50. There will be no other costs associated with your participation in this study.

Is the study confidential?

All information which is collected about you during the course of the research will be kept strictly confidential.

During testing, your data will be "coded" by the researcher, meaning that you will be allocated a unique identification code which will be used in place of your name on our

testing materials and computer databases. The 'key' that matches your name and unique identification code will be retained by the Research Manager (Mr. Mark Heverin, Academic Unit of Neurology), on behalf of the Principal Investigator, and will be stored on a password-protected, encrypted database in the Academic Unit of Neurology, Trinity College Dublin.

Paper files will be securely transported from the site of testing and will be stored in a locked cabinet in a dedicated office in the Academic Unit of Neurology, Trinity College Dublin. A log book will be retained by the Data Manager and those accessing the data will be required to sign to access the files. Electronic data will be securely transported from the site of testing and will be encrypted, password protected and held on a dedicated computer in a locked office in the Academic Unit of Neurology, Trinity College Dublin. Only staff members with login credentials will be able to access the computer. The login credentials will change every 6 months, and those accessing the computer will be tracked.

Your GP will not receive any of the details of the information that you provide unless you request that it be sent to him/her.

You will not be given direct feedback on the results of your individual assessments. Any participant who wishes to find out about the results of the study will be provided with a report on the publication of results. If participants express concern as to their cognitive functioning, contact details for the Principal Investigator, Prof. Orla Hardiman, will be provided. There is no intention to look for diseases using the recorded data. In the unlikely case of incidental findings in the EEG recordings that may be an indirect sign of a previously unknown disease, you will be asked for permission to discuss the findings with a neurologist, your GP or other appropriate doctor. Results of this study will be communicated to other scientists through peer-reviewed academic journals and conference presentations. In all cases, data will be anonymous and your name and personal details will not be included.

Information gathered from this study will be stored for 10 years to allow us to perform additional analyses with other scientists interested in understanding and finding treatments for thinking problems in MS. If you agree, we will also use information we have gathered from this study to in future studies with scientists interested in Multiple Sclerosis, subject to appropriate future approval by the relevant Research Ethics committees.

Data Protection

1. We will be using your personal information in our research study to help us understand changes in thinking in MS.
2. We will be processing your data for legitimate interest and for scientific research purposes under Article 6 and 9 of the General Data Protection Regulation 2016.
3. Only members of the research team, under the approval and supervision of Prof. Orla Hardiman, Principal Investigator will have access to research participants' information.

4. Hard-copy data will be retained for a period of time after the study has completed to comply with publishing guidelines. The length of time is dependent of the specific journal in which the data is published, but will likely be 10 years. Electronic data will be retained in Trinity College Dublin.

5. As your hard-copy data will be coded at the time of testing we do not envisage any situation where a data breach could cause harm. The data contained on any computers will also be coded and the key to link your name with the number will be kept separate. In the unlikely event of a data breach, it will only be possible for someone to see your raw test scores which will not be meaningful to an untrained third party.

6. You have a right to withdraw your consent at any stage during the research study without giving a reason and without penalty. You can inform any member of the research team of your decision to withdraw at any time and they will accommodate your request.

7. You have the right to lodge a complaint about the research study with the Data Protection Commissioner.

8. You have a right to request access to your data and a copy of it, unless your request would make it impossible or make it very difficult to conduct the research.

9. You have a right to restrict or object to processing, unless your request would make it impossible or make it very difficult to conduct the research.

10. You have a right to have any inaccurate information about you corrected or deleted, unless your request would make it impossible or make it very difficult to conduct the research.

11. You have a right to have your personal data deleted, unless your request would make it impossible or make it very difficult to conduct the research

12. You have a right to data portability, meaning they you have the right to move your data from one controller to another in a readable format.

13. There will be no automated decision making or profiling using your data.

14. If automated decision making or profiling were to occur, you have the right to object to this if you wish.

15. You will be informed if we intend to further process your personal data and you will be provided with information on that other purpose.

16. You will be informed if we wish to transfer your data to a country outside of the EU or an international organisation and will be advised on the safeguards you have in place

to protect your data. We do not foresee any situation where we will be transferring data outside the EU.

Consent to Further Contact

In addition to seeking consent for your data to be used for the purposes of the current research study, we are also seeking your permission to contact you about possible future research related and unrelated to the current study for which you may be eligible.

Consent to Future Uses

If you choose to take part, we are also seeking your permission for your data to be used in future research projects, either related or unrelated to the current study. This would involve giving permission for these research projects, as yet unknown, to use your data in a coded or anonymised format without future consent being required. The use of this data in future research projects is subject to appropriate future approval by the relevant Research Ethics committees.

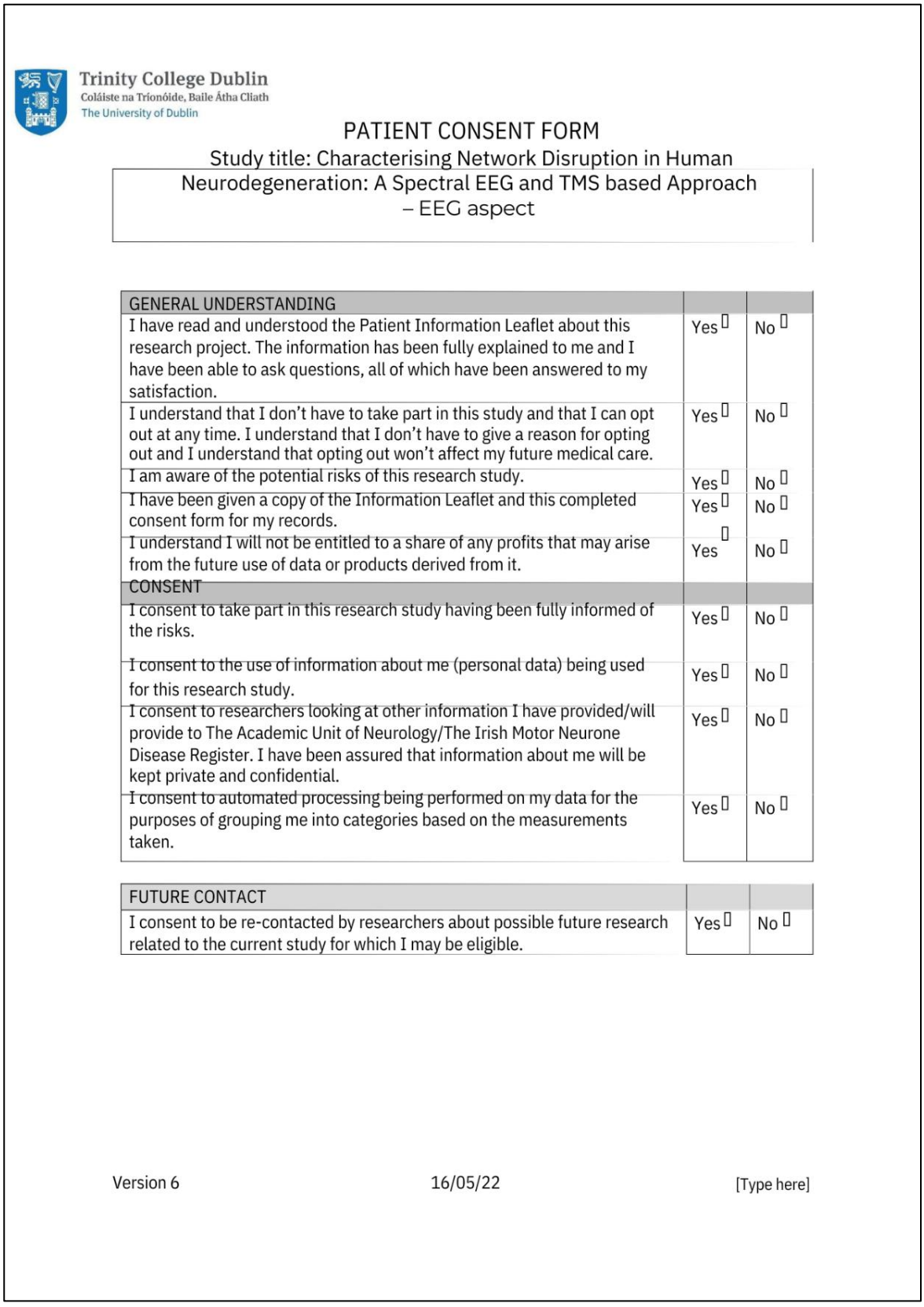
Where can I get further information?

If you have any questions about the study now, or in the future, please contact the Principal Investigator, Prof. Orla Hardiman via the Research Manager Mr. Mark Heverin.

Name: Mr. Mark Heverin
Position: Research Manager
Address: Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Trinity College Dublin
Email: mark.heverin@tcd.ie
Phone: +353 1896 4376

Consent forms

Patient consent form (TCD/SJH)



Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

PATIENT CONSENT FORM

Study title: Characterising Network Disruption in Human Neurodegeneration: A Spectral EEG and TMS based Approach – EEG aspect

GENERAL UNDERSTANDING		
I have read and understood the Patient Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	Yes ☐	No ☐
I understand that I don't have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical care.	Yes ☐	No ☐
I am aware of the potential risks of this research study.	Yes ☐	No ☐
I have been given a copy of the Information Leaflet and this completed consent form for my records.	Yes ☐	No ☐
I understand I will not be entitled to a share of any profits that may arise from the future use of data or products derived from it.	Yes ☐	No ☐
CONSENT		
I consent to take part in this research study having been fully informed of the risks.	Yes ☐	No ☐
I consent to the use of information about me (personal data) being used for this research study.	Yes ☐	No ☐
I consent to researchers looking at other information I have provided/will provide to The Academic Unit of Neurology/The Irish Motor Neurone Disease Register. I have been assured that information about me will be kept private and confidential.	Yes ☐	No ☐
I consent to automated processing being performed on my data for the purposes of grouping me into categories based on the measurements taken.	Yes ☐	No ☐

FUTURE CONTACT		
I consent to be re-contacted by researchers about possible future research related to the current study for which I may be eligible.	Yes ☐	No ☐

Version 6 16/05/22 [Type here]

STORAGE AND FUTURE USE OF INFORMATION *		
I agree for the information I provide in this study (personal data) to be used for other future research related to ALS, FTD, MS, PPS and/or HD by not for profit organisations (research institutes, hospitals etc.) without further consent being required but only if the research is approved by a Research Ethics Committee.	Yes ☐	No ☐
I agree for data I provide to be used for future research projects related to ALS, FTD, MS, PPS and/or HD which may be carried out by researchers working for commercial/pharmaceutical companies but only if the research is approved by a Research Ethics Committee	Yes ☐	No ☐
I agree for data I provide to be used for future neurological research relatedto ALS, FTD, MS, PPS and/or HD to be performed outside of the EEA.	Yes ☐	No ☐
I give permission for my contact details to be kept on file by the research team.	Yes ☐	No ☐

*See "Consent to Future Uses" section of information leaflet for more information

Patient Name (Block Capitals)	Patient Signature	Date

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals)	Qualifications	Signature	Date

Control consent form (TCD/SJH)

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

CONTROL CONSENT FORM

Study title: Characterising Network Disruption in Human Neurodegeneration: A Spectral EEG and TMS based Approach – EEG aspect

GENERAL UNDERSTANDING		
I have read and understood the Control Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	Yes ☐	No ☐
I understand that I don't have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical care.	Yes ☐	No ☐
I am aware of the potential risks of this research study.	Yes ☐	No ☐
I have been given a copy of the Information Leaflet and this completed consent form for my records.	Yes ☐	No ☐
I understand I will not be entitled to a share of any profits that may arise from the future use of data or products derived from it.	Yes ☐	No ☐
CONSENT		
I consent to take part in this research study having been fully informed of the risks.	Yes ☐	No ☐
I consent to the use of information about me (personal data) being used for this research study.	Yes ☐	No ☐
I consent to researchers looking at other information I have provided/will provide to The Academic Unit of Neurology. I have been assured that information about me will be kept private and confidential.	Yes ☐	No ☐
I consent to automated processing being performed on my data for the purposes of grouping me into categories based on the measurements taken.	Yes ☐	No ☐

FUTURE CONTACT		
I consent to be re-contacted by researchers about possible future research related to the current study for which I may be eligible.	Yes ☐	No ☐

Version 6 16/05/22 [Type here]

STORAGE AND FUTURE USE OF INFORMATION *		
I agree for the information I provide in this study (personal data) to be used for other future research related to ALS, FTD, MS, PPS and/or HD by not for profit organisations (research institutes, hospitals etc.) without further consent being required but only if the research is approved by a Research Ethics Committee.	Yes ☐	No ☐
I agree for data I provide to be used for future research projects related to ALS, FTD, MS, PPS and/or HD which may be carried out by researchers working for commercial/pharmaceutical companies but only if the research is approved by a Research Ethics Committee	Yes ☐	No ☐
I agree for data I provide to be used for future neurological research relatedto ALS, FTD, MS, PPS and/or HD to be performed outside of the EEA.	Yes ☐	No ☐
I give permission for my contact details to be kept on file by the research team.	Yes ☐	No ☐

*See "Consent to Future Uses" section of information leaflet for more information

Control Name (Block Capitals)	Control Signature	Date

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals)	Qualifications	Signature	Date

Patient consent form (BH)

PATIENT CONSENT FORM

Study title: A Multidisciplinary Study of Cognition in Multiple Sclerosis

I have read and understood the Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	Yes ☐	No ☐
I understand that I don't have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical care.	Yes ☐	No ☐
I am aware of the potential risks, benefits and alternatives of this research study.	Yes ☐	No ☐
I give permission for researchers to look at my medical records to get information. I have been assured that information about me will be kept private and confidential.	Yes ☐	No ☐
I have been given a copy of the Information Leaflet and this completed consent form for my records.	Yes ☐	No ☐
I consent to take part in this research study having been fully informed of the risks, benefits and alternatives.	Yes ☐	No ☐
I give informed explicit consent to have my data processed as part of this research study.	Yes ☐	No ☐
I consent to be contacted by researchers as part of this research study.	Yes ☐	No ☐

FUTURE CONTACT		
I consent to be re-contacted by researchers about possible future research related to the current study for which I may be eligible.	Yes ☐	No ☐
I consent to be re-contacted by researchers about possible future research unrelated to the current study for which I may be eligible.	Yes ☐	No ☐

Version 1 02/11/2018 Page 1

STORAGE AND FUTURE USE OF INFORMATION		
I give permission for material/data to be stored for possible future research related to the current study without further consent being required but only if the research is approved by a Research Ethics Committee.	Yes ☐	No ☐
I give permission for material/data to be stored for possible future research unrelated to the current study without further consent being required but only if the research is approved by a Research Ethics Committee.	Yes ☐	No ☐

Patient Name (Block Capitals) | Patient Signature | Date

Legal Representative/Guardian Name | Legal Representative/Guardian Signature | Date

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals) | Qualifications | Signature | Date

3 copies to be made: 1 for patient, 1 for PI and 1 for hospital records.

Control consent form (BH)

HEALTHY CONTROL CONSENT FORM

Study title: A Multidisciplinary Study of Cognition in Multiple Sclerosis

I have read and understood the Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	Yes ☐	No ☐
I understand that I don't have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out and I understand that opting out won't affect my future medical care.	Yes ☐	No ☐
I am aware of the potential risks, benefits and alternatives of this research study.	Yes ☐	No ☐
I have been given a copy of the Information Leaflet and this completed consent form for my records.	Yes ☐	No ☐
I consent to take part in this research study having been fully informed of the risks, benefits and alternatives.	Yes ☐	No ☐
I give informed explicit consent to have my data processed as part of this research study.	Yes ☐	No ☐
I consent to be contacted by researchers as part of this research study.	Yes ☐	No ☐

FUTURE CONTACT		
I consent to be re-contacted by researchers about possible future research related to the current study for which I may be eligible.	Yes ☐	No ☐
I consent to be re-contacted by researchers about possible future research unrelated to the current study for which I may be eligible.	Yes ☐	No ☐

Version 1 02/11/2018 Page 1

STORAGE AND FUTURE USE OF INFORMATION		
I give permission for material/data to be stored for possible future research related to the current study ~~without further consent being required~~ but only if the research is approved by a Research Ethics Committee.	Yes ☐	No ☐
I give permission for material/data to be stored for ~~possible future research unrelated~~ to the current study ~~without further consent~~ being required but only if the research is approved by a Research Ethics Committee.	Yes ☐	No ☐

_____ | | |

Name (Block Capitals) | Signature | Date

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above patient the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned them.

Name (Block Capitals)	Qualifications	Signature	Date

3 copies to be made: 1 for patient, 1 for PI and 1 for hospital records.

Page 2

Appendix E: Questionnaires

MSNQ

MSNQ Patient

Name: _____

Date: _____

Circle one: MALE / FEMALE

INSTRUCTIONS:
The following questions ask about problems that you may experience. Rate how often these problems occur **AND** how severe they are. Base your ratings on how you have been over the **last three months**.

Please check the appropriate box.

	Very often, very disruptive (4)	Quite often, interferes w/ life (3)	Occasionally, seldom a problem (2)	Very rarely, no problem (1)	Never, does not occur (0)
1. Are you easily distracted?					
2. Do you lose your thoughts while listening to somebody speak?					
3. Are you slow when trying to solve problems?					
4. Do you forget appointments?					
5. Do you forget what you read?					
6. Do you have trouble describing shows or programs recently watched?					
7. Do you need to have instructions repeated?					
8. Do you have to be reminded to do tasks?					
9. Do you forget errands that were planned?					
10. Do you have difficulty answering questions?					
11. Do you have difficulty keeping track of two things at once?					
12. Do you miss the point of what someone is trying to say?					
13. Do you have difficulty controlling impulses?					
14. Do you laugh or cry with little cause?					
15. Do you talk excessively or focus too much on your own interests?					

HADS

		Yes definitely	Yes sometimes	No, not much	No, not at all
1.	I feel tense or wound up	3	2	1	0
2.	I still enjoy things I used to enjoy	0	1	2	3
3.	I get a sort of frightened feeling as if something awful is about to happen	3	2	1	0
4.	I can laugh and see the funny side of things	0	1	2	3
5.	Worrying thoughts go through my mind	3	2	1	0
6.	I feel cheerful	3	2	1	0
7.	I can sit at ease and feel relaxed	0	1	2	3
8.	I feel as if I am slowed down	3	2	1	0
9.	I get a sort of frightened feeling like 'butterflies' in the stomach	0	1	2	3
10.	I have lost interest in my appearance	3	2	1	0
11.	I feel restless as if I have to be on the move	3	2	1	0
12.	I look forward with enjoyment to things	0	1	2	3
13.	I get sudden feelings of panic	3	2	1	0
14.	I can enjoy a good book, radio or TV program	0	1	2	3

EHI

Edinburgh Handedness Inventory1

Participant ID: _____

Please indicate with a one (1) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put a two (2).

If you are indifferent, put a one in each column (1|1).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Stop here.		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH – LH =	
Result	R = (D / CT)x100 =	
Interpretation: (Left Handed:R<40) (Ambidextrous: -40>R<+40) (Right Handed: R > +40)		

[1]Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia, 9, 97-113.

Appendix F: Neuropsychological battery

- Test of Premorbid Functioning (TOPF)
- Wechsler Abbreviated Scale of Intelligence (WASI-II)
- F-A-S test
- Semantic Fluency Test
- Digit Span Test
- CAVLT-II
- Logical Memory Test
- Brief visuospatial memory test (BVMT-R)
- Symbol Digit Modalities Test (SDMT)
- Color Word Interference Test (CWIT)
- Brixton Spatial Anticipation Test
- Reading the Mind in the Eyes Test (RMET)
- Boston Naming Test (BNT)
- Action Naming Test (ANT)

Appendix G: Supplementary Data

Supplementary Table 1. ICC values for SART ERPs

		P2						N2						P3					
		ICC	LB	UB	F	df1	df2	p	ICC	LB	UB	F	df1	df2	p	ICC	LB	UB	F	df1	df2	p
Amplitude of peak	Go	0.93	0.69	0.98	12.18	9	9	**<0.0005**	0.90	0.59	0.98	9.97	8	9	**0.001**	0.90	-0.14	0.99	9.25	3	4	**0.030**
	No-Go	0.79	0.02	0.95	4.46	8	8	**0.024**	0.34	-1.68	0.86	1.55	7	8	0.277	0.79	-0.13	0.97	5.48	5	6	**0.035**
Mean amplitude	Go	0.91	0.65	0.98	10.60	9	10	**0.001**	0.93	0.70	0.98	12.49	9	9	**<0.0005**	0.79	0.10	0.95	4.43	9	9	**0.018**
	No-Go	0.69	-0.19	0.92	3.20	9	10	**0.043**	0.64	-0.50	0.91	2.69	9	9	**0.074**	0.85	0.38	0.96	6.26	9	9	**0.006**
Latency of peak	Go	0.92	0.67	0.98	11.47	9	9	**0.001**	0.98	0.86	1.00	70.12	8	5	**<0.0005**	0.94	0.38	1.00	16.02	3	4	**0.011**
	No-Go	0.63	-0.32	0.91	3.25	8	9	**0.067**	0.94	0.73	0.99	16.50	7	8	**<0.0005**	0.95	0.70	0.99	20.78	5	6	**0.001**
Mean Latency	Go	0.81	0.20	0.95	4.89	9	9	**0.013**	0.90	0.57	0.98	9.60	8	9	**0.001**	0.93	0.30	1.00	14.20	3	4	**0.013**
	No-Go	0.95	0.79	0.99	18.77	8	9	**<0.0005**	0.81	0.13	0.96	6.42	7	6	**0.016**	0.96	0.67	1.00	40.77	5	4	**0.002**
Area under component	Go	0.87	0.48	0.97	7.26	9	9	**0.003**	0.89	0.52	0.98	8.52	8	8	**0.003**	0.92	0.23	0.99	15.65	3	4	**0.015**
	No-Go	0.83	0.22	0.96	5.52	8	9	**0.013**	0.16	-3.19	0.83	1.19	7	7	0.407	0.75	-0.30	0.96	4.69	5	5	**0.051**
Amplitude of peak	Go	0.96	0.80	0.99	20.22	8	9	**<0.0005**	0.97	0.81	0.99	38.31	6	6	**<0.0005**	0.91	0.47	0.98	9.93	6	6	**0.006**
	No-Go	0.97	0.84	0.99	27.68	7	9	**<0.0005**	0.93	0.65	0.99	13.03	7	7	**0.001**	0.89	0.52	0.97	7.99	9	9	**0.002**
Mean amplitude	Go	0.98	0.91	0.99	39.03	9	9	**<0.0005**	0.93	0.71	0.98	12.94	9	10	**<0.0005**	0.96	0.85	0.99	24.06	9	9	**<0.0005**
	No-Go	0.97	0.87	0.99	27.12	9	9	**<0.0005**	0.90	0.60	0.98	9.40	9	9	**0.001**	0.90	0.58	0.97	8.94	9	9	**0.002**
Latency of peak	Go	0.94	0.72	0.99	14.44	8	9	**0.001**	0.96	0.82	0.99	31.04	6	7	**<0.0005**	-2.03	13.47	0.63	0.43	6	6	0.839
	No-Go	0.95	0.72	0.99	24.14	7	9	**0.001**	0.95	0.78	0.99	24.78	7	7	**<0.0005**	0.84	0.34	0.96	5.87	9	9	**0.007**
Mean Latency	Go	0.69	-0.38	0.93	3.10	8	9	**0.059**	0.92	0.30	0.99	21.90	6	3	**0.010**	0.85	0.21	0.97	6.53	6	7	**0.013**
	No-Go	0.91	0.52	0.98	9.64	7	9	**0.004**	0.92	0.58	0.98	10.74	7	7	**0.002**	0.86	0.41	0.97	6.50	9	9	**0.005**
Area under component	Go	0.95	0.80	0.99	19.70	8	9	**<0.0005**	0.98	0.86	1.00	35.58	6	6	**<0.0005**	0.94	0.66	0.99	15.51	6	6	**0.002**
	No-Go	0.94	0.67	0.99	13.70	7	9	**0.001**	0.92	0.62	0.98	11.96	7	8	**0.001**	0.90	0.59	0.97	9.13	9	9	**0.001**
Amplitude of peak	Go	0.89	0.31	0.98	8.75	5	9	**0.011**	0.92	-0.27	1.00	10.73	3	3	**0.033**	0.95	0.74	0.99	19.40	6	7	**<0.0005**
	No-Go	0.49	-4599.89	0.95	1.79	4	9	0.291	0.84	0.15	0.97	6.08	6	7	**0.017**	0.94	0.76	0.98	15.20	9	10	**<0.0005**
Mean amplitude	Go	0.90	0.57	0.97	8.76	9	9	**0.002**	0.92	0.68	0.98	11.99	9	10	**<0.0005**	0.95	0.80	0.99	18.29	9	9	**<0.0005**
	No-Go	0.84	0.38	0.96	6.80	9	9	**0.004**	0.88	0.53	0.97	8.08	9	10	**0.002**	0.96	0.83	0.99	21.07	9	9	**<0.0005**
Latency of peak	Go	0.91	0.29	0.99	16.77	5	9	**0.011**	0.85	-8.18	0.99	5.12	3	3	**0.107**	0.97	0.66	0.99	51.17	6	3	**0.002**
	No-Go	0.86	-0.09	0.99	6.99	4	9	**0.029**	0.94	0.61	0.99	13.62	6	6	**0.003**	0.61	-0.73	0.91	2.44	9	9	**0.098**
Mean Latency	Go	0.43	-11.09	0.93	1.63	5	9	0.301	0.55	-1.14	0.97	2.73	3	4	0.186	0.93	0.37	0.99	23.10	6	3	**0.008**
	No-Go	0.93	0.24	0.99	12.05	4	9	**0.017**	0.74	-0.89	0.96	3.42	6	6	**0.079**	0.57	-0.43	0.89	2.53	9	9	**0.087**
Area under component	Go	0.76	-0.54	0.97	4.09	5	9	**0.060**	0.92	-0.74	1.00	10.17	3	3	**0.043**	0.95	0.74	0.99	19.14	6	7	**0.001**
	No-Go	-4.26	6.49	0.74	0.34	4	9	0.838	0.91	0.53	0.98	12.52	6	6	**0.003**	0.96	0.83	0.99	21.07	9	9	**<0.0005**
Amplitude of peak	Go	0.86	0.18	0.98	8.57	5	9	**0.015**	0.92	-1.23	1.00	10.22	2	3	**0.054**	0.77	-0.49	0.96	3.97	6	6	**0.055**
	No-Go	0.17	-0.97	0.97	1.37	2	9	0.378	0.84	0.00	1.00	2826.57	2	1	**0.013**	0.93	0.73	0.98	14.20	9	10	**<0.0005**
Mean amplitude	Go	0.89	0.57	0.97	8.77	9	9	**0.001**	0.92	0.70	0.98	12.45	9	9	**<0.0005**	0.82	0.24	0.96	5.16	9	9	**0.011**
	No-Go	0.89	0.57	0.97	9.74	9	9	**0.001**	0.93	0.73	0.98	17.99	9	8	**<0.0005**	0.91	0.66	0.98	10.79	9	10	**0.001**
Latency of peak	Go	0.98	0.84	1.00	37.52	5	9	**<0.0005**	0.93	20.30	1.00	9.87	2	2	**0.087**	0.99	0.97	1.00	175.95	6	7	**<0.0005**
	No-Go	0.92	6.74	1.00	8.44	2	9	**0.106**	0.48	3.80	0.99	1.66	2	2	0.369	0.87	0.48	0.97	7.19	9	10	**0.003**
Mean Latency	Go	0.92	0.16	0.99	25.62	5	9	**0.016**	0.93	-1.72	1.00	11.20	2	3	**0.055**	0.94	0.50	0.99	24.35	6	4	**0.004**
	No-Go	0.79	-0.29	0.99	14.96	2	9	**0.098**	0.79	6.24	0.99	3.71	2	2	0.192	0.90	0.63	0.98	10.07	9	10	**0.001**
Area under component	Go	0.86	0.14	0.98	9.12	5	9	**0.017**	0.91	-0.56	1.00	10.96	2	3	**0.043**	0.79	-0.28	0.96	4.43	6	6	**0.042**
	No-Go	0.19	-0.11	0.93	3.24	2	9	0.268	0.91	-0.17	1.00	47.20	2	1	**0.056**	0.91	0.66	0.98	10.79	9	10	**0.001**

Supplementary Table 2. Correlations between P2 features and neuropsychological screening tools. No significant associations were seen between P2 waveform features and the MSNQ, HADS-A, or HADS-D.

				MSNQ		HADS-A		HADS-D	
				rho	p	rho	p	rho	p
P2	Go	peak amplitude	Fz	0.02	0.890	-0.01	0.933	-0.03	0.778
			FCz	-0.03	0.775	0.02	0.879	-0.15	0.213
			Cz	-0.14	0.283	0.10	0.413	-0.11	0.387
			Pz	-0.14	0.263	0.15	0.242	0.02	0.879
		mean amplitude	Fz	0.10	0.353	-0.08	0.454	-0.08	0.495
			FCz	0.04	0.719	-0.12	0.299	-0.22	0.046
			Cz	-0.02	0.855	-0.03	0.817	-0.22	0.046
			Pz	-0.12	0.287	0.14	0.199	-0.04	0.707
		standard latency	Fz	0.11	0.330	-0.12	0.318	0.04	0.750
			FCz	0.14	0.253	-0.07	0.580	0.01	0.912
			Cz	-0.04	0.768	-0.10	0.452	0.01	0.920
			Pz	-0.01	0.946	0.15	0.235	0.04	0.730
		amplitude-weighted latency	Fz	0.20	0.087	-0.09	0.420	0.12	0.313
			FCz	0.13	0.272	-0.02	0.864	0.05	0.663
			Cz	0.01	0.917	0.13	0.288	0.07	0.563
			Pz	-0.05	0.689	0.16	0.194	-0.14	0.279
		area	Fz	0.11	0.360	0.00	0.998	0.00	0.994
			FCz	0.03	0.781	0.03	0.782	-0.14	0.240
			Cz	-0.07	0.569	0.14	0.269	-0.10	0.422
			Pz	-0.08	0.507	0.20	0.109	-0.06	0.617
	NoGo	peak amplitude	Fz	0.04	0.729	0.05	0.680	-0.03	0.768
			FCz	-0.01	0.924	0.12	0.316	-0.07	0.567
			Cz	-0.06	0.647	0.15	0.239	0.04	0.748
			Pz	-0.08	0.522	0.27	0.036	0.03	0.825
		mean amplitude	Fz	0.06	0.594	-0.17	0.136	-0.17	0.136
			FCz	-0.04	0.755	-0.17	0.137	-0.27	0.016
			Cz	0.10	0.380	0.08	0.491	-0.14	0.219
			Pz	-0.09	0.415	0.18	0.115	-0.04	0.746
		standard latency	Fz	0.20	0.083	0.00	0.968	0.18	0.121
			FCz	0.20	0.093	0.01	0.930	0.22	0.061
			Cz	0.17	0.166	0.10	0.429	0.10	0.428
			Pz	-0.09	0.475	0.11	0.403	-0.02	0.852
		amplitude-weighted latency	Fz	0.25	0.029	-0.02	0.896	0.09	0.448
			FCz	0.16	0.166	0.00	0.966	0.15	0.191
			Cz	0.16	0.210	0.18	0.156	0.06	0.626
			Pz	-0.09	0.505	0.20	0.123	-0.08	0.554
		area	Fz	0.08	0.471	-0.01	0.925	-0.10	0.403
			FCz	0.00	0.988	0.03	0.798	-0.16	0.166
			Cz	-0.02	0.871	0.12	0.318	-0.03	0.825
			Pz	-0.10	0.455	0.26	0.039	-0.09	0.485

Supplementary Table 3. Correlations between N2 features and neuropsychological screening tools. No significant associations were seen between N2 waveform features and the MSNQ, HADS-A, or HADS-D.

				MSNQ		HADS-A		HADS-D	
				rho	p	rho	p	rho	p
N2	Go	peak amplitude	Fz	-0.03	0.810	-0.24	0.044	-0.25	0.038
			FCz	-0.03	0.802	-0.31	0.010	-0.28	0.019
			Cz	0.08	0.519	-0.16	0.224	-0.23	0.081
			Pz	-0.08	0.608	-0.09	0.520	-0.15	0.293
		mean amplitude	Fz	0.12	0.286	-0.07	0.557	-0.07	0.563
			FCz	0.00	0.968	-0.10	0.369	-0.21	0.057
			Cz	-0.04	0.753	-0.03	0.794	-0.20	0.074
			Pz	-0.15	0.184	0.11	0.323	-0.06	0.623
		standard latency	Fz	0.13	0.267	0.07	0.563	0.07	0.586
			FCz	0.24	0.047	0.05	0.711	0.05	0.710
			Cz	0.10	0.469	0.13	0.311	0.20	0.128
			Pz	0.21	0.143	0.06	0.688	0.13	0.361
		amplitude-weighted latency	Fz	0.03	0.772	-0.08	0.516	0.00	0.996
			FCz	0.21	0.087	-0.01	0.950	0.07	0.583
			Cz	0.11	0.383	0.11	0.419	0.07	0.590
			Pz	0.25	0.089	0.07	0.647	0.12	0.419
		area	Fz	-0.02	0.880	-0.14	0.239	-0.18	0.129
			FCz	-0.07	0.579	-0.26	0.033	-0.29	0.018
			Cz	0.02	0.864	-0.13	0.339	-0.22	0.095
			Pz	-0.10	0.481	-0.07	0.614	-0.12	0.422
	NoGo	peak amplitude	Fz	-0.09	0.483	-0.20	0.124	-0.14	0.285
			FCz	-0.10	0.432	-0.20	0.100	-0.13	0.281
			Cz	0.05	0.663	-0.04	0.761	-0.11	0.374
			Pz	-0.10	0.467	-0.18	0.180	-0.26	0.048
		mean amplitude	Fz	0.05	0.651	-0.13	0.265	-0.11	0.319
			FCz	-0.07	0.522	-0.11	0.349	-0.16	0.144
			Cz	0.04	0.753	0.13	0.245	-0.04	0.731
			Pz	-0.09	0.442	0.18	0.107	-0.03	0.812
		standard latency	Fz	0.03	0.849	-0.13	0.325	-0.15	0.249
			FCz	0.09	0.484	-0.02	0.897	-0.20	0.101
			Cz	0.04	0.773	-0.02	0.902	-0.12	0.323
			Pz	0.01	0.939	-0.05	0.708	0.06	0.634
		amplitude-weighted latency	Fz	0.00	0.989	-0.20	0.135	-0.24	0.065
			FCz	0.02	0.864	-0.10	0.401	-0.27	0.022
			Cz	0.00	0.981	-0.06	0.635	-0.21	0.085
			Pz	0.00	0.995	-0.05	0.704	0.00	0.970
		area	Fz	-0.06	0.649	-0.14	0.307	-0.12	0.370
			FCz	-0.13	0.279	-0.20	0.102	-0.16	0.172
			Cz	0.04	0.773	0.05	0.691	-0.10	0.403
			Pz	-0.19	0.154	-0.09	0.493	-0.27	0.038

Supplementary Table 4. Correlations between P3 features and neuropsychological screening tools. No significant associations were seen between P3 waveform features and the MSNQ, HADS-A, or HADS-D.

				MSNQ		HADS-A		HADS-D	
				rho	p	rho	p	rho	p
P3	Go	peak amplitude	Fz	0.04	0.764	0.22	0.103	0.17	0.221
			FCz	-0.03	0.838	0.07	0.568	0.01	0.961
			Cz	-0.12	0.319	-0.07	0.549	-0.10	0.404
			Pz	-0.21	0.070	-0.09	0.477	-0.05	0.687
		mean amplitude	Fz	0.15	0.171	0.22	0.047	0.02	0.842
			FCz	-0.09	0.444	0.05	0.657	-0.13	0.265
			Cz	-0.18	0.106	-0.08	0.457	-0.18	0.101
			Pz	-0.14	0.208	-0.21	0.054	-0.11	0.319
		standard latency	Fz	0.23	0.099	0.25	0.065	0.04	0.767
			FCz	0.19	0.127	0.06	0.621	0.03	0.791
			Cz	0.17	0.175	-0.04	0.757	-0.14	0.265
			Pz	-0.05	0.689	-0.23	0.049	-0.12	0.317
		amplitude-weighted latency	Fz	0.32	0.019	0.21	0.131	0.15	0.294
			FCz	0.28	0.023	0.14	0.276	0.08	0.544
			Cz	0.06	0.646	-0.01	0.923	0.04	0.726
			Pz	-0.10	0.399	-0.14	0.253	-0.13	0.291
		area	Fz	0.05	0.741	0.18	0.186	0.14	0.329
			FCz	0.01	0.912	0.09	0.489	-0.05	0.704
			Cz	-0.07	0.584	-0.07	0.584	-0.13	0.299
			Pz	-0.16	0.179	-0.21	0.072	-0.11	0.368
	NoGo	peak amplitude	Fz	0.19	0.123	0.05	0.651	0.01	0.924
			FCz	-0.03	0.820	0.03	0.803	0.01	0.949
			Cz	-0.17	0.173	-0.03	0.815	0.05	0.684
			Pz	-0.10	0.396	-0.06	0.579	-0.13	0.262
		mean amplitude	Fz	0.04	0.699	0.07	0.514	-0.01	0.957
			FCz	-0.09	0.401	0.04	0.696	-0.08	0.490
			Cz	-0.16	0.166	0.00	0.965	-0.10	0.370
			Pz	-0.11	0.309	-0.07	0.537	-0.19	0.096
		standard latency	Fz	0.18	0.145	-0.07	0.538	-0.03	0.829
			FCz	0.20	0.089	-0.07	0.554	-0.06	0.607
			Cz	0.13	0.308	-0.06	0.643	-0.02	0.843
			Pz	0.06	0.588	0.05	0.692	0.10	0.412
		amplitude-weighted latency	Fz	0.32	0.007	0.02	0.839	0.01	0.915
			FCz	0.25	0.033	-0.03	0.783	-0.03	0.831
			Cz	0.18	0.138	-0.14	0.271	-0.06	0.619
			Pz	0.00	0.976	-0.19	0.106	-0.13	0.260
		area	Fz	0.18	0.129	0.00	0.973	-0.10	0.411
			FCz	-0.01	0.966	0.01	0.930	-0.05	0.647
			Cz	-0.22	0.066	-0.08	0.536	-0.09	0.478
			Pz	-0.10	0.403	-0.11	0.365	-0.14	0.214

Supplementary Table 5. Correlations between P2 characteristics and SART accuracy. *No significant associations were seen between P2 ERP characteristics and "Go" accuracy, "No-Go" accuracy, total accuracy, or anticipation errors on the SART.*

				"Go" accuracy				"No-Go" accuracy				total accuracy				anticipation			
				MS		Control		MS		Control		MS		Control		MS		Control	
				rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
P2	Go	peak amplitude	Fz	0.07	0.574	-0.15	0.314	0.03	0.801	-0.21	0.146	0.03	0.830	-0.18	0.210	-0.17	0.137	0.19	0.196
			FCz	0.21	0.076	0.05	0.736	0.10	0.403	-0.14	0.366	0.16	0.178	-0.10	0.519	-0.28	0.019	0.18	0.233
			Cz	0.14	0.280	0.16	0.302	0.03	0.823	-0.06	0.679	0.07	0.582	-0.05	0.771	-0.12	0.357	0.13	0.382
			Pz	0.06	0.611	0.31	0.042	0.00	0.971	-0.28	0.068	0.03	0.804	-0.26	0.100	-0.14	0.248	0.03	0.845
		mean amplitude	Fz	-0.01	0.922	-0.24	0.079	0.08	0.485	-0.13	0.356	0.03	0.768	-0.14	0.307	-0.16	0.147	0.17	0.235
			FCz	0.05	0.672	-0.07	0.620	0.04	0.709	-0.11	0.436	0.04	0.744	-0.12	0.402	-0.20	0.068	0.09	0.501
			Cz	0.12	0.289	0.06	0.690	-0.02	0.857	-0.12	0.395	0.03	0.789	-0.13	0.346	-0.10	0.395	0.03	0.812
			Pz	0.20	0.070	0.34	0.012	-0.06	0.612	-0.04	0.754	0.04	0.723	-0.03	0.821	-0.01	0.950	-0.01	0.959
		standard latency	Fz	-0.10	0.379	0.08	0.569	0.23	0.049	0.07	0.652	0.13	0.279	0.07	0.631	0.03	0.800	-0.05	0.726
			FCz	-0.15	0.226	0.04	0.794	0.20	0.095	0.02	0.916	0.10	0.433	0.02	0.870	0.07	0.572	-0.11	0.446
			Cz	-0.01	0.933	0.02	0.878	-0.01	0.962	-0.10	0.533	-0.02	0.847	-0.10	0.519	0.01	0.926	-0.14	0.366
			Pz	-0.10	0.440	0.01	0.935	-0.07	0.552	-0.12	0.433	-0.09	0.491	-0.12	0.447	0.00	0.986	0.03	0.859
		amplitude-weighted latency	Fz	-0.05	0.684	-0.01	0.955	0.17	0.150	-0.11	0.460	0.09	0.439	-0.11	0.438	-0.13	0.280	-0.01	0.965
			FCz	-0.06	0.598	0.10	0.510	0.15	0.225	-0.09	0.531	0.05	0.705	-0.07	0.620	-0.14	0.235	-0.11	0.476
			Cz	-0.01	0.915	0.14	0.382	-0.06	0.620	-0.17	0.265	-0.08	0.546	-0.17	0.261	-0.03	0.789	-0.11	0.464
			Pz	-0.09	0.459	-0.10	0.511	-0.04	0.772	-0.28	0.073	-0.03	0.782	-0.29	0.065	-0.12	0.357	0.13	0.396
		area	Fz	0.04	0.745	-0.18	0.213	0.07	0.555	-0.20	0.168	0.04	0.754	-0.19	0.200	-0.19	0.100	0.16	0.280
			FCz	0.17	0.155	0.08	0.572	0.09	0.440	-0.13	0.366	0.13	0.296	-0.10	0.499	-0.27	0.023	0.12	0.424
			Cz	0.12	0.358	0.19	0.207	0.02	0.894	-0.03	0.824	0.04	0.751	-0.02	0.877	-0.11	0.389	0.05	0.748
			Pz	0.11	0.362	0.32	0.036	0.00	0.975	-0.25	0.111	0.06	0.646	-0.23	0.140	-0.12	0.343	0.00	0.987
	NoGo	peak amplitude	Fz	-0.08	0.520	-0.16	0.269	-0.15	0.201	-0.11	0.452	-0.15	0.211	-0.10	0.509	-0.11	0.353	0.16	0.266
			FCz	0.08	0.512	-0.07	0.610	-0.06	0.588	-0.13	0.392	0.00	1.000	-0.10	0.474	-0.18	0.131	0.19	0.179
			Cz	0.06	0.630	0.08	0.624	0.00	0.970	-0.01	0.954	0.02	0.848	0.02	0.888	-0.03	0.813	0.10	0.521
			Pz	0.16	0.203	0.18	0.313	-0.04	0.765	-0.24	0.158	0.00	0.971	-0.20	0.261	-0.05	0.722	0.32	0.063
		mean amplitude	Fz	-0.06	0.570	-0.33	0.017	-0.06	0.572	-0.12	0.410	-0.09	0.442	-0.13	0.342	-0.13	0.247	0.15	0.284
			FCz	0.11	0.331	-0.22	0.118	0.02	0.835	-0.05	0.735	0.05	0.657	-0.07	0.607	-0.16	0.147	0.09	0.509
			Cz	0.18	0.110	-0.05	0.744	0.10	0.383	-0.02	0.904	0.14	0.216	-0.04	0.803	-0.02	0.839	0.03	0.837
			Pz	0.24	0.030	0.35	0.010	0.08	0.500	0.08	0.556	0.15	0.194	0.08	0.562	-0.05	0.661	0.05	0.720
		standard latency	Fz	-0.12	0.300	-0.02	0.885	0.02	0.867	-0.20	0.168	-0.01	0.949	-0.22	0.127	0.00	0.978	0.15	0.306
			FCz	-0.21	0.077	-0.07	0.637	-0.02	0.862	-0.25	0.081	-0.09	0.444	-0.27	0.057	0.06	0.611	0.16	0.282
			Cz	-0.09	0.472	0.29	0.050	-0.02	0.888	-0.05	0.733	-0.05	0.697	-0.03	0.838	0.09	0.472	-0.10	0.494
			Pz	0.10	0.424	0.22	0.195	-0.16	0.210	-0.08	0.639	-0.09	0.484	-0.07	0.681	0.05	0.688	0.07	0.672
		amplitude-weighted latency	Fz	-0.07	0.576	-0.30	0.032	-0.02	0.867	-0.17	0.245	-0.05	0.679	-0.22	0.119	-0.07	0.561	-0.10	0.505
			FCz	0.03	0.812	-0.19	0.195	0.05	0.663	-0.13	0.361	0.02	0.844	-0.19	0.181	-0.10	0.374	-0.07	0.611
			Cz	-0.01	0.942	0.11	0.471	-0.03	0.784	0.03	0.866	-0.02	0.901	0.01	0.939	0.08	0.507	-0.14	0.355
			Pz	0.24	0.064	0.31	0.071	0.05	0.717	0.03	0.866	0.13	0.328	0.04	0.807	0.02	0.874	0.15	0.386
		area	Fz	-0.04	0.760	-0.27	0.057	-0.07	0.550	-0.18	0.223	-0.08	0.479	-0.18	0.222	-0.13	0.282	0.14	0.318
			FCz	0.15	0.186	-0.15	0.311	0.02	0.895	-0.10	0.489	0.08	0.514	-0.10	0.490	-0.22	0.064	0.16	0.270
			Cz	0.13	0.293	0.02	0.884	0.03	0.805	-0.01	0.924	0.07	0.593	0.00	0.980	-0.03	0.806	0.09	0.571
			Pz	0.28	0.029	0.35	0.039	0.04	0.779	-0.17	0.329	0.11	0.404	-0.11	0.514	-0.07	0.566	0.32	0.063

***Supplementary Table 6. Correlations between N2 characteristics and SART accuracy**. No significant associations were seen between N2 ERP characteristics and "Go" accuracy, "No-Go" accuracy, total accuracy, or anticipation errors on the SART.*

				"Go" accuracy				"No-Go" accuracy				total accuracy				anticipation			
				MS		Control		MS		Control		MS		Control		MS		Control	
				rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p	rho	p
N2	Go	peak amplitude	Fz	0.02	0.897	-0.12	0.427	0.12	0.330	-0.13	0.373	0.09	0.472	-0.14	0.339	-0.17	0.147	0.01	0.970
			FCz	0.12	0.339	-0.11	0.489	0.13	0.280	-0.16	0.308	0.11	0.380	-0.17	0.263	-0.19	0.125	0.14	0.360
			Cz	0.09	0.505	0.11	0.506	0.01	0.958	-0.15	0.372	0.05	0.729	-0.15	0.377	0.10	0.438	0.02	0.922
			Pz	0.10	0.487	0.19	0.288	-0.17	0.238	0.19	0.290	-0.05	0.731	0.18	0.316	0.02	0.910	-0.03	0.855
		mean amplitude	Fz	0.00	0.965	-0.21	0.140	0.10	0.396	-0.12	0.376	0.05	0.664	-0.14	0.307	-0.17	0.131	0.19	0.169
			FCz	0.08	0.452	-0.05	0.727	0.04	0.706	-0.17	0.225	0.05	0.688	-0.18	0.188	-0.20	0.080	0.12	0.389
			Cz	0.09	0.447	0.09	0.528	-0.05	0.642	-0.18	0.203	0.00	0.980	-0.19	0.173	-0.08	0.500	0.02	0.901
			Pz	0.20	0.069	0.29	0.032	-0.04	0.734	-0.09	0.503	0.06	0.600	-0.08	0.574	-0.07	0.561	0.01	0.944
		standard latency	Fz	-0.08	0.488	-0.45	0.002	0.06	0.621	-0.17	0.253	0.07	0.545	-0.20	0.184	0.20	0.098	0.13	0.372
			FCz	-0.05	0.712	-0.32	0.032	0.05	0.713	-0.05	0.730	0.06	0.617	-0.08	0.596	0.15	0.235	-0.18	0.236
			Cz	0.04	0.756	-0.10	0.534	0.21	0.105	0.27	0.093	0.14	0.292	0.28	0.079	-0.05	0.698	-0.09	0.575
			Pz	-0.16	0.275	-0.02	0.922	-0.11	0.452	0.19	0.285	-0.19	0.193	0.16	0.381	0.21	0.147	-0.06	0.729
		amplitude-weighted latency	Fz	-0.04	0.760	-0.37	0.011	0.12	0.322	-0.09	0.553	0.12	0.304	-0.10	0.505	0.06	0.633	0.12	0.435
			FCz	-0.06	0.650	-0.22	0.142	0.07	0.584	0.10	0.525	0.06	0.620	0.08	0.603	0.10	0.395	-0.17	0.262
			Cz	0.06	0.652	-0.09	0.569	0.21	0.108	0.35	0.027	0.17	0.199	0.35	0.027	-0.07	0.593	-0.10	0.549
			Pz	-0.19	0.197	0.07	0.699	-0.02	0.873	0.31	0.082	-0.11	0.443	0.28	0.108	0.14	0.351	-0.08	0.665
		area	Fz	0.00	0.988	-0.10	0.492	0.05	0.689	-0.12	0.439	0.02	0.879	-0.13	0.403	-0.11	0.355	-0.01	0.970
			FCz	0.13	0.279	-0.08	0.620	0.08	0.503	-0.14	0.361	0.07	0.566	-0.15	0.315	-0.18	0.151	0.13	0.380
			Cz	0.11	0.396	0.09	0.586	-0.06	0.676	-0.20	0.221	0.00	0.971	-0.21	0.210	0.10	0.459	0.10	0.532
			Pz	0.12	0.404	0.15	0.404	-0.17	0.252	0.01	0.968	-0.05	0.729	0.00	0.985	0.03	0.829	-0.03	0.851
	NoGo	peak amplitude	Fz	0.15	0.267	-0.22	0.172	0.16	0.216	-0.15	0.376	0.16	0.227	-0.17	0.288	-0.22	0.087	0.17	0.303
			FCz	0.08	0.512	-0.35	0.017	0.06	0.644	-0.07	0.660	0.06	0.621	-0.13	0.381	-0.10	0.426	0.10	0.507
			Cz	0.14	0.263	-0.19	0.225	0.14	0.260	-0.02	0.877	0.14	0.237	-0.10	0.511	-0.02	0.882	0.09	0.571
			Pz	0.25	0.054	0.27	0.109	0.22	0.086	0.12	0.471	0.28	0.032	0.16	0.340	-0.22	0.085	-0.02	0.898
		mean amplitude	Fz	-0.04	0.736	-0.33	0.014	-0.05	0.672	-0.15	0.291	-0.07	0.521	-0.18	0.207	-0.14	0.229	0.17	0.225
			FCz	0.15	0.188	-0.19	0.164	-0.05	0.680	-0.13	0.356	0.01	0.946	-0.17	0.225	-0.12	0.304	0.08	0.587
			Cz	0.21	0.066	-0.02	0.897	0.00	0.985	-0.07	0.599	0.08	0.468	-0.10	0.459	0.05	0.635	0.05	0.720
			Pz	0.24	0.033	0.33	0.016	0.04	0.697	0.00	0.995	0.13	0.261	0.01	0.963	-0.04	0.726	0.08	0.572
		standard latency	Fz	0.13	0.309	-0.27	0.096	0.03	0.813	-0.07	0.669	0.08	0.532	-0.10	0.551	-0.07	0.600	-0.04	0.786
			FCz	-0.06	0.627	-0.26	0.082	0.15	0.202	-0.09	0.543	0.12	0.317	-0.11	0.463	-0.06	0.598	0.02	0.896
			Cz	-0.07	0.552	-0.22	0.148	0.19	0.125	0.03	0.848	0.09	0.453	0.04	0.795	-0.09	0.451	-0.05	0.735
			Pz	0.02	0.876	0.05	0.790	-0.11	0.421	0.16	0.356	-0.12	0.357	0.17	0.314	-0.09	0.509	-0.01	0.961
		amplitude-weighted latency	Fz	0.05	0.715	-0.32	0.051	0.10	0.458	-0.12	0.458	0.11	0.394	-0.16	0.344	-0.10	0.435	0.04	0.792
			FCz	-0.08	0.528	-0.26	0.078	0.19	0.112	-0.01	0.941	0.12	0.324	-0.04	0.809	-0.15	0.226	-0.05	0.747
			Cz	-0.04	0.729	-0.10	0.527	0.19	0.115	0.09	0.575	0.13	0.282	0.11	0.480	-0.16	0.196	-0.04	0.808
			Pz	0.02	0.854	-0.04	0.825	-0.06	0.628	0.26	0.133	-0.08	0.543	0.22	0.188	-0.12	0.366	-0.17	0.318
		area	Fz	0.13	0.313	-0.28	0.079	0.15	0.242	-0.19	0.259	0.14	0.289	-0.23	0.167	-0.19	0.143	0.26	0.116
			FCz	0.12	0.329	-0.38	0.010	0.00	0.973	-0.11	0.474	0.03	0.783	-0.18	0.244	-0.09	0.437	0.10	0.501
			Cz	0.23	0.063	-0.19	0.212	0.08	0.503	-0.10	0.507	0.14	0.251	-0.16	0.295	0.01	0.967	0.08	0.629
			Pz	0.35	0.006	0.27	0.108	0.23	0.079	-0.02	0.929	0.31	0.015	0.03	0.884	-0.17	0.183	-0.01	0.954

Supplementary Table 7. MMN associations with neuropsychological screening. No significant associations were seen between MMN waveform features and the MSNQ, HADS-A, or HADS-D.

MMN		MSNQ		HADS-A		HADS-D	
	channel	**rho**	**p**	**rho**	**p**	**rho**	**p**
peak amplitude	**Fz**	0.06	0.612	0.10	0.407	-0.19	0.132
	FCz	0.13	0.305	-0.04	0.745	-0.12	0.334
	Cz	0.11	0.365	-0.05	0.695	0.00	0.974
	Pz	0.11	0.415	0.15	0.261	0.22	0.098
mean amplitude	**Fz**	-0.01	0.959	0.08	0.546	-0.11	0.396
	FCz	0.07	0.560	-0.04	0.752	-0.03	0.779
	Cz	0.02	0.875	-0.18	0.138	0.05	0.695
	Pz	0.09	0.468	-0.04	0.730	0.21	0.082
standard latency	**Fz**	-0.14	0.277	0.00	0.992	-0.07	0.565
	FCz	-0.15	0.218	0.08	0.504	-0.07	0.603
	Cz	-0.04	0.749	0.09	0.468	-0.09	0.480
	Pz	-0.05	0.736	-0.03	0.834	-0.32	0.016
amplitude-weighted latency	**Fz**	-0.05	0.697	0.04	0.722	0.06	0.629
	FCz	-0.18	0.140	0.10	0.445	-0.05	0.661
	Cz	-0.02	0.901	0.11	0.369	-0.15	0.236
	Pz	-0.07	0.587	0.02	0.856	-0.15	0.272
area	**Fz**	0.04	0.775	0.09	0.467	-0.18	0.158
	FCz	0.16	0.206	0.00	0.995	-0.07	0.591
	Cz	0.03	0.788	-0.11	0.397	0.06	0.644
	Pz	0.08	0.536	0.12	0.365	0.28	0.035