Determining who benefits most from cognitive rehabilitation for multiple sclerosis.

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system characterised by lesions throughout the brain and spinal cord. Up to 70% of people with MS experience cognitive problems including difficulties with memory, attention, problem-solving, and language. These cognitive difficulties are debilitating and reduce the quality of life of people with MS and their families.

Cognitive rehabilitation is a type of therapy that helps retrain cognitive skills. It is a specialised intervention that focuses on providing people with MS with the knowledge of and information about their cognitive difficulties, and in turn teaching them to use both internal and external aids to address them. This PhD project aimed to establish the effectiveness of cognitive rehabilitation for people with MS and understand which groups of people with MS are most likely to benefit from this intervention. This PhD involved three main studies.

The first study involved the update of a Cochrane review investigating the effectiveness of cognitive rehabilitation for memory problems in MS. This Cochrane review was first published in 2012 and updated in 2016 prior to our current update. We selected randomised controlled trials (RCTs) or quasi-RCTs of memory rehabilitation or cognitive rehabilitation for people with MS in which the rehabilitation treatment group was compared with a control group. We performed a 'best evidence' synthesis based on the methodological quality of the primary studies included. Outcomes were considered separately for 'immediate' (within the first month after completion of intervention), 'intermediate' (one to six months after intervention completion), and 'longer-term' (more than six months after intervention completion) time points. Forty-four studies comprising 2730 participants were analysed in the systematic review. The risk of bias amongst the included studies was generally low, but we found eight studies to have high risk of bias related to certain aspects of their methodology (e.g., poor outcome reporting). All outcomes except for anxiety symptoms and activities of daily living were found to be improved following cognitive rehabilitation. We found that improvements in subjective memory and quality of life were sustained longer-term, thus supporting the effectiveness of cognitive rehabilitation for people with MS.

The second study involved the analysis of the Cognitive Rehabilitation of Memory and Attention in Multiple Sclerosis (CRAMMS) trial data to identify factors that may predict how likely a person with MS is to benefit from cognitive rehabilitation. We grouped baseline data into four possible categories (socio-demographics, clinical characteristics, self-report cognitive symptoms, and objective neuropsychological test performance). We used regression models to identify specific factors/characteristics that could predict the likelihood that an individual will benefit from cognitive rehabilitation. We found that younger people with relapsing-remitting or primary-progressive MS, with higher education, no recent relapses in the six months prior to receiving the cognitive rehabilitation, with mild to moderate cognitive difficulties, and who lived with others are more likely to benefit from cognitive rehabilitation compared to people with MS who did not show these characteristics. These findings suggest that it is possible to predict which people with MS are most likely to show more improvements in neuropsychological function following group-based cognitive rehabilitation. We then tested these findings in the third study.

The third study involved a feasibility RCT to assess the feasibility and acceptability of an online group-based cognitive rehabilitation programme. The aims of this feasibility RCT were twofold: (1) to assess the feasibility and acceptability of undertaking a definitive RCT to investigate the clinical efficacy of an online group-based cognitive rehabilitation programme with specific groups of people with MS and, (2) to explore preliminary signals of efficacy of the algorithm developed in study 2. We recruited 36 people with MS who reported experiencing cognitive difficulties. This trial took place entirely remotely; all assessments and interventions were delivered online via Microsoft Teams, which meant that we were able to recruit participants from across the UK. Participants were randomised to either receive the 10-week cognitive rehabilitation programme plus their usual care or their usual care only. Participants were randomised on a 3:1 ratio in favour of the intervention group. Participants reported that the intervention was acceptable in post-intervention interviews. We identified five key themes which related to participants management of their cognition before the trial, the online format of the intervention, experienced cognitive changes, perceived mechanism of change and potential improvements.

We determined that delivering group-based cognitive rehabilitation online was feasible however, we noted that some improvements are required for the recruitment

period, the outcome measures and the patient work booklet before a definitive trial could take place. We determined that delivering group-based cognitive rehabilitation online was acceptable to people with MS. Our analysis was exploratory and was not powered to determine statistical significance. We found preliminary signals of efficacy for the Selective Reminding Test (SRT) and the Multiple Impact of Multiple Sclerosis-Physical subscale, with large signals of efficacy. We also found large signals of efficacy for the EQ-5D visual analogue scale (VAS) score, which measures quality of life, and moderate signals of efficacy for the MSIS-Psychological subscale. Furthermore, this study provided preliminary signals of efficacy for the algorithm developed in study 2, as we found notable differences between those predicted most likely to benefit and those predicted less likely to benefit for the SRT, Everyday Memory Questionnaire and EQ-5D VAS, with large signals of efficacy.

A further robust, large-scale, multi-centre RCT, using ecologically valid outcome assessments (including health economic outcomes) assessed at longer-term time points is needed to establish the effectiveness of online group-based cognitive rehabilitation for people with MS. Further investigations are also needed to refine the predictive algorithm and conduct further testing in larger samples.

The findings of this thesis may lead to the optimisation of limited neuropsychology resources available as part of routine clinical care in the NHS by offering cognitive rehabilitation to those most likely to benefit from it and offering other more appropriate therapies to those less likely to benefit which may include individual cognitive rehabilitation.

PhD Publications and Disseminations

Peer Reviewed Publications:

Taylor LA, Mhizha-Murira JR, Smith L, Potter K-J, Wong D, Evangelou N, Lincoln NB, das Nair R. Memory rehabilitation for people with multiple sclerosis. Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD008754. DOI: 10.1002/14651858.CD008754.pub4.

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Conference poster presentations:

Taylor LA, Mhizha-Murira JR, Law G, Evangelou N, das Nair R. Who benefits most from cognitive rehabilitation: An algorithm based on a secondary data analysis. Rehabilitation in Multiple Sclerosis conference, Genoa, Italy. 4-6th May 2023.

Taylor LA, Swain P, Morris H, Ponda D, Evangelou, das Nair R. Online cognitive screening for people with multiple sclerosis: Is it inclusive? MS Trust conference, UK, March 2023.

Taylor LA, Mhizha-Murira JR, Smith L, Potter K-J, Wong D, Evangelou N, das Nair R. Memory rehabilitation for people with multiple sclerosis. European Committee for treatment and research in multiple sclerosis (ECTRIMS) conference, Amsterdam, October 2022.

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Taylor LA, Swain P, Morris H, Ponda D, Evangelou, das Nair R. Online cognitive screening for people with multiple sclerosis: Is it inclusive? MS Trust conference, UK, March 2023.

MS Frontiers conference (July 2022), oral presentation. Taylor LA, Mhizha-Murira JR, Law G, Evangelou N, das Nair R. Understanding who benefits most from cognitive rehabilitation: A secondary data analysis.

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Finally, I would like to thank my 16-year-old self who decided 10 years ago that she was going to be a psychologist and never stopped pursuing that dream – we did it.

Declaration

I, Lauren Taylor, certify that this is my own work, except where indicated by referencing. No part of this thesis has been submitted elsewhere for any other degree or qualification.

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Abbreviations

BRBN	Brief Repeatable Battery of Neuropsychological tests
CNS	Central Nervous System
CRAMMS	Cognitive Rehabilitation for Attention and Memory in Multiple Sclerosis
DMT	Disease Modifying Treatment
EMQ	Everyday Memory Questionnaire
EQ5D	Euroqol
MS	Multiple Sclerosis
MSIS	Multiple Sclerosis Impact Scale
NHS	National Health Service
NUH	Nottingham University Hospital
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
RCT	Randomised Controlled Trial
RRMS	Relapsing-Remitting Multiple Sclerosis
SDMT	Symbol Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
SRT	Selective Reminding Test
TIDieR	Template for intervention and description and replication
UK	United Kingdom

Chapter 1: Introduction & Aims of the PhD

1.1 Multiple sclerosis

1.1.1 What is multiple sclerosis?

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system characterised by lesions or plaques throughout the brain and spinal cord.[1] These lesions (plaques) affect the myelin sheath, thus causing inhibitions of the axonal transmission.[2] Because these lesions are widespread throughout the brain and spinal cord, MS results in a wide array of symptoms including physical,[3] cognitive,[4–6] and neuropsychiatric problems,[7–10] . Due to the variable location of those lesions, even those diagnosed with the same subtypes of MS at onset will still show variability in their symptom profiles and/or disease course.[11] MS symptoms can significantly impair an individual's ability to conduct everyday tasks which often lead to distress for the person with MS and their family.[12–14]

It is estimated that 2.8 million people are now living with MS worldwide (35.9 per 100,000 population)[15] and it is the most common cause of neurological disability in young adults globally.[16] In the United Kingdom (UK), approximately 130,000 people have been diagnosed with MS with 7000 people newly diagnosed every year. In other words, one in every 500 people in the UK has MS and each week, 130 people are diagnosed.[17] The exact aetiology and pathogenesis of MS is currently unclear; however, it is generally accepted that the cause of MS is multifactorial and includes genetic predisposition together with environmental factors such as exposure to infectious agents, vitamin deficiencies, and smoking.[18,19] Recent studies have provided compelling evidence that the Epstein Barr Virus (EBV) plays a causal role in the onset and development of MS.[20] MS can occur at any age, but onset primarily occurs between the ages of 20 and 40 years old.[21] MS affects 2-3 times more women than men, this prevalence ratio has increased markedly in the last decades.[22–24] While the exact effect gender has on clinical presentation of the disease is unclear, there is evidence to suggest that women generally have an earlier onset and that they show less disease progression compared to men.[25]

MS presents in different forms that follow distinct patterns of evolution and rates of disability progression.[26] Although there is continuing debate on the classification of the disease course, most clinicians refer to four MS phenotypes: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS),

and progressive relapsing MS (PRMS).[25] The most common presenting phenotype is RRMS with approximately 85% of people with MS presenting with this type.[27] RRMS is defined by episodes of acute worsening of neurological function followed by full or partial recovery and approximately 80% of individuals diagnosed with RRMS will later be diagnosed with secondary progressive MS.[28] PPMS is defined as steadily worsening neurological function without the presentation of relapses or recoveries and is the least common phenotype with only 10-15% of people with MS diagnosis with this type. SPMS is usually diagnosed a few years after a RRMS diagnosis and is defined as a steadily worsening neurological function with or without relapses. In PRMS there is steadily worsening neurological function from the beginning with no or only the occasional relapses.[29] In the 2013 revision of the phenotypes, a new course was added known as clinical isolated syndrome.[28] This refers to the first episode of neurological symptoms that may result in an MS diagnosis if additional activity occurs.[30]

In 2020, Lublin et al. provided a clarification for the 2013 definitions which highlighted the importance of time framing the disease course modifiers, activity and progression. Traditionally, MS phenotypes had been categorised as either relapsing or progressive based on the patient's current medical status and history. However, these categories did not provide temporal information about the ongoing disease process. The MS Phenotype Group recommended using additional descriptors such as disease activity, detected by clinical relapses or imaging findings (e.g., gadolinium-enhancing lesions or new/enlarging T2 lesions), and progression of disability. These descriptors were significant as they reflected ongoing inflammatory or neurodegenerative processes, thereby impacting prognosis, therapeutic decisions, and clinical trial designs and outcomes.

Therefore, it is recommended that disease activity using clinical criteria and brain imaging are reviewed annually for both relapsing and progressive MS. Disease activity could be identified through clinical relapses or imaging findings, such as new gadolinium-enhancing lesions or new/enlarging T2 lesions. Clinical evidence of disease progression, independent of relapses, was noted as additional modifier of the disease course. Progressive disease does not progress uniformly and could remain relatively stable over periods. Therefore, it was suggested that progression be determined annually by history or objective measures of change. For instance, a

patient with PPMS who had not progressed over the past year would be classified as "PPMS–not progressing." A patient with SPMS who had gradually worsened and had gadolinium-enhancing lesions on MRI would be classified as "SPMS–active and progressing."

To provide a practical assessment period, the Group suggested at least annual evaluations, though shorter or longer periods might be appropriate in certain situations. It was crucial to specify the assessment period for both clinical and imaging outcomes. For example, a patient with RRMS who showed a new gadolinium-enhancing lesion on a current MRI would be classified as "RR–active." Conversely, a patient with no relapses, gadolinium-enhancing activity, or new/enlarging T2 lesions during the assessment period would be considered "not active." Patients who had not been assessed within a designated time frame were categorised as "activity indeterminate." The guidelines also highlighted the importance of maintaining consistency in serial scanning procedures and interpretation, particularly when assessing new or enlarging T2 lesions, to ensure accurate and reliable assessments.

The revision also clarified the terminology for worsening disability, recommending the use of "confirmed" rather than "sustained" worsening. Many studies had used the term "sustained worsening" to describe a persistent increase in the EDSS score over a specific period (usually 3 or 6 months), which had been interpreted as a measure of worsening disability. However, "sustained" implied permanence, which might not accurately characterise MS disease changes. Instead, "confirmed accumulation of disability" was defined by a worsening of EDSS that persisted over a specified period, regardless of the functional system affected. A more rigorous definition required that the worsening be confirmed in the same functional system.

1.1.2 MS and the central nervous system

MS is a demyelinating condition of the central nervous system (CNS).[31] The CNS primarily consists of the brain and spinal cord.[32] The blood-CNS barrier form a physical barrier that separates the CNS from the circulatory system[33] and is important to the pathophysiology of MS.[34] Activated leukocytes are bound and anchored by it, allowing them to pass through the blood-CNS barrier and enter the CNS.[33] Once there, these immune cells start a cascade of neuroinflammation that causes the blood-

CNS barrier to break down and the development of perivascular plaques,[35] one of MS's defining characteristics.

Put simply, MS occurs when the immune system attacks the nerve fibres and myelin sheathing in the central nervous system. These attacks lead to inflammation of the nerve fibres and subsequently, the development of plaques or lesions. These lesions then disrupt the communication signals sent to and from the brain and it is this disruption that causes the symptoms of MS. Because these lesions can be so widespread, occurring in many different areas of the brain and spinal cord, the symptoms of MS and the subsequent severity of these symptoms vary greatly.

Common symptoms of MS include sensory disturbances (numbness, itching and/or tingling),[36] weakness that can cause walking difficulties,[37] fatigue,[38,39] disturbances of vision,[40] intestinal and urinary system dysfunction,[41,42] cognitive difficulties[43] and swallowing problems (dysphagia)[44]. Less common but at times very severe symptoms include speech difficulties,[45] breathing problems,[46] hearing loss[47] and seizures.[48] The symptoms that a person with MS experiences depends on several factors, one of which being the type of MS they are diagnosed with. For example, people diagnosed with RRMS are more likely to experience problems with their vision, sensory disturbances, fatigue, intestinal and urinary system dysfunction, spasticity, and cognitive difficulties due to the inflammatory attacks on the myelin and nerve fibres.[49] People diagnosed with PPMS typically experience weakness, stiffness, and trouble with their balance, as PPMS largely affects the nerves in the spinal cord.[50]

There are many disease modifying therapies for MS with different mechanisms of action that target distinct areas of the immune-mediated disease process which appear to improve short term and long-term outcomes.[51] These include self-injecting therapies, oral therapies, and infusion therapies. Similarly, there are many symptomatic treatments offered to people with MS, that can improve spasticity, pain, and other symptoms. Taking a multidisciplinary approach is essential to effective MS care, this involves the presence of specialists from different groups, who work together with MS neurologists and nurses such as physiotherapists and occupational therapists to provide personalised care plans.[52]

1.2 Cognition and MS

Cognition refers to the function of several neural pathways which are responsible for an individual's ability to attend to, acquire, process, store, manipulate and retrieve information.[53] Cognition plays a huge role in who we are as individuals as the way in which we process and understand information, directly impacts our thoughts and subsequent behaviour.[54] Various cognitive domains are responsible for regulating behaviour or actions such as executive function, working memory, planning, attention, problem solving and information processing.[55] These cognitive processes are commonly known as higher-order abilities, and they are subserved by the prefrontal cortex.[56] The prefrontal cortex regulates our thoughts, actions, and emotions through extensive connections with other brain regions.[57,58] However, in MS, the nerve fibres are damaged, which leads to these connections being compromised. This means that the signals being passed from the different brain regions to the prefrontal cortex may be slower or they may be inhibited.[59] For example, during a conversation a person with MS may find that their verbal skills are strong, but they have difficulty finding the word that they want to use. Another example would be that it may take a person with MS longer to recall information such as their address, because this request is being processed in the prefrontal cortex, but the connection between the prefrontal cortex and the brain region wherein this information is stored has been comprised by the damage to the brain.

1.2.1 Prevalence of cognitive impairment in MS

Difficulties with these cognitive processes is a common symptom of MS that can significantly impact the quality of life of people with MS and their families. The prevalence of cognitive difficulties varies with exact figures depending on the country, however, most studies conclude that between 40-70% of people with MS will experience cognitive difficulties at some point following their diagnosis.[60–63] Cognitive difficulties in MS most frequently present as impaired information processing speed, as well as impaired episodic and working memory.[60,64] People with MS also may experience difficulties with verbal fluency and executive function.[12]

Cognitive difficulties can be experienced by any person with MS, regardless of disease duration and physical disability,[65] however, the type of cognitive problems experienced by people with MS can be affected by the subtype they are diagnosed with. Cognitive difficulties are likely to be more frequent and more severe in

progressive types of MS, compared to RRMS.[66,67] However, studies vary when comparing progressive MS with secondary progressive MS. An Italian study reported that people with SPMS had a higher prevalence of cognitive difficulties, compared to PPMS (57% vs 7%), although it is important to note that this study had a relatively small sample size.[68] Similarly, a study in the Netherlands reported that people with SPMS experienced more cognitive difficulties than people with PPMS, who in turn both experienced more severe cognitive difficulties compared to people with RRMS.[69] In contrast, larger population studies have found that 27%-87% of people with PPMS experienced cognitive difficulties, and in other studies, the degree of cognitive difficulties experienced between SPMS and PPMS is comparable.[70,71]

As MS is a progressive disease, once cognitive function is lost it is very difficult to regain. Several longitudinal studies have shown that the degree of cognitive difficulties experienced by people with MS increases over time. Duque et al.[60] assessed the cognitive function of 44 people with MS every three months over a 2-year period.[72] At baseline, 31% were considered cognitively impaired, and at 2 years, this had increased to 41%, with difficulties in verbal memory and processing speed being to most prominent change. These findings have been supported by other studies.[73,74]

Amato et al.[61] followed 45 people with MS over 10 years, all of whom had on average been diagnosed within 1.5 years of participating in this study.[73] At baseline, 74% were considered to have no cognitive difficulties, however, this decreased to 51% after four years, and to 44% at the 10-year follow-up. The above studies conducted further investigations to identify predictors of worsening cognitive difficulties over time, but the only apparent predictor was the presence of cognitive difficulties at baseline.

All cognitive domains can be affected by MS, but the most commonly affected cognitive domains are episodic memory (20-75%) and information processing speed (15-50%).[75,76] Working memory (15-60%), learning memory (4-65%), executive function (15-25%), verbal fluency (15-25%), complex attention (5-25%) and language (20-58%) are also heavily affected by MS.[60,64,77–80] Social cognition is also suspected to be affected by MS, although this is a more recent finding.[81,82] Physical disability and age, especially age at disease onset, may be linked to the severity and prevalence of cognitive impairment,[83] as well as gender, genetic factors, and cognitive reserve.[84]

Cognitive reserve is the brain's ability to improvise and problem solve. The cognitive reserve theory suggests that people develop a reserve of their thinking abilities and that this protects them against losses that can occur through ageing and disease.[85] Intelligence and education, which are commonly thought to be factors which determine cognitive reserve, may also affect the degree of cognitive impairment in people with MS.[86]

Benedict et al.[86] conducted a five-year longitudinal study to determine whether individual differences in estimated cognitive reserve can act as a protective factor against the progression of cognitive impairment in MS. This study found that people with MS with lower baseline cognitive reserve showed significant cognitive decline, in contrast to people with MS with higher a cognitive reserve who showed no cognitive deficits over the five-year period. The authors concluded that higher cognitive reserves were determined by higher premorbid intelligence or more years of education and that this subsequently protects people with MS against the progression of cognitive impairment. These findings supported the previous work of Sumwoski et al.[87] who found that the relationship between brain atrophy and information processing speed efficiency was moderated by cognitive reserve.

Age may also play a significant role in predicting cognitive resilience or degree of cognitive impairment as younger adults are thought to have higher cognitive reserves compared with older adults.[88] Studies have suggested that age can not only influence initial cognitive abilities but could also play a moderating role in the improvement of cognition during rehabilitation.[89,90]

Cognitive impairment in MS affects many cognitive domains. These cognitive domains allow us to function in everyday society and thus, impairment in any of these domains can have devastating impact people with MS's ability to function in their everyday life. Memory, attention, executive function, and information processing speed are the most affected cognitive domains in MS.

1.2.1 Memory

1.2.1.1 Definition

Memory is the term given to the structures and processes involved in the storage and subsequent retrieval of information. Long term memory refers to the ability to learn, store and then later recall new information. In theory, long-term memory represents a

potential unlimited storage to be maintained for an uncapped length of time.[91] Long-term memory is achieved through a consolidation process whereby structural and molecular changes integrate information into a stable memory. There are two different types of long-term memory: explicit memory and implicit memory.

Explicit memory refers to information that we consciously attempt to recall, such as memories involving personal experiences (episodic memory) or information about facts (semantic memory). Episodic memory is our ability to learn, store and retrieve information about our past and our unique experiences.[92] Semantic memory involves the capacity to recall words, concepts, or numbers, which is an essential skill for the use and understanding of language.

Implicit memory encompasses all unconscious memories as well as the skills or abilities we have developed. There are four types of implicit memory: procedural, associative, non-associative, and priming.[93] Procedural memory involves recalling motor or executive skills that are required to perform certain tasks, these memories are retrieved automatically to allow the execution of these skills e.g., walking.[94] Associative memory refers to the storage and retrieval of information through association with other information whereas non-associative memory refers to newly learned behaviours.[95] The acquisition of associative memory is carried out with two types of conditioning: classical conditioning and operant conditioning.[96] Classical conditioning is associative learning between stimuli and behaviour. Meanwhile, operant conditioning is a form of learning in which new behaviours develop in terms of their consequences.[97,98] Lastly, the priming influence is an effect whereby exposure to certain stimuli influences the response given to stimuli presented later.

Working memory refers to the processes in the brain that maintain and manipulate information for a short period of time.[99] This is sometimes referred to by researchers as information processing efficiency and is often linked with the speed at which one can process this information (processing speed).[12] Working memory facilitates planning, comprehension, reasoning, and problem solving.[100] Working memory depends on neural mechanisms that allow for the encoding, upkeep, and modification of information that is stored as well as the integration of that knowledge with present and future objectives.[101]

1.2.1.2 Anatomy and Neural mechanisms of memory

Episodic memory is thought to involve cortical and subcortical structures of medial temporal lobe and mainly the perirhinal and the entorhinal cortex, the hippocampus and parahippocampal cortex.[102] As the primary point of contact between the hippocampus and the neocortex, the entorhinal cortex is linked to the flow of information to and from the hippocampus.[103] The perirhinal cortex is linked to visual object recognition, while the parahippocampal cortex is linked to perception and processing of information relating to the environment.[104] The hippocampus itself is responsible for the formation and retrieval of memories. Thus, all structures mentioned above send information to the hippocampus wherein it can be processed, stored, and later retrieved as episodic memories.[105,106]

Semantic memory is thought to involve large areas of the heteromodal cortex.[107] Recent neuroimaging and transcranial magnetic stimulation studies have demonstrated two primary findings: the participation of modality-specific sensory, motor, and emotion systems in language comprehension, and the existence of large brain regions that participate in comprehension tasks but are not modality-specific.[108–112] These latter areas, which encompass a large portion of the temporal lobe and the inferior parietal lobe, are where different perceptual processing streams merge. These convergences make it possible to represent perceptual experience in increasingly abstract, supramodal ways, supporting a range of conceptual abilities like object recognition, social cognition, language, and the amazing ability of humans to recall the past and imagine the future.[113]

Working memory processes are mediated through distributed subcortical and cortical networks that include different subregions of the prefrontal cortex.[114–122] Recent models suggest that brain regions that are involved in perceptual and mnemonic processing can temporarily maintain representations of sensory information; however, prefrontal cortex is selectively involved in linking such upheld representations with task-relevant information about goals, actions, rules, and strategies to achieve these goals.[123,124] These findings suggest that the neural networks supporting working memory include several crucial hubs such as the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and the posterior parietal cortex (PPC).[125–128] Recent studies have proposed that the prefrontal cortex is not necessarily responsible for information storage in working memory, instead postulating that the

PFC facilitates working memory processes by differentiating relevant information from irrelevant information (differentiating capacity).[129]

Neuroimaging studies in humans showed that, during the delay period of cognitive tasks, the prefrontal cortex (PFC) did not encode stimulus-specific information to be held in working memory,[130,131] instead the posterior sensory areas encoded stimulus-specific information for that purpose.[132–134] This idea is further supported by PFC lesion studies in humans and monkeys showing that individuals with large lesions in lateral PFC did not always exhibit deficits in verbal memory, and/or delayed recognition tasks.[135] Similarly, monkeys with lesions in the ventral PFC exhibited impairments in stimulus selection and attention, but not the working memory component in the context of a modified visual association task with delay periods ranging from 2 to 8 s.[136] Previous studies also indicate a close interaction between the PFC, the parietal cortex, and posterior sensory regions and subcortical brain structures in supporting working memory processes.[132–134,137–140]

1.2.1.3 Theory/Model related to memory difficulties.

Working memory is a limited capacity system responsible for the processing, manipulation, and storage of information during the performance of cognitive tasks. There are three primary aspects within the working memory model that are of particular importance; these are the visuo-spatial scratch pad, the central executive, and the phonological loop.[141] The visuo-spatial scratch pad stores and processes visual or spatial information, the central executive drives the whole system by allocating data to a specific subsystem, and the phonological loop stores and processes spoken and written material.

More recently, the model has been updated to include the episodic buffer.[142] The episodic buffer is theorised to be capable of storing information in a multidimensional code, thus providing a temporary interface between the visuospatial sketchpad and phonological loop to long-term memory (Figure 1). This buffer is thought to be separate from long-term memory, but it is recognised as an important stage in long-term episodic learning. In the model below, the shaded areas represent cognitive systems that are well-established and capable of storing long-term knowledge whereas the unshaded areas represent more fluid systems such as attention and temporary storage.

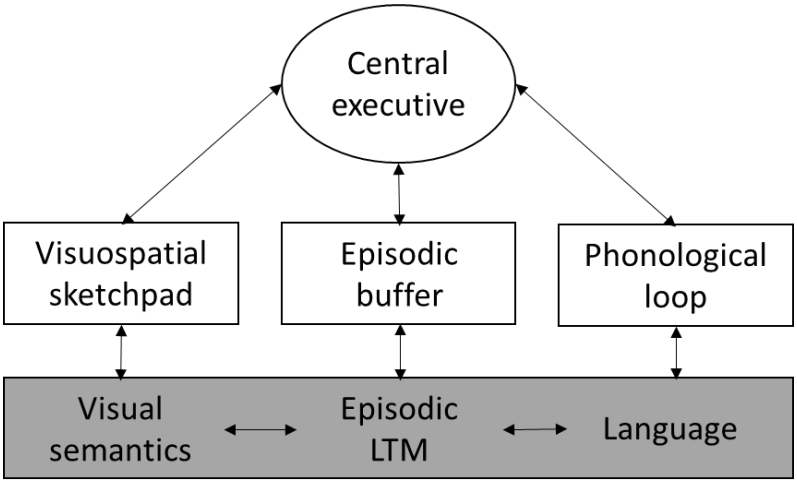


Figure 1 The current multi-component working memory model. Adapted from Baddeley et al.[143]

Working memory and long-term memory were once considered to be separate, this was because patients with clear short-term memory deficits appeared to have intact long-term memory. However, subsequent research has shown that patients with phonological loop deficits have great difficulty acquiring novel vocabulary. Researchers now consider working memory to act as a gateway to long-term memory. Working memory is an in-between space wherein sensory information can be processed. Information can only be held in working memory for a limited time, therefore, information that enters working memory either must be moved into long-term memory or forgotten.

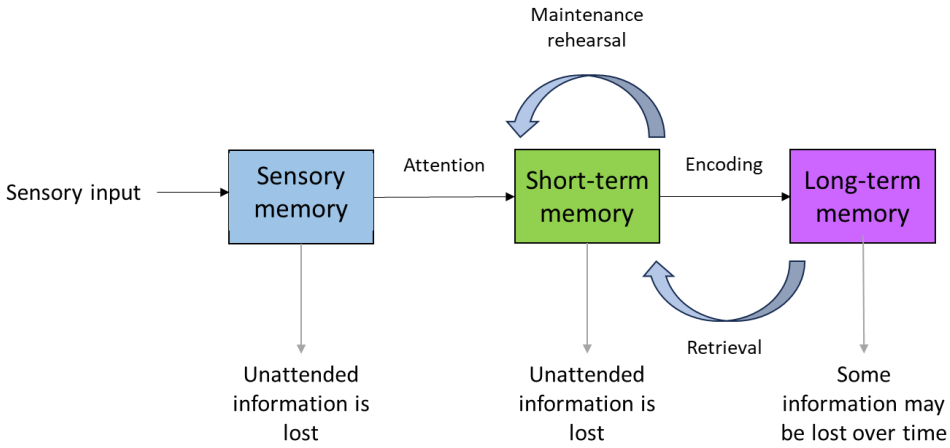


Figure 2 Memory processes. Adapted from Atkinson et al.[144]

Memory is an incredibly complex system and creating new memories involves a series of linked processes (Figure 2). The first is attention which involves the ability

to focus on the information that is important and filter out irrelevant stimuli, this process is what allows information to enter working memory in the first instance. Once the information is in working memory, it must then be encoded. Encoding involves understanding, making sense of, and later storing the information. If the information has been encoded correctly, it will then move into long-term storage to be stored and consolidated. However, if the information being held temporarily in working memory is not properly rehearsed, then it will be lost making it impossible to retrieve later. If information is encoded and stored correctly, then it can be retrieved from long-term memory, held in working memory when needed and then sent back to long-term memory. In MS, often it is these earlier processes of attention and encoding which are more difficult due to the damaged connections in the brain, leading to memory impairment.

1.2.1.4 Extent of memory difficulties in MS

One of the most frequently reported cognitive impairments in MS is memory decline. Long term memory and working memory are the most reported impairments. Clinically, these often manifest in various ways, with patients often struggling to recall past events or even words leading to the commonly referred to problem of it being 'on the tip of their tongue'. There has been some debate about the underlying cause of this, earlier research suggested that retrieval difficulties in long term storage was the primary cause for this impairment,[145] however, more recent research suggested the problem occurs much earlier in the process during the initial learning of information.[146,147] DeLuca et al.[147] found that in 44 people with MS, brain atrophy was associated with inefficient learning across initial acquisition trials, and unrelated to delayed recall among, and proposed that this indicated that initial learning mediates the relationship between brain atrophy and subsequent retrieval. Weak initial learning refers to the difficulty in acquiring new information efficiently and accurately at the first exposure. This can be due to various factors, including attentional deficits, slowed information processing, and impaired working memory, all of which are common in MS.

When initial learning is weak, the subsequent consolidation and retrieval of information are compromised. This means that even if a patient tries to learn new information, the efficiency with which this information is stored and later recalled is significantly reduced. DeLuca et al.[147] therefore, suggested that people with MS may

require more repetitions of information to reach a predetermined learning criterion, but that once the information has been acquired successfully, recall and recognition are on par with those without MS.

1.2.1.5 Impact of memory difficulties in MS

Memory impairments are very common for people with MS,[12,148] with negative consequences for employment,[149] psychological wellbeing,[150] and overall quality of life.[151,152] People with MS who are more cognitively impaired are more likely to report lower self-esteem, participate in fewer social activities, and have higher rates of divorce.[153,154] Memory impairments have a negative association with other areas of cognition, such as slow processing speed, executive dysfunction, and perception, which can be a source of frustration and distress for people with MS.

There has been some debate regarding the impact of memory impairment in MS. Some researchers argue that it is an impairment of the retrieval processes,[155,156] while others argue it is due to an inefficient initial learning as the core deficit. Determining the core memory deficit is important for explaining the true impact of memory impairment in MS. Recent findings have demonstrated that MS is associated with weak initial learning, which then leads to poor retrieval.[147] As demonstrated previously in the working memory models, if the early memory processes of attention and encoding cannot be carried out correctly due to damage in the brain, this has a significant impact on people with MS's ability to retrieve information. Magnetic Resonance Imaging (MRI) findings have supported this by demonstrating that brain atrophy accounts for approximately 10-15% of the variance in memory tasks of initial learning and delayed retrieval in MS.[157,158]

1.2.2 Attention

1.2.2.1 Definition

The ability to actively analyse specific environmental information while blocking out unrelated stimuli is referred to as attention. Modulation refers to the process whereby attention influences other functions such as memory, perception, emotion, and language.[159] Different processes within cognitive functions will be given varying amounts of attention depending on the goals. It has been suggested that not only is attention capacity limited and therefore, must be consciously divided in a goal-weighted way, but it may also be controlled in a selective way.[160,161] Selective attention has been the focus of research for decades. Selective attention refers to the

process of directing one's attention toward relevant stimuli while ignoring irrelevant stimuli, such as focusing on writing an essay while simultaneously ignoring construction noise.[162]

1.2.2.2 Anatomy and neural mechanisms involved in attention.

The role of attention is to prioritise incoming sensory processing to enable optimised behavioural responses given the task at hand.[163,164] The main neural mechanisms associated to the attentional modulation of sensory processing are target amplification and distractor suppression. By combining these two mechanisms, sensory regions would be able to selectively amplify target-related neural signals to facilitate the transmission of target-related information further along the information processing chain.[165]

1.2.2.3 Theories/models of attention

Treisman[166] developed a model of attention that was based on the earlier work of Broadbent[167] who developed the bottleneck models; however, the main difference was that in the Treisman model, unattended material is attenuated rather than eliminated. Attenuation is like turning down the volume on multiple stimuli to allow you to focus on one, which suggests that people can still process the meaning of the attended messages. Treisman[166] later demonstrated in her experiments that participants were still able to identify the contents of both the attended and unattended messages. The Attenuation Model accounts for the 'cocktail party effect' which is the phenomenon of the brain's ability to focus one's auditory attention on a particular stimulus while filtering out a range of other stimuli, such as someone at a party that's able to focus on a conversation whilst filtering out the background noise.[168,169]

1.2.2.4 Extent of attention difficulties in MS

Attention difficulties in MS are often linked to multitasking and quickly switching attention back and forth between competing thoughts and tasks.[170,171] Attention is a complex cognitive function as it is closely linked with information processing speed and working memory and because of this, it is a difficult cognitive domain to measure independently. The cause of attention deficits in MS is thought to be routed in the thalamus as it plays an important role in attention. This is supported by studies that have reported significantly lower thalamic volumes in people with MS compared to controls.[172,173]

In MS, attention difficulties are often variable and linked to cognitive fatigue and demyelination, causing selective and sustained attention issues that can fluctuate with disease activity.[174] This contrasts with other neurological disorders such as Alzheimer's whereby attention deficits progressively worsen due to neurodegenerative processes, leading to a consistent decline in sustained and divided attention. Similar patterns can be seen for other cognitive deficits experienced by people with MS and those with alzhimers.

1.2.2.5 Impact of attention difficulties in MS

Attention difficulties are very common for people with MS.[175] These attention difficulties can negatively impact a person with MS's everyday life in that they may struggle to do several jobs at once or to hold a conversation with a friend or family member.[176] Attention difficulties can affect a people with MS's daily functioning as attention is essential for efficiently processing information from the environment and carrying out tasks. Individuals with attention difficulties might struggle with tasks that require sustained focus, divided attention (juggling multiple tasks simultaneously), and selective attention (focusing on specific stimuli while ignoring others). This can affect their ability to manage daily activities, such as following conversations, reading, cooking, and organizing their surroundings.

Attention is closely linked to memory processes. Individuals with attention difficulties might have difficulty encoding new information and experiences into memory. This can affect their ability to learn and remember new names, facts, and instructions. These attention difficulties can be impacted by fatigue which is experienced by up to 90% of people with MS.[177,178] Cognitive fatigue is associated with significant impairment in daily functioning and quality of life and thus, can further impact people with MS's ability to pay attention.[179] The impact of attention difficulties in MS can vary significantly depending on the degree of impairment but can have negative consequences for employment, relationships, and activities of daily living.[180]

1.2.3 Executive functions

1.2.3.1 Definition

Executive functions refer to a set of higher-order cognitive processes that are responsible for controlling, coordinating, and regulating other cognitive and behavioural functions to achieve specific goals and adapt to different situations. These functions are crucial for effective problem-solving, decision-making, planning,

organizing, goal setting, initiating, and inhibiting actions, shifting between tasks, and monitoring one's own behaviour.[181,182]

1.2.3.2 Anatomy and neural mechanisms of executive function

Executive functions are primarily associated with the prefrontal cortex and its connections to other cortical and subcortical structures through top-down signalling. These functions develop over time and play a crucial role in various aspects of daily life, including academic and occupational success, interpersonal relationships, and independent living.[183] The precise neural mechanisms in the prefrontal cortex that are responsible for executive functions are not fully understood, however, it is generally accepted that the prefrontal cortex is responsible for higher cognitive functions such as judgement and decision making.[184–188]

Neurotransmitters like dopamine, serotonin, and norepinephrine also play a critical role in modulating executive functions by influencing neural activity and communication within these networks.[189] It is important to note that executive functions are not localised in a single brain area but emerge from the dynamic interactions between multiple regions and networks. Damage or dysfunction in any of these areas or their connections can lead to deficits in executive functions, as seen in MS.

1.2.3.3 Theory/model related to executive function.

There are several theories and models that may explain executive function, but there is no one accepted model. It is generally agreed that there are three core execution functions: inhibition, working memory and cognitive flexibility.[190,191] Inhibition or inhibitory control refers to a person's ability to control their thoughts, behaviours, and impulses. Cognitive flexibility builds on inhibition and working memory in that it allows a person to change their perceptions by considering additional viewpoints or information.[192] From these three core executive functions, higher order executive functions are then built including planning, reasoning and problem solving. Executive functions are essential skills for cognitive, social, and psychological development.[193–195] Executive dysfunction is often attributed to demyelination and neural damage in regions of the prefrontal cortex and associated neural networks and has profound implications for daily functioning and quality of life.

1.2.3.4 Extent of executive dysfunction in MS

Executive dysfunction, encompassing deficits in cognitive processes such as planning, decision-making, problem-solving, and goal-directed behaviours, emerges as a significant cognitive impairment in people with MS.[196] Studies have reported varying prevalence rates depending on the methods used to assess executive function and the specific characteristics of the MS sample being studied.[197] The wide range in prevalence may be due to factors such as disease duration, disease subtype (relapsing-remitting, primary progressive, etc.), and the sensitivity of the cognitive assessment tools used. Additionally, the severity of executive dysfunction can vary, ranging from mild to more severe impairments that significantly impact daily life activities.[198]

1.2.3.5 Impact of executive dysfunction in MS

Executive dysfunction in MS can have a profound impact on various aspects of an individual's life, affecting their daily functioning, quality of life, and overall independence. Some of the key impacts of executive dysfunction in MS include activities of daily living as executive functions are crucial for organizing, planning, and executing everyday tasks.[199] Individuals with executive dysfunction may struggle with activities such as managing finances, meal planning and preparation, maintaining personal hygiene, and adhering to medication schedules.[200] These difficulties can lead to increased reliance on caregivers and decreased autonomy.[152]

Work and employment can also be significantly affected as executive dysfunction can hinder an individual's ability to perform complex tasks, make decisions, and prioritise work-related activities.[201] This can lead to decreased job performance, difficulties in multitasking, and challenges in adapting to changes in the work environment.[202] In some cases, individuals with MS-related executive dysfunction might need to modify their work responsibilities or even consider early retirement.[202]

Overall, the impact of executive dysfunction in MS is far-reaching and multi-dimensional. It underscores the importance of comprehensive assessment, rehabilitation strategies, and support systems tailored to address the specific cognitive challenges faced by individuals with MS.

1.2.4 Processing speed

1.2.4.1 Definition

Processing speed refers to the ability of an individual to perform cognitive tasks quickly and efficiently. It encompasses the rate at which the brain can receive,

process, and respond to incoming information from the environment.[203] Processing speed is a fundamental cognitive function that underlies a wide range of cognitive processes, including perception, attention, memory, and decision-making.[204,205]

In more technical terms, processing speed involves the speed at which neurons transmit signals, synapses relay information, and different brain regions communicate with each other to complete a cognitive task.[206] It's closely related to reaction time which is the time it takes to respond to a stimulus.[207] Reaction time can serve as a practical and objective indicator of processing speed to provide valuable insights into a person with MS's cognitive status.[208] Processing speed is crucial in many aspects of daily life such as reading, conversations, problem solving, decision making, and learning.

1.2.4.2 Anatomy and neural mechanisms of processing speed

Processing speed involves intricate neural mechanisms that facilitate the rapid transmission of information within the brain.[209] A variety of neurological processes, including rapid neural transmission, improved synaptic connectivity, well-connected neuronal networks, effective white matter pathways, synchronised neural oscillations, and neurotransmitter system regulation, work together to control these mechanisms.[210] Myelination, which improves the conduction of action potentials along axons, speeds up neuronal transmission.[211] Rapid communication between neurons at synapses is ensured by synaptic transmission, which is driven by neurotransmitters with rapid onset of action like glutamate.[212] While white matter pathways serve as conduits for rapid communication between distant areas, neural networks made of interconnected neurons allow for the seamless coordination of information across many brain regions.[209,213] The precise timing of signals is made possible by brain synchronisation and oscillations, which improves the effectiveness of neural processing.[214,215]

1.2.4.3 Theories/models relating to processing speed.

Several theories and scientific models have been proposed to explain the phenomenon of processing speed and its underlying cognitive and neural mechanisms. The neural hypothesis theory which has been support by several studies posits that individuals with higher cognitive abilities exhibit more efficient neural processing, requiring fewer neural resources to complete cognitive tasks.[216,217] In other words, more intelligent individuals can process information more quickly and accurately by using optimised neural pathways and strategies. Furthermore, the cognitive resource

allocation theory suggests that processing speed is influenced by the allocation of cognitive resources to different tasks.[218,219] Individuals with greater cognitive resources can allocate more attention and mental effort to a task, resulting in faster processing.

1.2.4.4 Extent of processing speed difficulties in MS

Processing speed is the most common domain of cognitive problems in people with MS and can be used to predict long-term cognitive decline.[220] Processing speed deficits often occur concurrently with both working memory and long-term memory deficits. Notably, information processing speed deficits are very likely to be an early indicator of MS.[221] This may be attributed to a correlation between the reduction in grey matter within the posterior lobes of the cerebellum and a decline in information processing speed. Previous research has established a connection between the cerebellum in the posterior lobes and both cognitive impairment and motor deficits in individuals with MS.[222–224] Grey matter damage has been detected in the earliest stages of MS by MRI sequencing and this accrues with disease progression.[224] Recent autopsy studies have also demonstrated significant grey matter demyelination and microglia activation.[225]

1.2.4.5 Impact of processing speed difficulties in MS

Processing speed impairment is a common cognitive deficit in individuals with MS and can have significant impact across various aspects of their lives.[75,226,227] Processing speed deficits can affect an individual's ability to perform everyday tasks efficiently. Activities that require quick decision-making, multitasking, and managing information become challenging.[226] This can lead to difficulties in managing schedules, following instructions, and organising daily routines. Processing speed deficits can impact learning abilities.[228,229] Individuals might have trouble processing and retaining new information quickly, which can affect academic performance and the ability to learn new skills.[230] Struggling with processing speed impairments can also lead to frustration, anxiety, and lowered self-esteem.[231] These emotional responses can contribute to overall stress and negatively impact mental well-being. Overall, processing speed impairments can lead to reduced independence, increased reliance on others, and decreased overall quality of life.[229] These challenges can impact an individual's sense of control, autonomy, and well-being.

1.2.5 Cognitive phenotypes in MS

Cognitive phenotypes may be the key to developing our understanding of pathophysiological mechanisms of MS-related cognitive changes. Cognitive phenotypes differ from the cognitive domains detailed above as cognitive phenotypes may include several cognitive domains as well as other behavioural symptoms.[232] Recently, there has been an increase in research to identify these distinct cognitive phenotypes in MS. A promising approach in this area was introduced by Leavitt et al.[233] who identified three cognitively homogenous subgroups of people with MS that they defined as cognitive phenotypes. These cognitive phenotypes were isolated memory impairment, isolated information processing speed impairment, and combined deficits in processing speed and memory. However, as mentioned above, deficits in several cognitive domains have been identified in MS, and Leavitt's classification was based on the dichotomous definition of impairment for each domain which did not consider people with MS who have reported mild decreased cognitive performance.

Another limitation to highlight is the issue of measuring these cognitive domains. Typically, cognitive measures capture more than one cognitive domain which means that the measures are not 'pure' of any one specific construct. For example, Leavitt et al.[233] chose to use the Symbol Digit Modalities Test (SDMT) and The Stroop Colour and Word Test (SCWT) as measures of processing speed, however, the SDMT and SCWT are also considered to be measures of attention and concentration with the SCWT test also measuring executive function[234] and general cognitive efficiency.[235] This is means that the cognitive phenotypes identified may be more complex than stated in this paper, involving multiple cognitive domains.

Following on from this, De Meo et al.[236] conducted a cross-sectional study with the aim of identifying cognitive phenotypes in a clinical cohort of 1212 MS patients, ensuring they included a broad spectrum of disease subtypes, and further aimed to characterise their clinical and MRI features. Using latent profile analysis, the authors reported a five profile model: (1) preserved cognition (people with MS who showed no cognitive impairment), (2) mild-verbal memory/semantic fluency, (3) mild-multidomain (people with MS who showed mildly decreased performance in several cognitive domains), (4) severe-executive/attention (people with MS who showed severely decreased performance in executive function and attention domains), and (5)

severe-multidomain (people with MS who showed severely decreased performance in several cognitive domains).

De Meo et al.[236] stated that the first phenotype included people with MS who had shorter disease durations and less severe disability compared with other phenotypes. They also speculated that those with this phenotype may have a higher cognitive reserve due to people with MS with this phenotype having a lower thalamic volume compared with controls. It is well established that the thalamus is involved in cognitive functioning.[237] Therefore, the higher cognitive reserve may explain why people with MS with this phenotype are exhibiting normal cognitive functioning despite their reduced thalamic volume. This is in line with previous research suggesting that a higher cognitive reserve protects people with MS against cognitive decline.[238] Understanding these cognitive phenotypes will allow researchers and clinicians to measure the cognitive status of people with MS more meaningfully and encourage the development of personalised treatments.

In summary, Leavitt et al.[233] identified four cognitive phenotypes while De Meo et al.[236] identified five cognitive phenotypes. Both authors identified a 'not-impaired' phenotype and used some of the same cognitive tests including the SDMT, the SCWT, and the selective Reminding Test (SRT). De Meo et al.[236] appears to acknowledge that the cognitive tests measure multiple domains as the participants' performances in these cognitive tests is outlined for multiple phenotypes. But the degree of impairment on each test led to the creation of both mild and severe impairment phenotypes. Furthermore, the phenotypes were named after the cognitive test performances that correlated with each other rather than being decided beforehand, i.e., identifying the SDMT as a processing speed measure so therefore, poor performance in this test means impairment in processing speed phenotype.

Understanding and identifying cognitive phenotypes in MS could be useful for the development and implementation of targeted cognitive rehabilitation strategies. By classifying MS patients into specific cognitive phenotypes, clinicians can tailor rehabilitation programmes to address the unique cognitive challenges faced by each subgroup. For example, individuals with isolated memory impairment may benefit from memory-specific interventions such as mnemonic strategies and spaced repetition, while those with isolated information processing speed impairment may

require exercises designed to enhance processing speed and attentional control. Additionally, people with MS with combined deficits in processing speed and memory, or those with severe multidomain impairments, may need comprehensive, multi-faceted rehabilitation approaches that simultaneously target multiple cognitive domains. This personalised approach could ensure that resources are allocated efficiently, ultimately leading to better outcomes for individuals with MS. By integrating cognitive phenotyping into clinical practice, researchers and healthcare professionals can advance the field of cognitive rehabilitation and provide more effective, individualised care for people with MS. However, more research is needed into establishing distinct phenotypes.

1.3 Cognitive rehabilitation

Cognitive rehabilitation is a specialised neuropsychological intervention that focuses on providing people with MS with the knowledge of and information about their cognitive problems, and in turn teaching them to use both internal and external aids to address them.[239,240] Attention and memory rehabilitation are major components in this type of intervention and are especially important as they are common cognitive difficulties reported by people with MS.[12] Attention rehabilitation teaches people better ways of paying attention, reducing distraction, and improving concentration. Memory rehabilitation teaches different strategies for encoding, storing, and retrieving memories.[241]

Studies have examined the effectiveness of memory rehabilitation using different methods. Single-case and small-group studies have reported positive results of memory rehabilitation, but the results obtained from RCTs, and some systematic reviews have been less positive and reported inconclusive evidence.[239,242–249] Some reviews have concluded that there is compelling evidence for memory strategy training with participants with mild memory problems. These reviews further suggested that the use of external memory aids may be beneficial for people with moderate to severe memory problems, and that errorless learning may be effective for those with severe memory impairments (albeit with limited generalisability to new tasks or overall memory problems).[250–252] Cicerone et al.[251] also suggests that group-based interventions may be considered as part of a comprehensive neuropsychological rehabilitation of memory deficits. However, these reviews focused mainly on people with traumatic brain injury. Cochrane Reviews by Majid et al.[253] and das Nair et al.[243]

found insufficient evidence to support or refute the effectiveness of memory rehabilitation following stroke. The previous version of this Cochrane review, das Nair et al.[254], found that the evidence for cognitive rehabilitation for multiple sclerosis was inconclusive. Some reviews have focused on generic psychological interventions for people with MS,[255] or neuropsychological interventions for people with MS,[256] however these were not specific to memory rehabilitation. The Thomas et al.[255] review did not consider grey literature and was unable to draw any "definite conclusions". The Rosti-Otajärvi et al.[256] review focused on neuropsychological rehabilitation across multiple cognitive domains, as well as associated health-related factors and emotional well-being. The Goverover et al.[257] review was similar in that it focused on cognitive rehabilitation in six cognitive domains: attention, learning and memory, processing speed and working memory, executive functioning, metacognition, or nonspecific/combined.

1.3.1 Types of cognitive rehabilitation

Cognitive rehabilitation programmes can be implemented in a variety of ways, depending on the goal of the intervention and the population. Cognitive rehabilitation encompasses a range of interventions and strategies aimed at improving or compensating for cognitive deficits resulting from MS. Different types of cognitive rehabilitation approaches are tailored to address specific cognitive functions and challenges. Individual cognitive rehabilitation involves people with MS meeting with a healthcare professional regularly for several weeks or months. The cognitive rehabilitation programmes vary with some studies including training programmes such as the modified Story Method Technique,[258] and others focusing on teaching the use of memory aids, often these programmes are individualised depending on the individual's need. The modified Story Memory Technique is a cognitive rehabilitation method designed to enhance memory and learning by creating a narrative or story that integrates the information to be remembered. This helps by providing a meaningful context, making the information more relatable and easier to recall. Compensatory strategies for attention difficulties such as breaking tasks into smaller steps, using external reminders, and creating structured routines, can help individuals manage attention difficulties and mitigate their impact on daily life.

Group-based cognitive rehabilitation involves people with MS meeting with a healthcare professional on a regular basis, but instead of attending alone, the meetings

are held with small groups.[259] This type of cognitive rehabilitation provide individuals with opportunities to practice cognitive skills in a supportive and social setting. A recent RCT investigated the clinical and cost effectiveness of a group-based cognitive rehabilitation programme for people with MS.[260] Four hundred and forty-nine participants were randomly allocated to either receive the cognitive rehabilitation or to receive their usual care. Lincoln et al.[260] found some significant differences at 6-months post-randomisation between the cognitive rehabilitation group and the usual care group for impact of MS and cognitive functioning, suggesting that there is evidence to support that group-based cognitive rehabilitation was effective for people with MS.

Computerised cognitive rehabilitation programmes typically involve a computer programme that has been specifically designed to the target population. One of the main advantages of these programmes is that they can often be completed by people with MS at home. Computer-based programs offer interactive exercises to target cognitive deficits. These programs can be customised to individual needs and provide real-time feedback on performance. RehaCom is a computerised software that was designed to improve people with MS's cognitive functions. There is some evidence to suggest that it is effective for people with MS to improve their cognitive functions as Naeeni Davrani et al..[261] showed that at both 5-week and 10-week follow-ups, participants significantly improved on multiple cognitive outcome measures.

It's important to note that cognitive rehabilitation should be tailored to the individual's specific cognitive deficits, goals, and preferences. A multidisciplinary approach involving neuropsychologists, occupational therapists, speech-language pathologists, and other relevant professionals can provide a comprehensive and effective cognitive rehabilitation plan. Additionally, the efficacy of cognitive rehabilitation approaches can vary based on the underlying condition, severity of cognitive deficits, and individual responsiveness to the interventions. Creating an individualised treatment plan that is tailored to the person with MS's specific needs and goals, can maximise the relevance, engagement, and overall impact of the cognitive rehabilitation process.

1.3.2 The underlying mechanisms of cognitive rehabilitation.

There is uncertainty about the precise mechanisms by which cognitive rehabilitation interventions work. However, it is widely believed that they provide people with the knowledge of, and information about, their memory problems, by

teaching them to use internal and external memory aids, different strategies to pay attention, and alternative ways of encoding, storing, and retrieving information. Targeted, repeated stimulation of certain brain areas using drill and practice cognitive exercises are thought to trigger the activation of neural networks. For group-based interventions, the therapeutic effects of being with others with similar problems may also help.[262,263] Some of these behavioural strategies (referred to as 'restitution' or 'compensation') are believed to map onto the neural networks engaged in performing memory functions.

Behavioural strategies refer to any type of strategy that is used to change a person's behaviour, in this case, to help them better cope with cognitive difficulties. Compensatory strategies are the most common strategy taught in cognitive rehabilitation programmes.[264] These can include internal aids such as mnemonics, associations, visual imagery, or external aids such as smartphones, diaries/calendars, alarms, and smart home devices. Using internal memory aids can lead to a deeper level of processing which involves understanding and attaching meaning to the information that you are trying to remember; this leads to the memory becoming stronger memory trace which means it is more likely to be remembered.[265] Restitution strategies focus on restoring an individual's cognition based on the theory of brain plasticity, which refers to the brain's ability to modify structure and function following changes in the body or in the external environment.[266] In theory, it is possible to rebuild neural pathways in the brain that have been damaged in MS, however, this can take a very long time and the evidence for these restitutions strategies is limited. Therefore, although they may be mentioned in cognitive rehabilitation programmes, they are not the focus. These behavioural strategies form the basis of cognitive rehabilitation. Cognitive rehabilitation aims to improve cognitive function through structured and goal-oriented therapeutic activities, and behavioural strategies are integral to this process.

Maintaining motivation and engagement is crucial for the success of cognitive rehabilitation. Therapists and intervention programs often incorporate engaging and challenging activities to keep individuals motivated and committed to the rehabilitation process.[267] Successful cognitive rehabilitation requires active

participation, patience, and commitment from both individuals undergoing rehabilitation and the professionals guiding the process.[268]

Cognitive rehabilitation is closely linked to cognitive theories, particularly those in the domains of cognitive psychology and neuropsychology. Cognitive theories, such as the Information Processing Model and the Theory of Multiple Intelligences, provide the framework for understanding how individuals process information, learn, and adapt.[269,270] These theories guide cognitive rehabilitation practitioners in tailoring interventions that address specific cognitive deficits, utilising techniques aimed at improving attention, memory, problem-solving, and executive functions. The integration of these cognitive theories allows for a personalised and targeted approach to cognitive rehabilitation, aligning the interventions with an individual's unique cognitive profile. In a group setting, participants will often be grouped according to those who report experiencing similar levels of cognitive difficulties, so that the intervention can be tailored to the needs of the group accordingly. For computerised interventions, baseline assessments are often completed by people with MS before they begin. This is so that the content offered during the intervention can then be tailored according to their level of reported difficulties.

Neuroplasticity is a fundamental concept that forms the cornerstone of cognitive rehabilitation. The theory of neuroplasticity posits that the brain has the remarkable ability to reorganize and adapt, even after injury or damage. Cognitive rehabilitation leverages this theory to drive therapeutic interventions.[271] By engaging individuals in structured and repetitive cognitive exercises, cognitive rehabilitation harnesses the brain's plasticity to create new neural pathways and optimise cognitive functioning.[272]

Cognitive rehabilitation is not solely confined to individual cognitive processes; it also involves social cognitive theories, which consider the influence of social interactions, self-regulation, and observational learning on cognitive functioning. Social cognitive theories, such as Bandura's Social Learning Theory, inform how individuals acquire and apply cognitive strategies.[273] In the context of cognitive rehabilitation, these theories underscore the importance of social support, modelling, and self-efficacy in the acquisition and utilisation of cognitive skills.

Determining the effectiveness of cognitive rehabilitation can be challenging due to various factors that impact the evaluation process. Heterogeneity of the MS population is a common problem in that people with MS often have unique cognitive profiles due to the extreme variability of the disease course.[274–276] This heterogeneity makes it difficult to apply a one-size-fits-all approach and compare outcomes across different groups. Similarly, cognitive difficulties can manifest in various ways, even within the same cognitive domain. For example, two individuals with memory deficits might experience different types and degrees of impairment. This variability makes it hard to establish standardised interventions and measures.

Because there is no universally agreed upon definition for cognitive impairment nor a gold standard for measuring cognitive deficits, measuring the effectiveness of this intervention is increasingly challenging. Furthermore, some cognitive deficits may be subtle and not easily captured by standardised assessment tools. Small changes in cognitive performance might not be detected, leading to difficulties in demonstrating meaningful improvements. Evaluating the long-term effectiveness of cognitive rehabilitation is complex. Short-term gains might not necessarily translate into sustained improvements over time, especially in real-world settings where various factors can influence cognitive functioning.

Addressing these challenges requires careful study design, appropriate outcome measures, and consideration of the individual characteristics of participants. Researchers must also acknowledge that the effectiveness of cognitive rehabilitation can vary based on factors such as the type and severity of cognitive deficits, the chosen intervention approach, the duration and intensity of intervention, and the individual's responsiveness to treatment. Future research should aim to refine assessment methods and interventions to better understand and improve the effectiveness of cognitive rehabilitation.

1.4 Rationale

There is a need to explore which subgroups of people with MS benefit most from memory rehabilitation so that we can use this information to guide clinicians to help make decisions as to whom the intervention is offered. Cognitive rehabilitation is not routinely provided on the National Health Service (NHS) due to lack of resources and the conflicting evidence surrounding its effectiveness for people with MS. This

research is important so that these resources can be optimised and made available to those that need them, and so that the effectiveness of cognitive rehabilitation can be established. Furthermore, this research will also allow clinicians to understand whether their patient is likely to benefit from cognitive rehabilitation before it is offered.

Before delving into subgroup analysis, it is imperative to establish the overall benefits of this treatment and identify key areas of cognition where substantial improvement can be achieved. The integration of clinical prediction tools becomes pivotal in making informed decisions about matching patients with treatments for optimal outcomes,[277] such as aligning with the Stratified Medicine agenda.[278]

The current literature lacks clinical prediction tools, except for the subjective and variable 'clinical judgement,' to identify those who would benefit most from group-based cognitive rehabilitation. We[1] therefore aimed to close this research gap, seeking to provide a more objective and standardised approach to determine the individuals most likely to benefit from this intervention. This research not only addresses the need for tailored cognitive rehabilitation but also contributes to advancing personalised and stratified approaches in the realm of medicine.

1.5 Aims of the PhD

The overall aim of this research was to establish the effectiveness of cognitive rehabilitation for people with MS and understand which groups of people with MS are most likely to benefit from this intervention.

Determining which groups of people with MS benefit most from cognitive rehabilitation could:

- Optimise limited NHS resources in a resource-efficient way, and
- Reduce the occurrence of treatment provision to those unlikely to benefit or improve from them, reduce unnecessary travel to the therapy sessions, and reduce any unnecessary distress or frustration of having participated in a treatment that did not work.

[1] I use the term 'we' in this PhD because although I led the work, there was a team (which included my supervisors) that supported this work. This is also in keeping with the Team Science philosophy, which seeks to acknowledge the contributions of many people to answer scientific questions.

Study 1: We conducted a systematic review to determine whether people with MS who received memory rehabilitation compared to those who received no treatment, or a placebo, showed better immediate, intermediate, or longer-term outcomes in their: (1) memory functions, (2) other cognitive abilities, and (3) functional abilities, in terms of activities of daily living, mood, and quality of life.

We conducted Study 1 first so that we could establish whether the existing research supports the use of cognitive rehabilitation as an intervention for people with MS who have experienced cognitive difficulties. If this was the case, then we could move away from asking the question "does memory rehabilitation benefit people with multiple sclerosis?" and move towards asking "who does it benefit the most?" in study 2.

Study 2: A secondary data analysis of the Cognitive Rehabilitation for Attention and Memory in Multiple Sclerosis (CRAMMS) trial that aimed to identify who benefited most from cognitive rehabilitation and to further identify which factors/characteristics (if any) could be used to predict an individual's improvement in cognition, psychological wellbeing, or daily function following cognitive rehabilitation. We aimed to create an algorithm that could be used to predict whether an individual is likely to benefit from cognitive rehabilitation. This would allow clinicians to target cognitive rehabilitation toward those most likely to benefit.

Study 3: Results from study 2 informed the final study which was a feasibility RCT. We recruited a sample of people with MS that included participants who had reported experiencing cognitive difficulties. Study 3 aimed to understand the feasibility and acceptability of conducting an online group-based cognitive rehabilitation for people with MS. Furthermore, this study aimed to identify preliminary signals of efficacy of the predictive algorithm developed in study 2.

Chapter 2: Memory rehabilitation for people with MS: A systematic review.

The previous chapter gave an overview of MS including the symptoms, subtypes and how MS affects cognition. Difficulties with cognition are experienced by up to 70% of people with MS, thus, highlighting the need for an effective treatment. Cognitive rehabilitation has consistently been highlighted as the most investigated treatment for cognitive difficulties, however, results of studies have yielded mixed results. Other treatments such as pharmacological treatments and psychosocial interventions can be used to address other MS symptoms such as depression and anxiety which are often linked to cognitive difficulties, but they do not target the root of the problem.

This chapter presents a systematic review exploring the effectiveness of cognitive rehabilitation for people with MS in improving several cognitive domains, mood, and activities of daily living. The findings of this review will not only inform the design of subsequent studies, but also inform clinical practice.

2.1. Rationale

Studies have examined the effectiveness of memory rehabilitation using different methods. Single-case and small-group studies have reported positive results of memory rehabilitation, but the results obtained from RCTs and some systematic reviews have been less positive and reported inconclusive evidence.[239,242–245,247,249] Some reviews have concluded that there is compelling evidence for memory strategy training with participants with mild memory problems following traumatic brain injury, that the use of external memory aids may be beneficial for people with moderate to severe memory problems, and that errorless learning may be effective for those with severe memory impairments (albeit with limited generalisability to new tasks or overall memory problems).[251,279,280] Cicerone et al.[251] also suggests that group-based interventions may be considered as part of a comprehensive neuropsychological rehabilitation of memory deficits. However, these reviews focused mainly on people with traumatic brain injury.

Some reviews have focused on generic psychological interventions for people with MS,[255] or neuropsychological interventions for people with MS,[256] however these were not specific to memory rehabilitation. The Thomas et al.[255] review did not consider grey literature and was unable to draw any "definite conclusions". The

Rosti-Otajärvi et al.[256] review focused on neuropsychological rehabilitation across multiple cognitive domains, as well as associated health-related factors and emotional well-being. The Goverover et al.[257] review was similar in that it focused on cognitive rehabilitation in six cognitive domains: attention, learning and memory, processing speed and working memory, executive functioning, metacognition, or nonspecific/combined.

The current systematic review focused solely on the effectiveness of memory rehabilitation for people with MS; databases were searched that were not searched as part of the Rosti-Otajärvi et al.[256] or Goverover et al.[257] reviews, and studies are included that were not in these reviews. This is an update of the Cochrane Review 'Memory rehabilitation for people with multiple sclerosis' (first published in the Cochrane Library 2012, Issue 3; das Nair 2012) which was last updated in 2016.[254] The previous update of the systematic review found inconclusive evidence to support the effectiveness of memory rehabilitation for people with MS.

2.2 Objectives

To determine whether people with MS who received memory rehabilitation compared to those who received no treatment, or an active control, showed better immediate, intermediate, or longer-term outcomes in their:

- memory functions,
- other cognitive abilities, and
- functional abilities, in terms of activities of daily living, mood, and quality of life.

2.3 Methods

2.3.1 Criteria for considering studies for this review.

2.3.1.1 Types of studies

For inclusion in the review, we sought randomised and quasi- randomised controlled trials, as defined by the Cochrane Handbook for Systematic Reviews of Interventions,[281] and the pre-cross-over component of randomised cross-over trials with people with MS, in which a memory treatment was compared to a control. Where papers were based on the same sample, or subset of a larger sample, we included only the study with the full sample to avoid double counting. If a study

was available through both grey literature (for example conference abstract) and a peer-reviewed publication, we used the peer-reviewed publication.

2.3.1.2 Types of participants

Trials included in this review were limited to those with people with MS (including relapsing remitting, secondary progressive, and primary progressive MS). We excluded trials with participants whose memory deficits were the result of traumatic brain injury, brain tumour, stroke, epilepsy, or any other neurological condition, unless we could define a subgroup of people with MS of at least 75% for which there were separate data. Included studies based a diagnosis of MS on well-established diagnostic criteria, for example Paty et al.[282] and Poser et al.[283] (and revised versions of the McDonald criteria).[284–286] We did not define the type of memory deficits participants needed to have in advance, because we assumed that those people with MS who were given treatment for impaired memory had memory deficits. We placed no restrictions on the type of memory deficits participants reported.

2.3.1.3 Types of interventions

We included trials in which there was a comparison between a treatment group that received memory rehabilitation strategies, and a control group that received either a comparable standard of treatment (active control) or no memory intervention. We considered rehabilitation to take place over more than a single session; therefore, we did not consider laboratory-based experiments (such as single-session list-recall or mnemonic strategy training) as rehabilitation.

Control groups needed to have people with MS, or a subgroup of people with MS amongst those with other diagnoses, for whom separate data were available. We considered memory rehabilitation to be any attempt to modify memory function by means of drill-and-practice, or using internal and/or external memory aids, or by teaching people with MS strategies to cope with their memory problems. We did not include pharmacological studies.

2.3.1.4 Types of outcome measures

We included trials in which the intervention group either received memory rehabilitation or comprehensive cognitive rehabilitation with a memory component. We considered all trials that met the listed inclusion criteria and did not discriminate based on the type of memory outcomes or other cognitive

outcomes they used. We considered memory outcomes to be any questionnaire or test that measures general memory or a specific domain such as verbal memory. The nine outcomes listed below were decided before the analysis was conducted to avoid bias.

Primary outcomes

Primary outcomes were measures of the extent of memory problems in everyday life. There are several ways in which this is assessed in clinical practice and research, but we only included measures that directly assessed this construct. Where multiple tests were used to assess the same construct, we followed a hierarchy that we developed prior to data analysis. We developed this hierarchy based on the reliability and validity of the tests in the MS population. Where tests had similar reliability and validity, we prioritised those that were most commonly used. By developing a hierarchy based on reliability and validity, then considering frequency of use, our approach ensures that the outcome measures selected are both scientifically rigorous and practically useful. We included the following commonly used tests.

For subjective reports of memory: we considered Everyday Memory Questionnaire (EMQ),[287] over the Cognitive Failures Questionnaire,[288] over the Subjective Memory Questionnaire,[289] over the Memory Assessment Clinics Questionnaire.[290] If more than one questionnaire was used, we used the following hierarchy: memory problems in daily life, over general forgetting, over domain-specific questions. If a questionnaire was used that was not in this hierarchy, we arrived at a consensus through discussion prior to data extraction to avoid bias.

For objective verbal measure of memory: we considered California Verbal Learning Test (CVLT-II)[291] over Selective Reminding Test (SRT)[292], over Doors and People Test[293]. For neuropsychological test batteries, we used verbal domain-specific scores over composite scores.

For objective visual measures of memory: we considered Brief Visuospatial Memory Test – Revised (BVMT-R),[294] 10/36 Spatial Recall Test (SPART),[295] Contextual Memory Text (CMT),[296] Rey-Osterrieth Complex Figure text (ROCF).[297,298] For neuropsychological test batteries, we used visual domain-specific scores over composite battery scores.

For objective measures of working memory: we considered Rivermead Behavioural Memory Test (RBMT),[299] over Wechsler Memory Scale (WMS),[300] over Cambridge Test of Prospective Memory,[301] over Doors and People Test.[293]

For information processing measures: we considered the Symbol Digit Modalities Test (SDMT)[302] over other measures, because we were aware that this is one of the most frequently used tests of information processing in MS research.[303] While distinct, information processing speed and memory are interrelated. Slow processing speed can affect the efficiency of memory encoding and retrieval, which is why information processing speed is included in the primary outcomes.

Where studies included more than one test for each outcome group, we used a hierarchy based on the tests' degree of sensitivity to assess everyday memory problems and the tests' ecological validity. If we were unsure about which outcome measure to consider in the analysis, we arrived at a consensus following a discussion with review authors which measure to consider as the primary outcome before the statistical analyses were conducted to minimise bias.

Secondary outcomes

Mood - depression, such as the General Health Questionnaire (GHQ),[304] Hospital Anxiety and Depression Scale (HADS);[305] Beck Depression Inventory-Fast Screen.[306] General mood outcomes such as the GHQ were included in both the depression and anxiety scales of the mood outcome.

Mood - anxiety, such as the General Health Questionnaire (GHQ),[304] Hospital Anxiety and Depression Scale (HADS),[305] State Trait Anxiety Inventory (STAI) (Spielberger 1983).[307]

Functional abilities, such as the Functional Independence Measure (FIM),[308] Functional Assessment Measure (FAM),[309] Nottingham Extended Activities of Daily Living (EADL).[310]

Quality of life, such as the Multiple Sclerosis Impact Scale (MSIS),[311] World Health Organization Quality of Life assessment (WHO-QoL),[312] 36-item Short Form Health Survey (SF-36).[313]

We also considered non-standardised measures, such as return to work and goal attainment, if studies had included these as a measure of outcome. If more than one of these scales was reported for each domain, we used the first scale in the list.

We categorised all outcomes into three separate time-points: "immediate", "intermediate", and "longer-term" and conducted separate analyses for each of these. We defined immediate as assessments conducted within the first month after completing the intervention, intermediate as assessments conducted between one to six months later, and longer-term as any assessments conducted more than six months later.

2.3.2 Search methods for identification of studies

We conducted an electronic search with no restriction and identified all potential studies. We included many terms in our search criteria, including attention. Including attention in the search terms for the systematic review was a strategic decision to ensure a comprehensive evaluation of cognitive rehabilitation interventions. Cognitive rehabilitation programmes frequently target multiple cognitive domains, including both attention and memory. Including attention in the search terms ensures that studies focusing on multi-domain interventions were not overlooked, which was crucial for a complete assessment of cognitive rehabilitation strategies. As long as studies had a memory component in their cognitive rehabilitation programmes, they were included in this review.

2.3.2.1 Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2 June 2015 to 6 September 2020) which contains records from the following databases.

- MEDLINE (PubMed).
- Embase (Embase.com).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO host).
- ClinicalTrials.gov.
- World Health Organization (WHO) International Clinical Trials Registry Portal (http://apps.who.int/trialsearch/).

The keywords used to search for studies for this review are listed in Appendix A.

We also searched the following databases.

- The NIHR Clinical Research Network database (2 June 2015 to 6 September 2020).
- PsycINFO (2 June 2015 to 6 September 2020).
- Allied and Complementary Medicine Database (AMED) (2 June 2015 to 6 September 2020).
- American and Caribbean Health Science Information Database (LILACS) (Bireme) (2 June 2015 to 6 September 2020).
- CAB Abstracts (2 June 2015 to 6 September 2020).

2.3.2.2 Searching other resources.

We citation tracked all primary study articles and scanned reference lists from book chapters and review articles. We also examined studies identified by the Rosti-Otajärvi et al.[256] and Thomas et al.[255] MS reviews for inclusion. We only hand searched the reference lists of identified studies, not the full scientific journals, as until the early 1990s cognitive impairments were not universally recognised as a common complaint in MS,[60] and most RCTs have been reported (or updated) on electronic databases or journals. Furthermore, we would have found relevant trials from the search of the CENTRAL database, for which handsearching is carried out periodically, and we did not wish to duplicate this effort. Where necessary, we contacted authors of relevant trials to enquire whether their registered trials had been published, and to solicit more data where data required for the meta-analysis were not presented in the published paper in a format that could be used.

We accessed grey literature by searching (http://www.greynet.org/) and the British Library's EThOS database (http://ethos.bl.uk/ Home.do). Grey literature is "a field in Library and Information Science that deals with the production, distribution, and access to multiple document types produced on all levels of government, academics, business, and organisation in electronic and print formats not controlled by commercial publishing i.e., where publishing is not the primary activity of the producing body".[314]

2.3.3 Data collection and analysis

2.3.3.1 Selection of studies

We used the search strategy that was developed in consultation with a senior librarian and the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group for the previous review update (see Appendix A). We evaluated abstracts of the studies obtained by this search strategy and identified trials for inclusion in the review using four inclusion criteria (Handbook for Systematic Reviews of Interventions (see Appendix B).[281]

The table includes the following domains.

- Random sequence generation
- Allocation concealment
- Blinding (of participants, personnel, and outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias

Based on the information provided in the studies or by the authors of the primary studies, five review authors independently judged each of these domains as being low or high risk of bias, or unclear if information was insufficient. As the primary author, I reviewed all abstracts and the other reviewers reviewed a selection of abstracts, so that all abstracts were judged by myself and one other person. Similarly, when it came to reviewing full texts and assessing risk of bias, I reviewed all studies and the review authors reviewed a selection. The review authors were all academics with expertise in MS research and a range of positions including professors (RdN, DW), neurologists (NE), research fellows (LS, JMM).

Any disagreements were arbitrated by my primary supervisor. As review authors working in the field of memory rehabilitation, we are familiar with the studies published in this area, and thus we could not be blinded to the names of the authors, institutions, or the publishing journal of the included trials. We made an evaluation of the overall risk of bias, based on the relative importance of the various domains listed. In addition to the risk of bias table, we used the GRADE approach to assessing quality of studies.[315] This was completed across outcomes

and is found in the summary of findings table. This approach allows for judgements to be made about the quality of the studies included in each outcome.

2.3.3.2 Measures of treatment effect

We planned to use odds ratio (OR) with 95% confidence intervals (CIs) for binary outcomes if reported. We used standardised mean difference (SMD) with 95% CIs for the continuous outcomes.

2.3.3.3 Unit of analysis issues

We included parallel-group, cluster-randomised, cross-over RCTs, and quasi-RCTs, and included the data from all these types of studies for the meta-analysis. For cross-over studies (as mentioned under Types of studies section), we only included the pre-cross- over phase of these trials. We did not combine the first and second phases of the cross-over studies because of uncertainty about the carry-over effects in such trials, given that they are psychological interventions, where the washout period is difficult to determine.

We included trials with more than two intervention groups and analysed them by pooling together the data on all the treatment groups (if appropriate) and compared them with the control group. If there was more than one control group, the results from the control groups were pooled together and compared with treatment.

We conducted separate analyses for the various outcomes and for the three different time-points (i.e., immediate, intermediate, and longer-term).

2.3.3.4 Dealing with missing data.

Where data were not available from or unclear in the reports, we contacted the corresponding author of the studies in question for further information. We assessed the rates of attrition and missing data from the included studies (where available) and explored how these may have affected the results of the studies. If following several attempts to contact the study author we had not received a response, the missing data were not included in the analysis. Furthermore, if standard deviations (SDs) were not available from the papers, these values were inputted using methods specified in section 16.1.3.1 of the Cochrane Handbook for Systematic Reviews of Interventions.[281]

2.3.3.5 Assessment of heterogeneity

We considered heterogeneity by comparing the distribution of important participant factors between trials (age, gender, type of MS), and trial factors (sequence generation, allocation concealment, blinding, losses to follow-up). We used the I2 statistic to statistically assess heterogeneity.[281,316] We further scrutinised the studies to explore the reasons for the heterogeneity if the I2 statistic was significant at >= 50%.

2.3.3.6 Assessment of reporting biases

We considered reporting bias by conducting an exhaustive search of the literature that included but was not limited to the CENTRAL database, Embase, PsycINFO, LILACS, grey literature, reference lists of included studies and relevant reviews. We also considered reporting bias by deciding what outcomes would be assessed and reported before the meta-analysis was conducted.

2.3.3.7 Data synthesis

We consulted the Cochrane Handbook for Systematic Reviews of Interventions to plan the data synthesis,[281] and followed the procedures outlined therein. As most psychological and neuropsychological outcome measures in memory rehabilitation tend to be ordinal-level measures, we treated these as continuous data (as recommended by Higgins et al.[281]). The SMD was used as a summary statistic, using a random-effects model, because we predicted that multiple trials would use various outcome measures to assess memory and because of the heterogeneity of sampling.

As the primary author, I conducted all statistical analyses for this review. For analyses, we used RevMan,[317] Cochrane's integrated software for writing and analysing Cochrane reviews. The random-effects model was set up in RevMan to account for variability both within and between studies. This approach was appropriate given the anticipated heterogeneity in the included studies. The model assumed that the true effects vary between studies, allowing for a more generalised conclusion.

If low scores represented a better outcome, the valence of the score was changed from positive to negative. We typically had to change the scores for questionnaires, such as the EMQ, where lower scores represented better everyday memory. In situations where studies combined scores from scales in

which high scores are in some instances good outcomes and in some instances poor outcomes, the signs of the discrepant scores were reversed to keep them consistent. We only considered data that we deemed to be similar or comparable enough to meaningfully pool based on of the outcome measures used for the meta-analysis.

2.3.3.8 Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses where at least two trials had separate data available for people with different subtypes of MS. Where significant heterogeneity was observed, we attempted to determine the causes of heterogeneity and explain this in our discussion. We did not plan on conducting subgroup analyses based on heterogeneity.

2.3.3.9 Sensitivity analysis

We considered sensitivity analyses to assess the impact of study quality (whether there was a difference between studies using an intention-to-treat analysis and an on-treatment analysis) where data needed to perform such analyses were available from the included papers. We also considered a sensitivity analysis to assess the influence of methodological quality on the intervention effect for each outcome by comparing the outcomes of those trials with low risk of bias with the outcomes of all the included studies. Following the Cochrane Handbook for Systematic Reviews of Interventions,[281] we made only informal comparisons (Table 20) and did not conduct individual forest plots for each sensitivity analysis but provided a summary table. Sensitivity analysis was also conducted to assess the impact of inputting the SD values as advised in the Cochrane Handbook for Systematic Reviews of Interventions.[281]

2.3.3.10 Summary of findings and assessment of the quality of the evidence

We used the GRADE approach to interpret findings and present them in a 'Summary of findings' table, as advised in the Cochrane Handbook.[281] We considered all our outcomes at each time point they were measured to be important in the table, and thus present them in the 'Summary of findings' table (Table 19; Appendix C).

The GRADE approach allows the quality of the evidence to be assessed clearly and without bias using four possible ratings: high, moderate, low, and very low.[318] This rating system measures the degree of confidence that the true effect is close

to that of the estimate of the effect, with high indicating very confident and very low indicating little confidence in the effect estimate. There are several factors that can lead to the downgrading of evidence such as risk of bias in included studies, inconsistency in results, and imprecision of effect estimates. If an outcome is downgraded, the reasons for this are detailed in the footnotes below the 'Summary of findings' table.

2.4 Results

2.4.1 Description of studies

2.4.1.1 Results of search

We identified a total of 29 studies using the above-mentioned search strategy. Fifteen studies from the previous review in 2016 were added to the 29 new studies in the final analysis. Please see Figure 3.

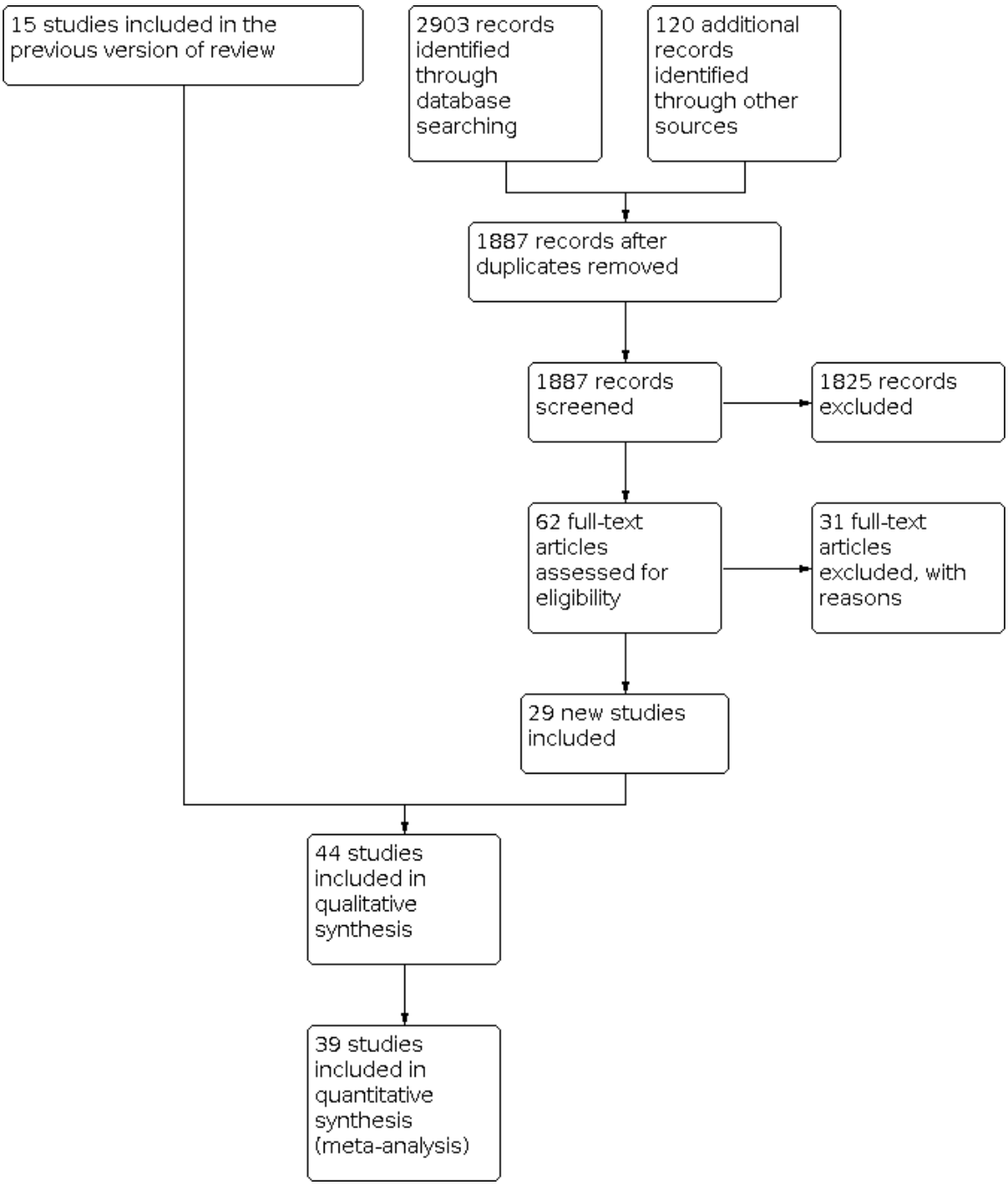


Figure 3 Flow diagram showing article screening process.

2.4.1.2 Included studies.

Forty-four studies, comprising 2714 participants in total, met the inclusion criteria for this review,[242,245–248,319–355] and three additional studies were included in the review,[356–358] but excluded from the meta-analysis because raw data were unattainable. I contacted the authors of these studies requesting the data (means and standard deviations) required for analysis but they declined to response, therefore, these studies could not be included in the meta-analysis. We checked

all studies to ensure that no samples were duplicated, if we found that samples were duplicated, then those studies were excluded.

Twenty-eight of the included studies were undertaken in Europe (Austria, Denmark, Germany, Italy, Norway, Spain, Greece, Czech Republic, the UK), seven were from Iran, and nine were from the USA. All the European studies were recruited at hospital clinics or rehabilitation centres, with seven of these European studies recruiting from multiple centres.[260,330,331,341,343,348,352] The maximum number of recruitment sites used was 10.[341] Seven of the USA studies recruited participants from both clinic and community settings, with two of these USA studies recruiting from multiple centres.[322,354]

There were nine multicentre trials.[260,330,332,341,343,344,348,352,354] In terms of randomisation and stratification by site, three studies used a site-stratified schedule.[343,344,352] Lincoln et al.[259] had a 6:5 randomisation ratio, stratified by site and minimised by type of MS. Stuifbergen et al.[354] used a closed envelope method but did not specify stratification. Chmelařová et al.[324], Perez-Martin et al.[348], Rahmani et al.[350], did not specify their method of randomisation. Chiaravalloti et al.[322], Goodwin et al.[330],and Mattioli et al.[341] used random number generators, but did not specify stratification, and Stuifbergen et al.[354] used the closed envelope method. Hancock et al.[332] used a block-stratified randomisation procedure to ensure that equal types of each MS subtype were included in the intervention and control groups.

There were 35 single-centre trials.[242,245–248,319–324,326–329,331,333–335,337,338,340–342,345–347,349–351,353,355,356,358,359] Five studies did not mention the method of generating the random schedule.[325,327,342,347,355] One study reported that randomisation was quote: “performed by a lottery by the director of the rehabilitation centre”.[246] Four studies used quasi-randomisation: Chiaravalloti et al.[320] used odd-even random allocation, Hildebrandt et al.[334] and Pusswald et al.[349] allocated by alternating between intervention and control, and Arian Darestani et al.[325] quote: “divided [the participants] into control (n = 30) and experimental (n = 30) groups”. Six trials reported independent randomisation (Carr 2014; Chiaravalloti 2013; das Nair 2012; Lincoln 2002; Solari 2004; Tesar 2005),[262,321,336,338,352,355] and Jønsson et al.[358] and Stuifbergen et al.[353] used a closed-envelope method. Mendozzi

et al.[342] randomised the first 30 participants, and purposefully assigned the last 30 to balance age, gender, and education between groups; all data were included in our analysis. Gich et al.[329] stratified by level of cognitive impairment.

Participants were diagnosed with MS using the Poser criteria[283] in seven studies, using the McDonald criteria in 18 studies,[284] and the Schumacher criteria[360] in one study. Eighteen studies did not report the criteria used to diagnose MS, but merely stated that participants had clinically-definite MS. Twenty-six studies included participants with mixed types of MS (relapsing remitting MS (RRMS) and secondary progressive MS (SPMS);[242,329,336,338,342,345,347,355,361] and 14 studies included participants with RRMS, SPMS, and primary progressive MS (PPMS).[246,248,260,262,320–323,332,340,348,351,356,358,362] Eight studies included participants with RRMS only.[247,327,328,334,341,343,350,363] Two studies Chiaravalloti et al.[322] and Huiskamp et al.[333] included participants with RRMS, SPMS, PPMS and progressive-relapsing MS, while Goodwin et al.[330] included these participants and participants with benign MS and "unknown" types. The type of MS was not reported in eight studies.[324,325,345,349,352,353,359,364] Type of MS was important to understanding the effectiveness of cognitive rehabilitation as it is possible that cognitive rehabilitation may be effective for relapsing MS but not progressive or vice versa. However, it could be argued that as the aim of this review was to determine the overall effectiveness of cognitive rehabilitation, rather than the differential impact on various types of MS, then knowing the type of MS may not be necessary. While type of MS can provide us with broader context for understanding the benefits of cognitive rehabilitation, it is more of a secondary factor.

The number of participants in the studies ranged from 16, in Huiskamp et al.[333], to 449, in Lincoln et al.[260], and the number of participants in treatment or control groups ranged from seven, in das Nair et al.[336] and Huiskamp et al.[333], to 245, in Lincoln et al.[260] Most participants were in their 40s. Varied gender ratios were reported, with the percentage of women ranging from 36.7%, in Impellizzeri et al.[340] 2020, to 100%, in Mani et al.[245] and Rahmani et al.[350] The participants had a minimum of elementary education in most studies, with the participants in the Chiaravalloti et al.[323] having the highest number of years of education (16.07 in intervention, 16.46 in control). De Luca et al.[359] and Perez-Martin et al.[348] had the lowest number of years of education (10.8 in intervention, 11.3 in control and

10.2 in intervention, 11.6 in control, respectively). Six studies did not report education.[247,248,324,345,355,365]

The groups were comparable on assessed baseline characteristics in 32 studies, and in the other studies where differences were observed, they were statistically corrected,[320,332–334,336,352,358] with the exception of Mendozzi et al.[342] and Stuifbergen et al.[353] Arian Darestani et al.[325] and Rahmani et al.[350] both appeared to be matched for baseline characteristics, but no statistics were reported, and Charvet et al.[356] had unequal groups due to stratification requirements but overall was well-matched.

Thirty-seven studies used two-group comparisons (treatment versus control), and six studies used three-group comparisons.[327,336,338,342,345,365] Lincoln et al.[338] used assessment versus assessment plus feedback versus assessment plus feedback and treatment; Mendozzi et al.[342] examined specific cognitive retraining versus non-specific cognitive retraining versus control; and das Nair et al.[336] investigated restitution versus compensation versus self- help control. Rahmani et al.[350] used computer-based versus manual-based versus mixed cognitive rehabilitation versus placebo versus control, five groups in total.

Twenty-nine studies used individual treatment, including clinic- based and home-based interventions,[242,257,322–325,328,332–335,338,341–344,350,352,354,356–358,364,366–371] and 13 had group interventions.[147,245,248,260,262,320,336,340,345,353,355,365,372] Hanssen et al.[246] used a mix of both group and individual sessions, and Stuifbergen et al.[353] used both group sessions and individual computerised sessions.

The structure and content of the treatment programmes varied. Most interventions were of four to eight weeks duration.[147,245–247,320,322–325,330,332–334,337,338,340,342,344,345,347,349,352,354,355,358,364,365,373] Carr et al.[262] , das Nair et al.[336], Lincoln et al.[260], and Messinis et al.[343] had 10-week programmes, Charvet et al.[356] and Perez-Martin et al.[348] had 12-week programmes, Mattioli et al.[341] had a 15-week programme, Rahmani et al.[350] had a 21-week programme, and Gich et al.[329] used a six-month programme. Four studies did not specify set durations of their treatment but either selected several sessions to be completed when the participants were available[248,327,328] or specified a timeframe for the sessions to be completed in.[338]

Sessions ranged from 30 minutes,[334,347,349], and two hours,[245,246,248] and participants met one to six times a week in all studies except Mendozzi et al.[342], where the treatment was bi-weekly. The Goodwin et al.[330] study lasted for two months, and the session frequency varied as it was dependent on the types of text message reminders each participant required. The lowest number of total sessions was six[327,328,331] and the highest number of total sessions was 60.[356] Fourteen studies had between eight and 10 sessions.[147,245,248,260,262,320,322,323,325,345,364,365,374,375] Nine studies had between 12 and 18 sessions.[242,247,336,342,348,349,352,355,358] Seven studies had between 20 and 30 sessions.[334,335,343,344,350,353,359] Six studies had between 32 and 48 sessions.[324,329,332,340,351,353] For two studies the frequency of sessions depended on individual need.[330,338]

In three studies, the contents of the treatment programmes were individualised,[246,368,376] depending on the needs of the participant. Seven studies used comprehensive memory rehabilitation programmes (including teaching participants to use internal and external memory aids).[260,262,336,338,358,370,377] Sixteen studies used computerised memory- and attention-retraining packages,[242,247,324,325,334,342,354,356,364,369–371,373,378–380] and Chiaravalloti et al.[320], Chiaravalloti et al.[321], and Chiaravalloti et al.[381] used the Story Memory Technique, which involved the use of imagery and story generation. De Luca et al.[359] used both computerised and paper-and-pencil training strategies but did not explain the specifics of what this entailed. Goodwin et al.[330] used mobile phones to deliver reminders throughout the day, and the number of messages delivered varied depending on each person's needs.

Studies that had a sham or attention control group reported having ensured that these groups had minimal memory content, thereby reducing contamination.[320,321,328,332,336,345,350,352,358,365]

Lincoln et al.[260] assessed fidelity of intervention using three methods: firstly, a the cognitive rehabilitation followed a manual that was developed and tested in a pilot study,[319] secondly; the training was delivered by psychology graduates with clinical experience and they received training from a clinical psychologist as well as monthly teleconferences to discuss specific challenges; and thirdly, the

intervention sessions were recorded and coded by an independent researcher using the time-sampling procedure and found that the intervention was delivered as intended. However, only three other studies assessed fidelity of intervention.

The 44 included studies used a range of outcome measures. All studies included at least one measure of learning or memory, except for Hanssen et al.[246], where outcomes were related to psychological functioning and impact of disease.

Seventeen studies used subjective measures of memory. Six studies used the Everyday Memory Questionnaire (EMQ),[248,260,262,330,336,382] and das Nair et al.[336] used the Internal and External Memory Aids Questionnaires based on the Memory Aids Questionnaire.[383] Four studies[245,320,331,384] used the Memory Failures Questionnaire (MFQ);[385] and three studies[348,353,365] used the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ);[386] Chiaravalloti et al.[322] used the Awareness Questionnaire (AQ);[387] Chmelařová et al.[324] used the Cognitive Failures Questionnaire (CFQ);[288] Stuifbergen et al.[354] used the strategy subscale of the Multifactorial Memory Questionnaire (MMQ).[388]

Twenty-five trials used list-learning tasks: two studies[320,351] used the Hopkins Verbal Learning Task-Revised (HVLT-R);[389] Tesar et al.[355] used the Verbal Learning Test (VLT);[390] 10 studies[242,321–323,325,331,334,353,354,371] used the California Verbal Learning Task-II (CVLT);[291] Messinis et al.[344] used the Greek Verbal Learning Trial (GVLT) (Messinis 2020); Hancock et al.[379] used the Auditory Verbal Learning Test (AVLT);[391] eight studies[260,340,341,343,348,367,369,392] used the Selective Reminding Test; and the list-learning task used by Jønsson et al.[358] Seven studies used neuropsychological test batteries or subtests of these. One study, Mendozzi et al.[342], used the memory scale of the Luria-Nebraska Neuropsychological Battery (LNNB) consisting of 13 items.[393] Subtests from other test batteries included Buschke Selective Reminding Test from an Italian version of the Brief Repeatable Battery of Neuropsychological Tests (BRBNT),[394] unspecified tests from the Rivermead Behavioural Memory Test (RBMT-E),[299] and the Doors and People Test.[395] Pusswald et al.[349] used the MUSIC assessment,[396] and Jønsson et al.[358] used an unspecified battery. Non-verbal memory was assessed using individual tests or part of a battery.

Individual tests included the Noverbaler Lerntest (NVLT) used by Tesar et al.[355], and an unspecified 50-faces recognition test was used by Jønsson et al.[358]

Seventeen trials used visual objective memory measures: eight studies used Brief Visuospatial Memory Test (BVMT-R);[242,247,322,323,354,371,373,397] seven studies used the 10/36 Spatial Recall Test (SPART);[260,295,337,340,341,347,348,359] Contextual memory test (CMT);[296,331] Rey-Osterrieth complex figure (ROCF).[297,361]

Fourteen trials used working memory measures: Paced auditory serial addition test (PASAT);[260,261,340,341,347,348,350,354,359,361] two studies used the N-back test;[333,347] Digit span WAIS subtest.[248,351]

In terms of 'other cognitive outcomes', the most frequently assessed cognitive domain was information processing. Nineteen studies included information processing measures: 16 studies[242,247,260,325,332,340,341,343,344,347,348,351–354,357] used the Symbol Digit Modalities Test (SDMT); Rahmani et al.[350] used the Stroop colour test (SCWT) (Stroop 1938); Chmelařová et al.[324] used the Trail Making Test (TMT); Hanssen et al.[246] used the Behaviour Rating Inventory of Executive Function – Adult version (BRIEF-A).

The most frequently used mood measure was the Beck Depression Inventory (BDI),[306] used in 11 studies.[248,320,324,332,334,335,340,344,345,355,359] Six studies, Carr et al.[262], das Nair et al.[336], Goodwin et al.[330], Lincoln et al.[338], Lincoln et al.[260], and Mousavi et al.[345], used the General Health Questionnaire (GHQ-28);[304] three, Chiaravalloti et al.[147], Chiaravalloti et al.[323], and Goverover et al.[331], used the Chicago Mood Depression Inventory (CMDI),[398] and two of these studies also used the STAI (depression and anxiety subscale); Chiaravalloti et al.[323] and Goverover et al.[331], and another, Solari et al.[352], used the Italian version of the CMDI.[399] Mattioli et al.[341] used the Montgomery-Asberg Depression Rating Scale (MADRS, depression and anxiety subscale), Stuifbergen et al.[354] used the Centre for Epidemiological Studies Depression (CES-D).

Nine studies[248,332,337,338,340,341,348,352,359] assessed quality of life using the Multiple Sclerosis Quality of Life (MSQOL-54),[400] three studies, Carr et al.[262], Hanssen et al.[246], and Lincoln et al.[260] used the Multiple Sclerosis Impact Scale (MSIS-29),[311] two studies, Goodwin et al.[330] and Messinis et al.[344], used the EQ-5D-5L, one,

Chiaravalloti et al.[323], used the SF-36 and one, Goverover et al.[331], used the Satisfaction with Life Scales (SWLS).

Only two studies[336,338] examined whether their rehabilitation programme affected instrumental ADL, by using the Extended Activities of Daily Living scale (EADL).[401] Four studies[147,242,323,331] assessed functional independence with the Functional Assessment of Multiple Sclerosis (FAMS).[402] One study, Stuifbergen et al.[354], used the Instrumental Activities of Daily Living (IADL).

Eighteen studies were observer-blinded RCTs or quasi-randomised trials,[245,247,260,262,329,330,334,336,338,340,342,344,348,355,358,361,365,373] and 14 stated that they were observer- and participant-blinded.[248,320,321,331–333,345,352,354,356,359,364,381,384] Hanssen et al.[246] reported that blinding of participants was not possible due to the nature of the intervention, and there was no mention of observer blinding. However, all outcomes were self-report questionnaire-based, therefore blinding was not deemed necessary. Twelve studies either did not use blinding procedures or were unclear in their methodology,[242,324,325,327,341,343,347,349–351,355,358] therefore we determined these studies to be at high risk of bias. Ernst et al.[327] reported that while the main scorer was not blinded, a blinded rater verified the scoring accuracy for 20% of memories randomly chosen with a reliability of .95 when assessed with intraclass correlations, therefore we determined this to be a low risk of bias.

2.4.1.3 Excluded studies.

We excluded 64 studies based on the exclusion criteria specified for this review. Two were studies of Alzheimer's disease, i.e. not MS;[403,404] four were unrelated to memory;[405–408] and one was a systematic review, not an intervention study.[255] Sixteen studies were not specific to memory, but general neuropsychological rehabilitation, attention, or information processing.[244,407–421] Seven studies used healthy controls instead of an MS control group,[422–428] and Wilson et al.[428] also did not distinguish between results for people with MS and others with acquired progressive brain injury. Eleven studies were not RCTs or quasi-RCTs (one quasi-experimental waiting-list control: Rodgers et al.[429]; one small group study: Allen et al.[430]; six without random allocation: Barker et al.[431] ; Barbarulo et al.[432]; Brenk et al.[433]; Brissart et al.[434]; Pineau et al.[435]; Shatil et al.[436] three with no control group: Bove et al.[437]; Brissart et al.[438]; Güçlü Altun et al.[439]). Bonavita et al.[440] was a brain imaging study and had an active control group. Thaut et al.[441]

used a "music intervention". Moore et al.[442] was not considered to be a rehabilitation study according to our inclusion criteria because it only involved one hour-long session of memory retraining. Three studies[443–445] used the same sample, or a subgroup of the sample, of Chiaravalloti et al.[321] which was an RCT included in this review, and another, Martin et al.[446], was a subgroup analysis of das Nair et al.[336], and was therefore not included. Two studies had abstracts in English but no full-text in English available.[447,448] Four studies were study protocols and therefore had no results attached to them.[449–452] Finally, 12 studies were conference poster presentations, and/or no full texts could be found.[242,249,437,453–461]

2.4.1.4 Risk of bias in included studies.

The risk of bias in the 44 included studies was generally low (see Figure 4 and Figure 5 – for individual study risk of bias assessments). However, high risk of selection and detection bias was found in the following: random sequence generation in four studies, allocation concealment in two studies, blinding procedures in 14 studies, incomplete outcome data in four studies, and possible selective reporting in four studies. Furthermore, we judged the risk of bias to be unclear in some instances due to insufficient reporting of methods for: randomised sequence generation in 11 studies, allocation concealment in 14 studies, blinding procedures in two studies, and incomplete outcome data in 10 studies. Studies with high risk of bias may overestimate treatment effects due to issues such as inadequate blinding, selective reporting, or small sample sizes. We did not remove any studies based on this risk of bias analysis but included this breakdown so that the findings could be interpreted with caution in the context of these methodological limitations.

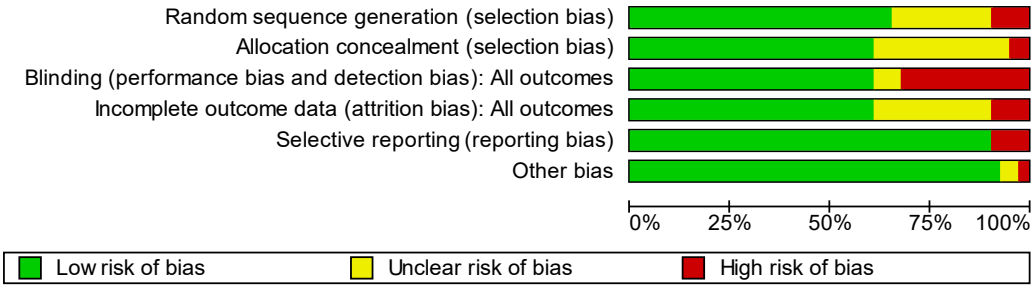


Figure 4 Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

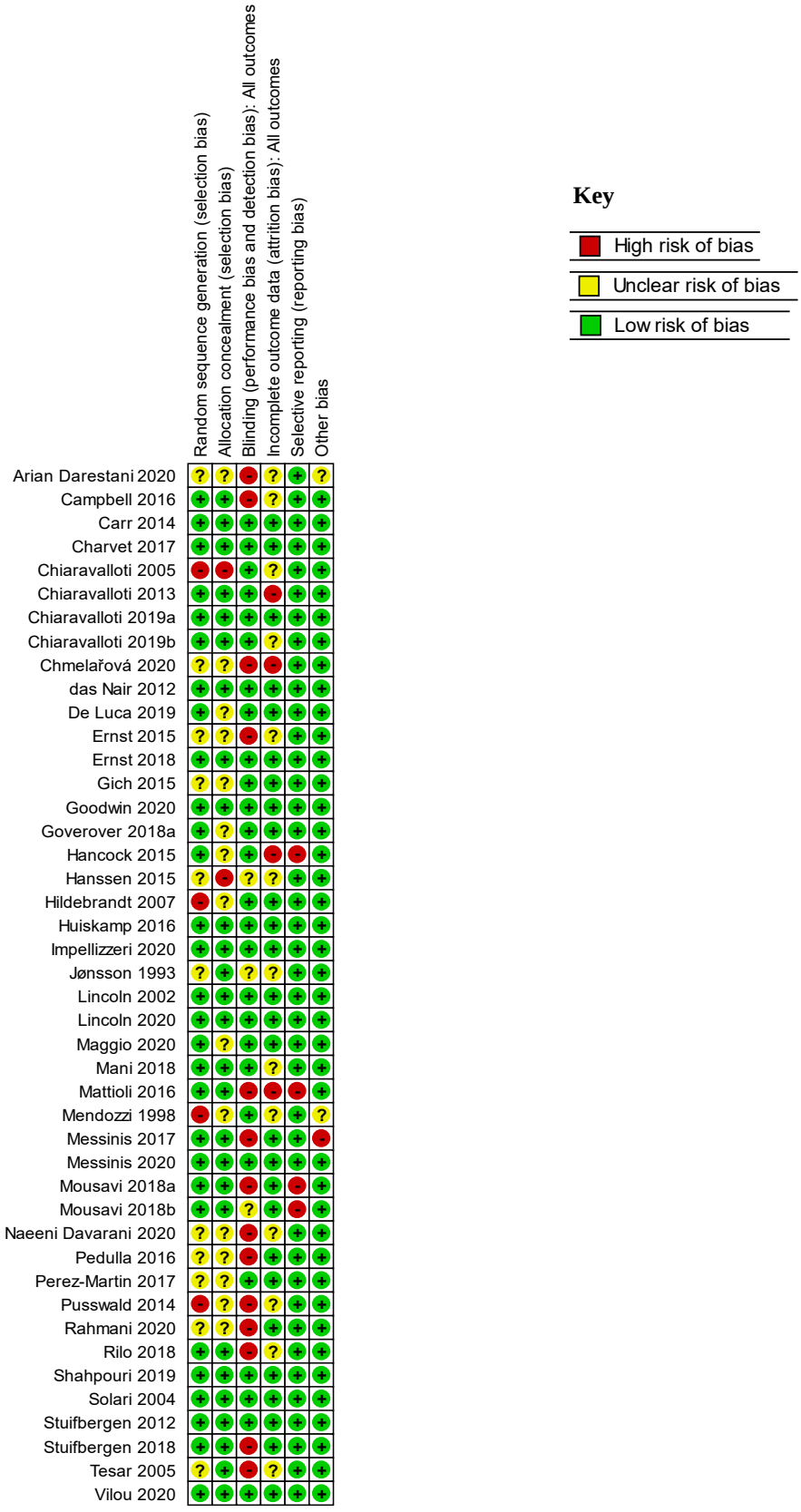


Figure 5 Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

2.4.1.5 Random sequence generation

Seventeen studies were judged to have a low risk of selection bias due to having adequate random sequence generation, having used a computerised random number generator by an independent unit,[242,248,319,321–323,328,333,338,340,341,343,344,351,352,363,462] two used a random number generator from the study data analyst that was created prior to recruitment and kept in sealed envelopes[353,354] and six used a block randomisation generated by a blind statistician.[260,330,331,337,356,359] Three studies used "randomised software" to randomly assign participants to three groups and therefore was determined to have low risk of bias.[345,346,371] Four studies were judged not to have adequate sequence generation and therefore a high risk of bias, as three of these studies involved quasi-random 'odd-even' or alternating allocation,[320,334,349] and Mendozzi et al.[342] only randomised half the sample with no generation method stated. The method used for random sequence generation and the risk of bias in 11 other studies was.[244,324,325,327,329,347,348,350,355,358,364]

2.4.1.6 Allocation

We judged 19 studies to have a low risk of selection bias due to effectively concealing allocation into groups using a computerized random number generator by an independent unit,[242,248,319,321–323,328,333,336,338,340,341,343–346,351,352,363] a closed envelope system,[247,353,354,358] or having a separate staff member who was not otherwise involved in the study complete allocation.[260,330,331,355,356] We judged two studies as not having concealed allocation to groups, suggesting a high risk of bias: Chiaravalloti et al.[320] used "odd-even" allocation completed by the principal investigator, and Hanssen et al.[244] stated that allocation concealment was not possible. Fourteen studies were unclear in their explanation of allocation concealment: Hildebrandt et al.[334] informed participants whether they were to receive the intervention or assessment only; Mendozzi et al.[342] stated that groups were allocated by the principal investigator but their other involvement in the study was not clearly explained; and 12 studies did not mention allocation concealment.[324,325,332,337,347,348,350,359,364,367,370,463]

2.4.1.7 Blinding

Sixteen studies were observer blinded.[245,247,260,319,329,330,334,336–338,340,342,344,353,359,458] 14 studies stated they were "double blind",[245,248,320–323,331–333,346,352,354,356,364] however, Mousavi et al.,[345] Davarani et al.,[364] and Stuifbergen et al.[354] were judged

to be high risk of bias due to lack of evidence of how they blinded the personnel and/or participants.

Ernst et al.[328] reported that while the main scorer was not blinded, a blinded rater verified the scoring accuracy for 20% of memories randomly chosen with a reliability of .95 when assessed with intraclass correlations, therefore we determined this to be a low risk of bias. Hanssen et al.[244] reported that blinding of participants was not possible due to the nature of the intervention, and there was no mention of observer blinding, but because the outcomes were self-report questionnaires, we deemed this study to have an unclear risk of bias. Jønsson et al.[358] was rated unclear bias due to discrepancies in the blinding procedures found when the study stated that "Healthcare providers were not told of patients' allocation, but a few words would have given it away". It was not clear whether this occurred or whether the authors made any attempt to prevent it by asking patients not to discuss their experience with the assessors. Eleven studies either did not use any blinding procedures or were unclear in their methodology, suggesting a high risk of bias.[242,324,325,327,341,343,347,349–351,355] Mousavi et al.[346] stated the patients and statisticians were blind to group allocation, but it is unclear whether the assessor was blind, therefore suggesting an unclear risk of bias.

2.4.1.8 Incomplete outcome data

We deemed four studies to be at high risk of attrition bias: in Chiaravalloti 2013 et al.,[321] Chmelařová 2020 et al.[324] Mattioli 2016 et al.[341] there was a post-randomisation attrition rate of 12%, 25% and 21%, respectively and/or no discussion of how missing data were dealt with, and the study did not use intention-to-treat analysis; in Hancock et al.[332] the post-randomisation attrition level was 44%. Eight studies did not address incomplete outcome data and did not use intention-to-treat analysis, which we deemed to be at unclear risk of bias: Chiaravalloti et al.[320] reported one dropout, two studies reported two dropouts,[244,351] three studies reported three dropouts,[242,245,327] two studies reported six dropouts;[322,364] Arian Darestani et al.[325] seven dropouts; in Mendozzi et al.[342] another, participant outcome data were replaced with mid-trial data if a participant dropped out; and two studies did not explain how dropout data were handled.[355,358] Lincoln et al.[338] conducted analyses on data for those participants

who completed the outcome assessments, das Nair et al.[336] used list-wise deletion and baseline data imputed for any missing follow-up data, and in two studies,[352,353] missing values were imputed according to the last observation carried forward method. In Carr et al.[319] one study, where less than 10% of items were missed on a questionnaire, these were replaced with the mean for the questionnaire.

2.4.1.9 Selective reporting

We deemed four studies to have a high risk of reporting bias.[332,341,345,346] Hancock et al.[332] only reported on the memory outcomes, despite other outcomes having been assessed at follow-up, and data were only reported for "good adherers" to the intervention. Pedulla et al.[347] did not report outcome comparisons for control group, only the intervention group. Three studies did not report several of their outcomes.[341,345,346]

2.4.1.10 Other potential sources of bias

We judged 39 studies to have a low risk of other potential sources of bias. Mendozzi et al.[342] had a potential source of bias, as one participant in the treatment group discontinued cognitive retraining and was replaced by a new entry without further explanation. Arian Darestani et al.[325] had a potential source of bias as it was unclear what the control group were told about the study. Messinis et al.[343] did not collect six-month follow-up data for the control group, therefore we determined this to be high risk of potential bias.

2.4.2 Effects of intervention

In this section, we first present study-specific information regarding intervention effect on memory outcomes, and then present the meta-analysis, synthesising results on various domains. As the primary author of this review, I conducted all analysis including the meta-analysis using RevMan software.

Nine studies concluded that there were no significant differences between the treatment and control groups on measures of memory, particularly after adjustments were made for multiple testing,[242,319,320,323,332,336,338,352,358] and Goodwin et al.[330] reported no significant within group improvements for the intervention group. Twenty- nine studies reported significant differences on memory measures favouring the treatment groups. However, it is crucial to note

that many of these studies had varying levels of risk of bias, which could influence the reported outcomes.

For instance, Hanssen et al.[244] did not use memory outcomes. Gich et al.[329] reported significant differences favouring treatment on some subtests of the Battery of Neuropsychological Tests (BRBN),[295] although no significant differences were reported on the list- learning task of the BRBN used in this meta-analysis. Campbell et al.[242] showed no significant improvement on the California Verbal Learning Test (CVLT-II) or Brief Visuospatial Memory Test (BVMT). Chiaravalloti et al.[322] showed significant improvements for the intervention group in the CVLT-II at immediate follow-up but not in the Rivermead Behavioural Memory Test (RBMT). These inconsistencies highlight the variability in outcomes and the potential influence of methodological differences.

Furthermore, Chmelařová et al.[324] showed significant improvement for the intervention group in the immediate memory component of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998) but showed no improvement for Cognitive Failures Questionnaire (CFQ). Goverover et al.[331] showed significant improvement for the intervention group in CVLT-II and: Contextual Memory Text (CMT), but not on the Memory Failures Questionnaire (MFQ). Hildebrandt et al.[334] reported improvements for the treatment group in the Learning Trials and Long Delay Free Recall subtests of the CVLT (Niemann 2003). These studies often employed different measures, further complicating direct comparisons and synthesis of results.

Stuifbergen et al.[353] reported improvements in the CVLT total both over time and by group and showed significantly more use of memory strategies in the intervention compared with control. Chiaravalloti et al.[321] and Chiaravalloti et al.[322] showed a greater learning slope for the treatment group compared to the control on the CVLT-II.[291] Lincoln et al.[260] showed significant group differences in Everyday Memory Questionnaire (EMQ-p) at both six and 12 months, in the Selective Reminding Test (SRT) total recall at six months and delayed recall at 12 months with no other significant group differences. However,

the high risk of bias in these studies, including issues like inadequate blinding and small sample sizes, may overestimate the effectiveness of the interventions.

Maggio et al.[337] showed significant group improvement in both groups with greater improvement in the intervention group for Spatial Recall Test (SPART) and a significant Group*Time interaction. Messinis et al.[343] showed significant improvement for the intervention group in SRT and BVMT-R. Messinis et al.[344] showed significant improvement in everyday memory at immediate follow-up but this was not sustained at longer-term follow-up. Pedulla et al.[347] showed significant Group*Time interaction for six out of 10 subtests of the BRBN. Tesar et al.[355] reported improvements on the computer-aided card-sorting test (CKV), Drühe-Wienholt et al.[464] , and the Mosaic Test of the Hamburg Wechsler Intelligence Test (HAWIE-R),[465] for the treatment group. The potential biases in these studies, such as selection bias and performance bias, must be considered when interpreting these findings.

Chiaravalloti et al.[320] observed no significant difference between the treatment and control groups on their list-learning task (HVLT-R),[389] but on subgroup analysis, we observed significant improvement on this task for the moderate-to-severe memory-impaired subgroup, but not for other groups. However, this subgroup analysis was carried out only on the treatment group, which had 14 participants. Mendozzi et al.[342] reported improvement in the specific cognitive-retraining group on seven measures of memory (Spatial Span from the Corsi, Digit Span Forward and Backward, Visual Reproduction, and Paired Associates-Hard from the Italian Weschler Memory Scale (WMS),[300] and the LNNB.[393] There was an improvement in Digit Span Forward only in the non-specific cognitive rehabilitation group. Again, the methodological quality of these studies, including potential biases, should be taken into account when considering the efficacy of the interventions.

In summary, while many studies reported positive outcomes favouring cognitive rehabilitation, the identified levels of bias in these studies highlight the need for cautious interpretation of the results. The methodological limitations and variability in study quality underscore the importance of high-quality, rigorously conducted

trials to more definitively ascertain the effectiveness of cognitive rehabilitation interventions for people with MS.

2.4.2.1 Outcome 1: Subjective memory measures

Fifteen studies included subjective measures of participants' memory functioning. Ten of these studies provided immediate outcomes;[245,320,322,324,330,331,345,354,373,458] 11 of these studies provided intermediate outcomes;[248,260,319,320,323,336,338,353,354,363,365] and five of these studies provided longer-term outcomes.[260,319,336,338,354] We found small to moderate differences between groups for subjective reports of memory for immediate, intermediate and longer-term follow ups: (standardised mean difference (SMD) 0.32, 95% confidence interval (CI) 0.05 to 0.58; 568 participants, moderate-quality evidence) (Figure 6); (SMD 0.23, 95% CI 0.11 to 0.35; 1045 participants, high-quality evidence) (Figure 7); and (SMD 0.16, 95% CI 0.02 to 0.30; 775 participants, high-quality evidence) (Figure 8), respectively. The intervention group performed better than the control group at each follow-up point.

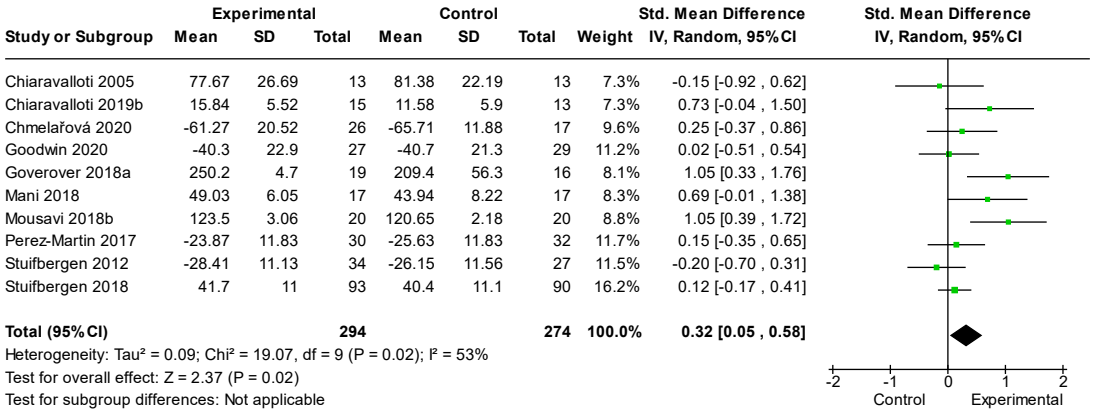


Figure 6 Meta analysis for subjective memory measures at immediate follow-up.

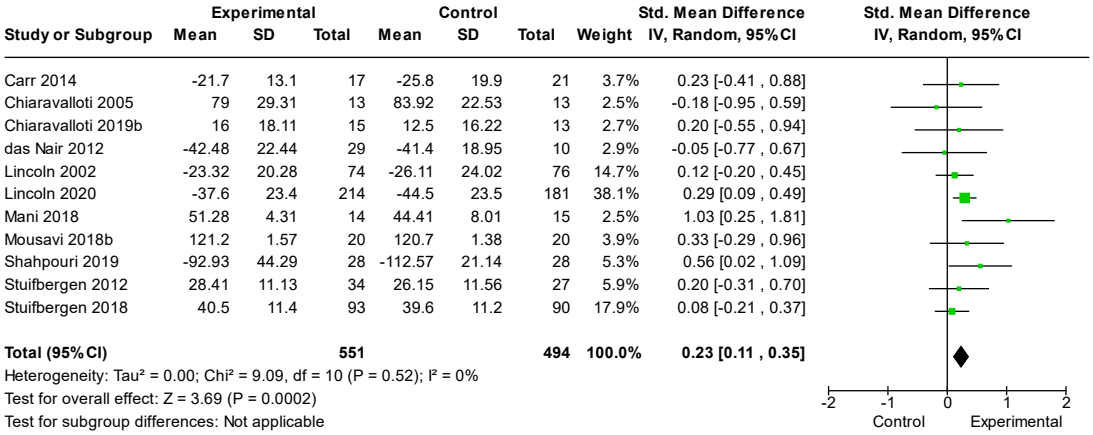


Figure 7 Meta analysis for subjective memory measures at intermediate follow-up.

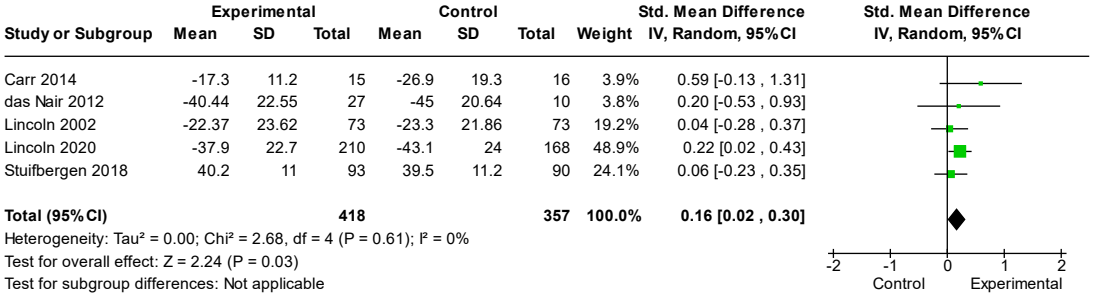


Figure 8 Meta analysis for subjective memory measures at longer-term follow-up.

2.4.2.2 Outcome 2: Objective verbal memory measures

Twenty-one studies included objective verbal memory measures of participants' memory functioning. Nineteen of these studies provided immediate outcomes,[242,247,320–323,325,331,332,340,343,344,347,348,351,354,355,367,373] six of these studies provided intermediate outcomes,[242,260,325,353–355] and four of these studies provided longer-term outcomes.[260,322,341,354] We found small to moderate differences between groups for objective verbal reports of memory at immediate (SMD 0.40, 95% CI 0.22 to 0.58; 922 participants, low-quality evidence) (Figure 9) and intermediate follow-up (SMD 0.25, 95% CI 0.11 to 0.40; 753 participants, low-quality evidence) (Figure 10), but no little to no difference at longer-term follow-up (SMD 0.13, 95% CI -0.03 to 0.29; 619 participants, moderate-quality evidence) (Figure 11). The intervention group performed better than the control group at immediate and intermediate follow-up.

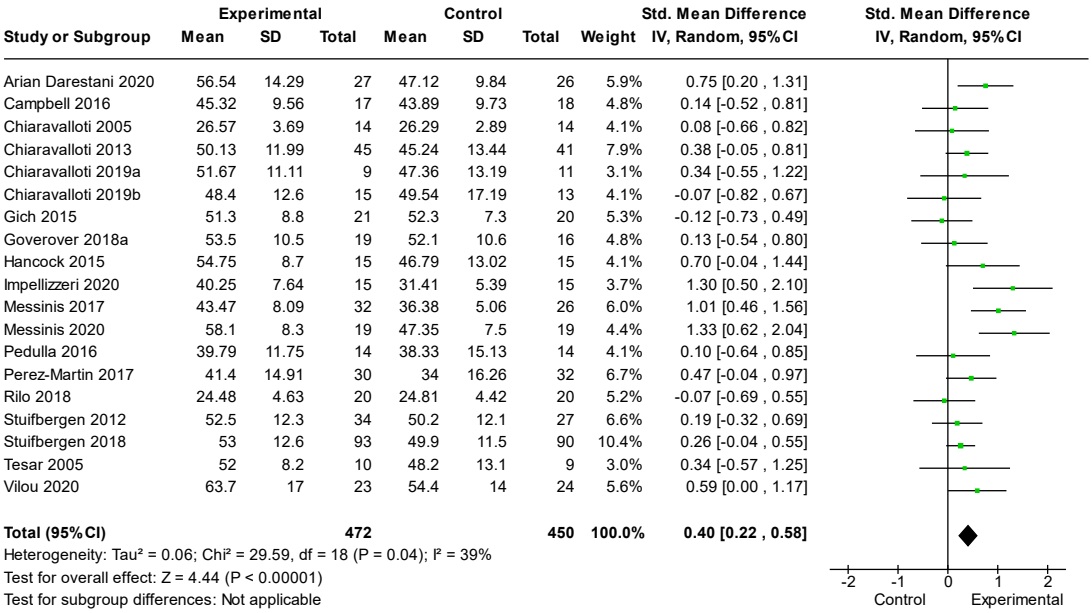


Figure 9 Meta-analysis for verbal memory measures at immediate follow-up.

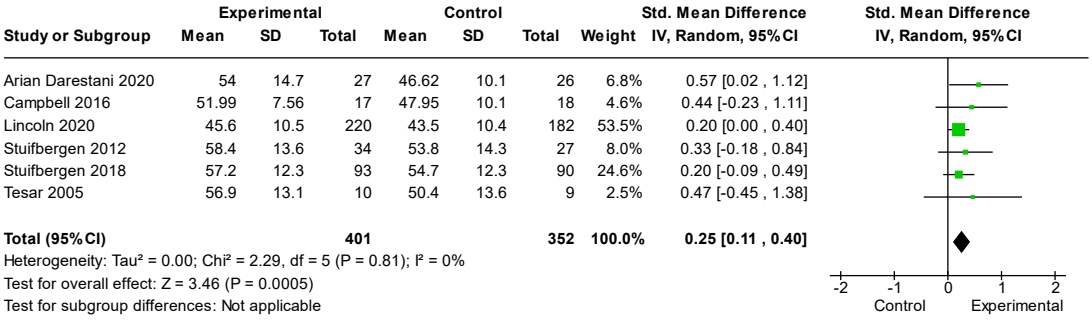


Figure 10 Meta-analysis for verbal memory measures at intermediate follow-up.

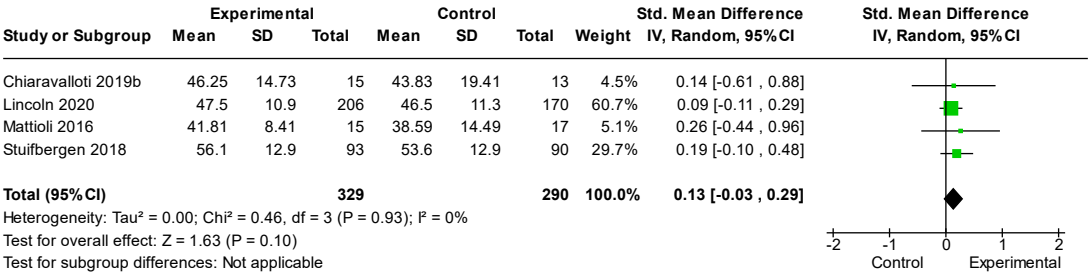


Figure 11 Meta-analysis for verbal memory measures at longer-term follow-up.

2.4.2.3 Outcome 3: Objective visual memory measures

Nineteen studies included objective visual measures of participants' memory functioning. Sixteen of these studies provided immediate outcomes,[242,322–324,331,337,340,343,344,348,353,354,369,371,377,466] six of these studies provided intermediate outcomes,[242,260,326,353,354,377] four of these studies provided longer-term

outcomes.[322,339,341,354] We found a moderate difference between groups for objective reports of visual memory at immediate follow-up (SMD 0.42, 95% CI 0.25 to 0.60; 799 participants, moderate-quality evidence) (Figure 12), but little to no between group differences at intermediate (SMD 0.20, 95% CI -0.11 to 0.50;751 participants, moderate-quality evidence) (Figure 13), and longer-term follow-up (SMD 0.12, 95% CI -0.13 to 0.37; 619 participants, high-quality evidence) (Figure 14). The intervention group performed better than the control group at immediate follow-up.

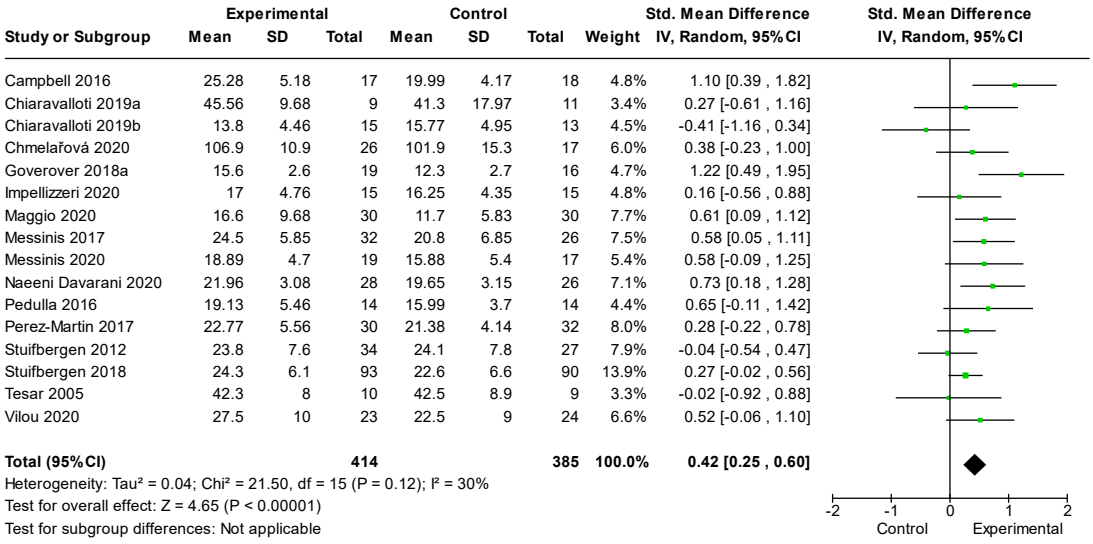


Figure 12 Meta-analysis for visual memory measures at immediate follow-up.

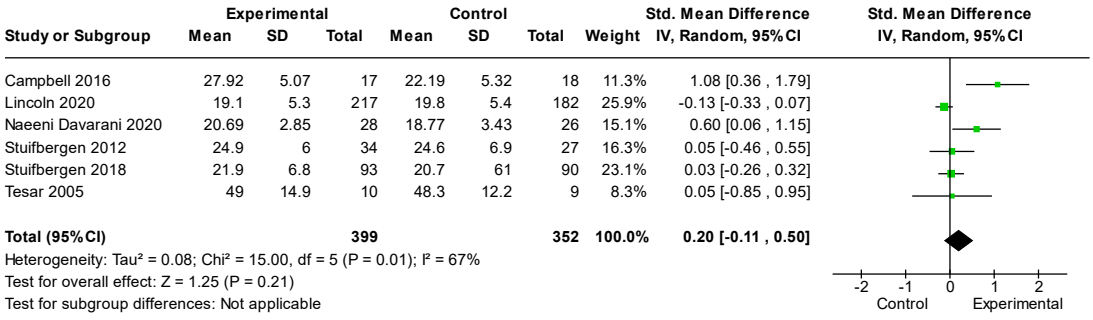


Figure 13 Meta-analysis for visual memory measures at intermediate follow-up.

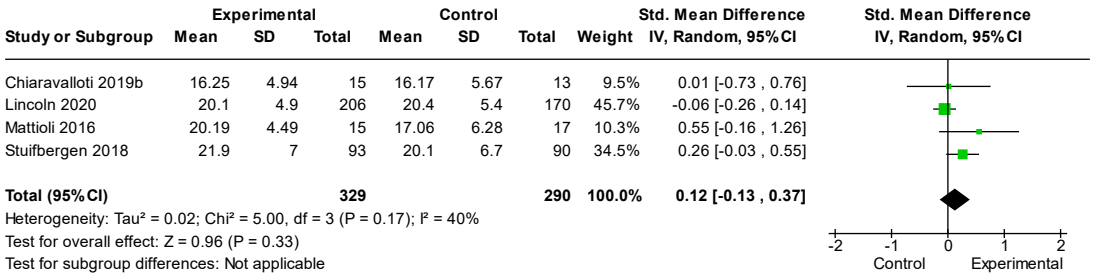


Figure 14 Meta-analysis for visual memory measures at longer-term follow-up.

2.4.2.4 Outcome 4: Objective working memory measures

Thirteen studies included objective working measures of participants' memory functioning. Twelve of these studies provided immediate outcomes,[322,324,326,337,340,345,347,348,350,351,354,373] eight of these studies provided intermediate outcomes,[260,333,345,350,354,364,373,462] five of these studies provided longer-term outcomes.[260,336,341,354,381] We found a moderate difference between groups for objective reports of working memory at immediate follow-up (SMD 0.45, 95% CI 0.18 to 0.72; 655 participants, low-quality evidence) (Figure 15), but little to no between group differences at intermediate (SMD -0.16, 95% CI -0.09 to 0.40; 821 participants, moderate-quality evidence) (Figure 16), or longer-term follow-up (SMD 0.04, 95% CI -0.11 to 0.20; 665 participants, moderate-quality evidence) (Figure 17). The intervention group performed better than the control group at immediate follow-up.

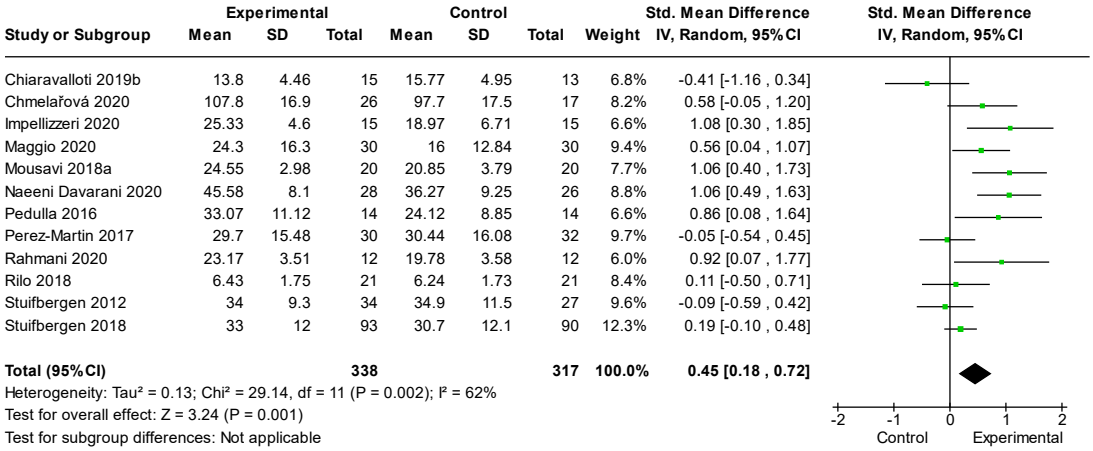


Figure 15 Meta-analysis for working memory measures at immediate follow-up.

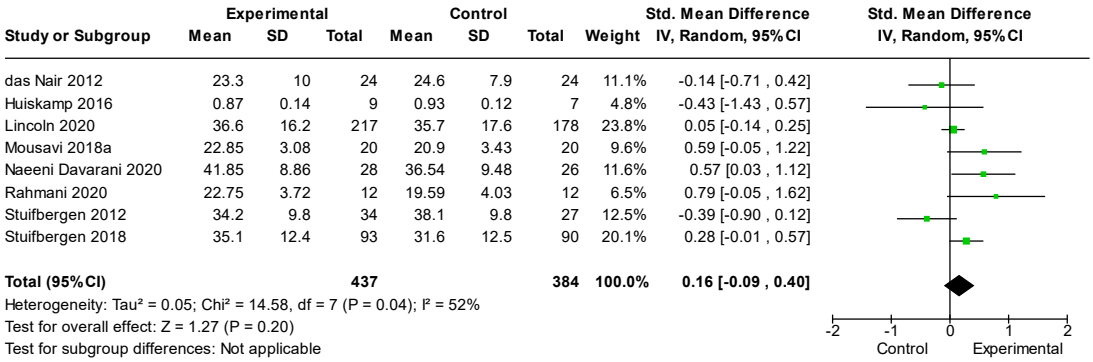


Figure 16 Meta-analysis for working memory measures at intermediate follow-up.

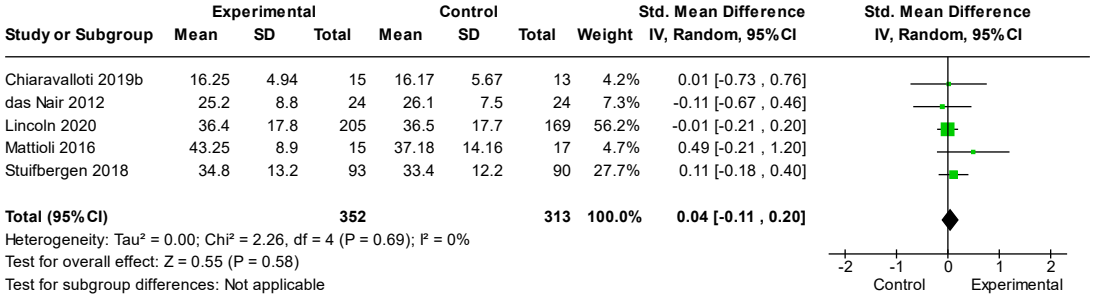


Figure 17 Meta-analysis for working memory measures at longer-term follow-up.

2.4.2.5 Outcome 5: Information processing

In terms of 'other cognitive outcomes', the most frequently assessed cognitive domain was information processing. Nineteen studies included information processing measures. Fifteen studies reported immediate outcomes,[242,247,322,324,332,343,344,348,350–352,354,364,369,373] eight studies reported intermediate outcomes,[242,244,260,350,352,354,364,373] five studies reported longer-term outcomes.[244,260,341,354,369] We found moderate between group differences for information processing measures at immediate (SMD 0.51, 95% CI 0.19 to 0.82; 808 participants, low-quality evidence) (Figure 18), and intermediate follow-up (SMD 0.27, 95% CI 0.00 to 0.54; 933 participants) (Figure 19), but little to no difference at longer- term follow-up (SMD 0.21, 95% CI -0.03 to 0.45; 723 participants, moderate-quality evidence) (Figure 20). The intervention group performed better than the control group at immediate and intermediate follow-up.

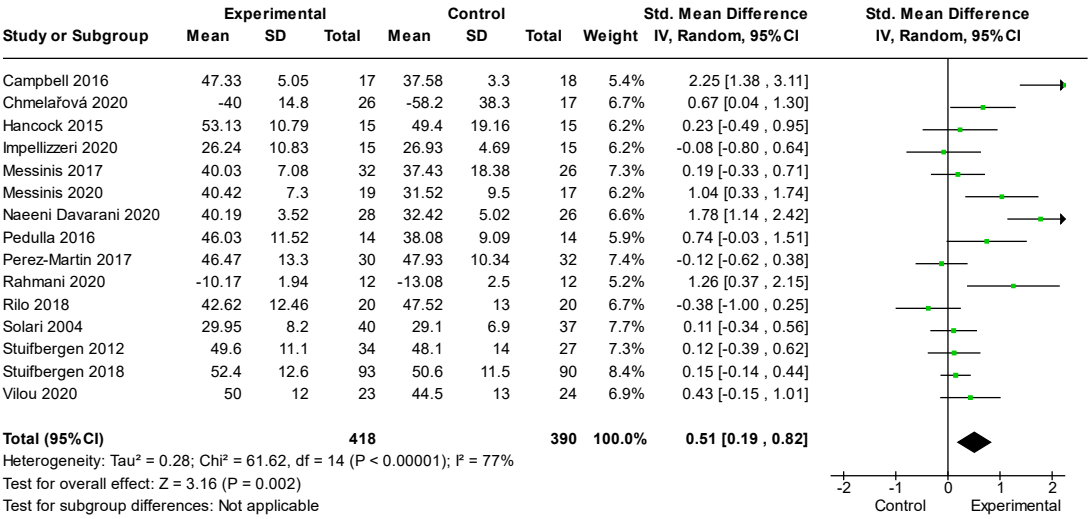


Figure 18 Meta-analysis for information processing measures at immediate follow-up.

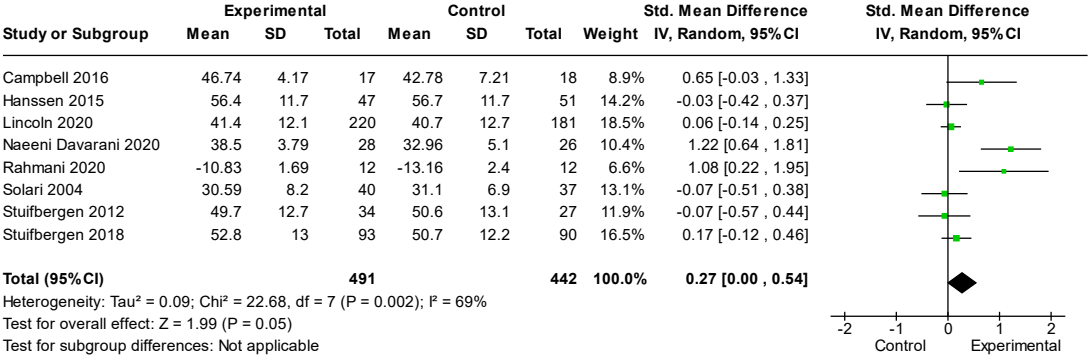


Figure 19 Meta-analysis for information processing measures at intermediate follow-up.

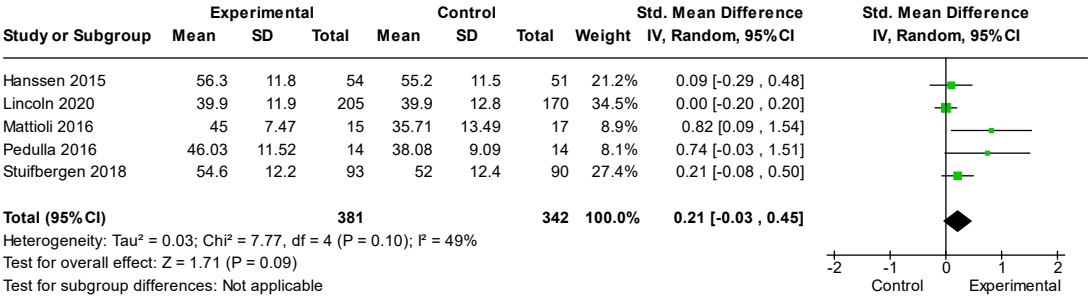


Figure 20 Meta-analysis for information processing measures at longer-term follow-up.

2.4.2.6 Outcome 6: Mood – depression

Twenty-two studies included measures of depression. Sixteen of these studies provided immediate outcomes,[242,320,321,324,330,334,337,340,343,344,348,352,354,355,362,379] 10 of these studies provided intermediate outcomes,[242,248,260,319,320,336,338,352,354,355] and seven of these studies provided longer-term outcomes.[260,319,321,336,338,341,354]

We found a moderate difference between groups for mood measures of depression

at immediate (SMD 0.34, 95% CI 0.15 to 0.53; 853 participants, moderate-quality evidence) (Figure 21), but little to no difference at intermediate (SMD 0.20, 95% CI -0.06 to 0.45; 1003 participants, moderate-quality evidence) (Figure 22), or longer-term follow-up (SMD 0.15, 95% CI -0.04 to 0.34; 891 participants, high-quality evidence) (Figure 23). The intervention group performed better than the control group at immediate follow-up.

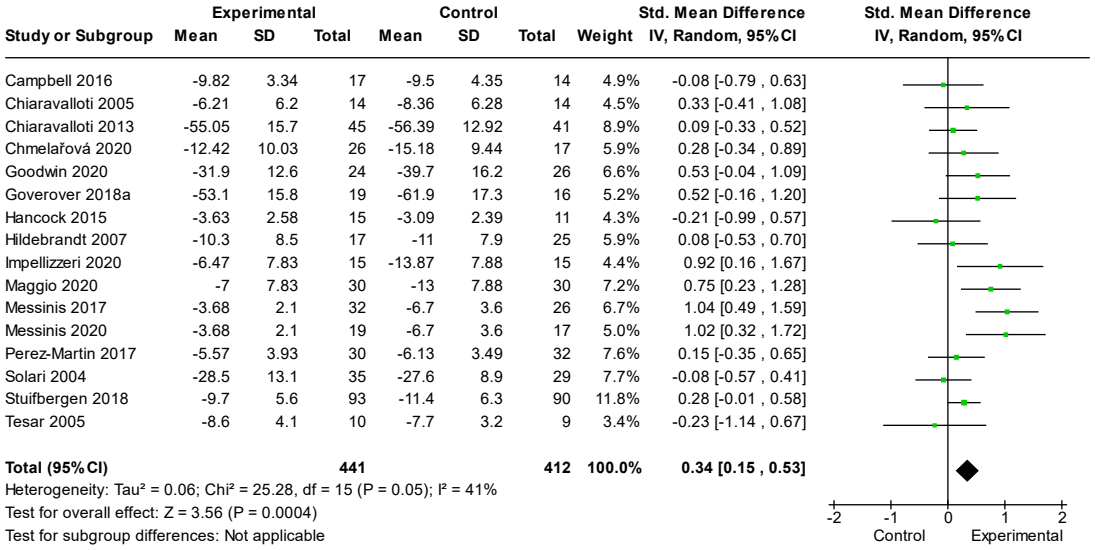


Figure 21 Meta-analysis for depressive symptom measures at immediate follow-up.

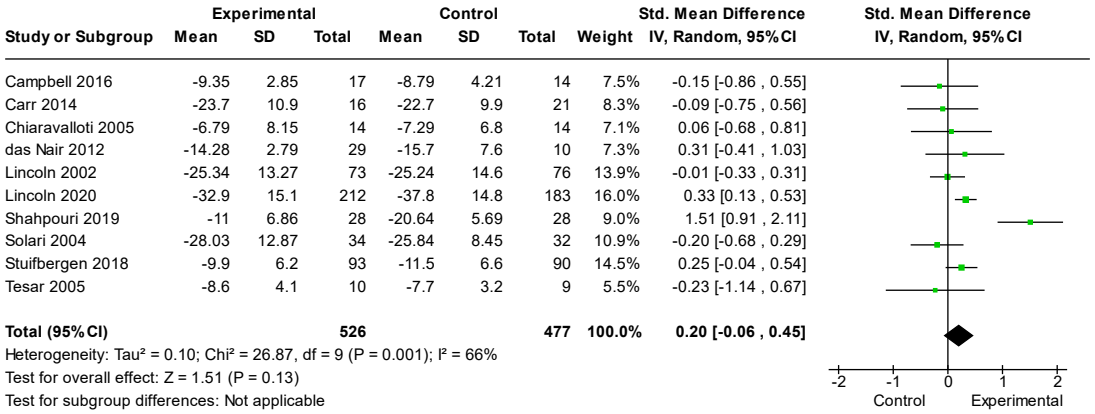


Figure 22 Meta-analysis for depressive symptom measures at intermediate follow-up.

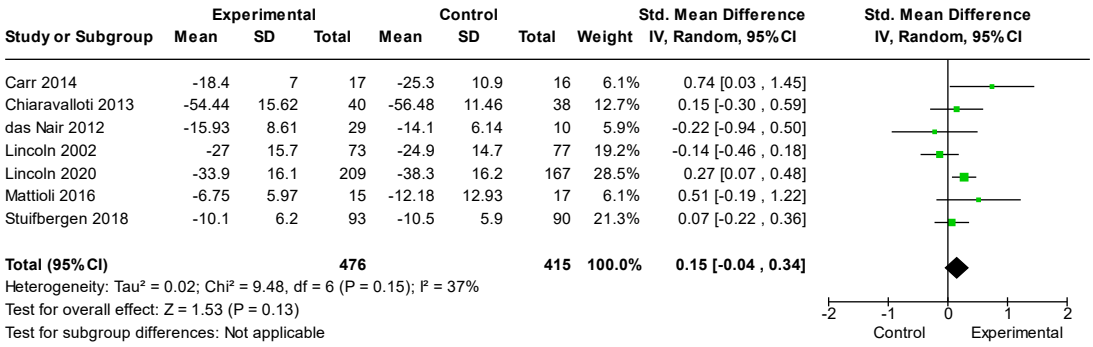


Figure 23 Meta-analysis for depressive symptom measures at longer-term follow-up.

2.4.2.7 Outcome 7: Mood – anxiety

Seven studies included measures of anxiety. Four of these studies provided immediate outcomes,[242,330,348,362] four of these studies provided intermediate outcomes,[242,260,319,467] and three of these studies provided longer-term outcomes.[260,319,336] We found little to no between group differences for mood measures of anxiety at immediate (SMD 0.29, 95% CI -0.01 to 0.59; 178 participants, high-quality evidence) (Figure 24), intermediate (SMD 0.16, 95% CI -0.15 to 0.46; 502 participants, high-quality evidence) (Figure 25), or longer-term follow-up (SMD 0.27, 95% CI -0.12 to 0.65; 448 participants. high-quality evidence) (Figure 26).

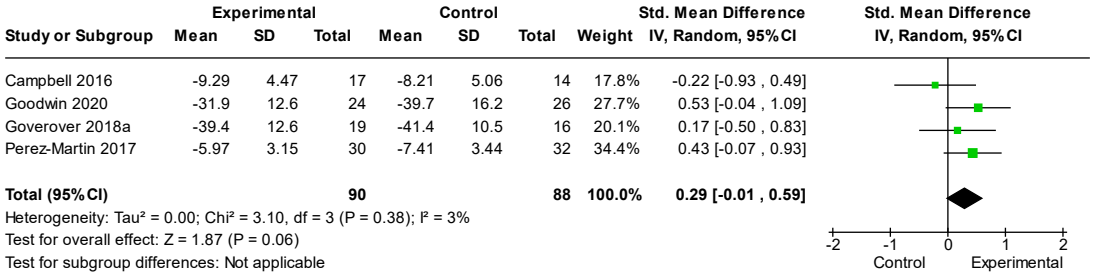


Figure 24 Meta-analysis for anxiety symptom measures at immediate follow-up.

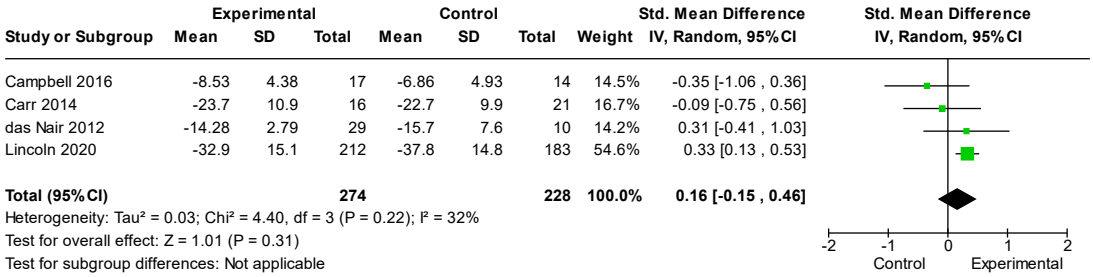


Figure 25 Meta-analysis for anxiety symptom measures at intermediate follow-up.

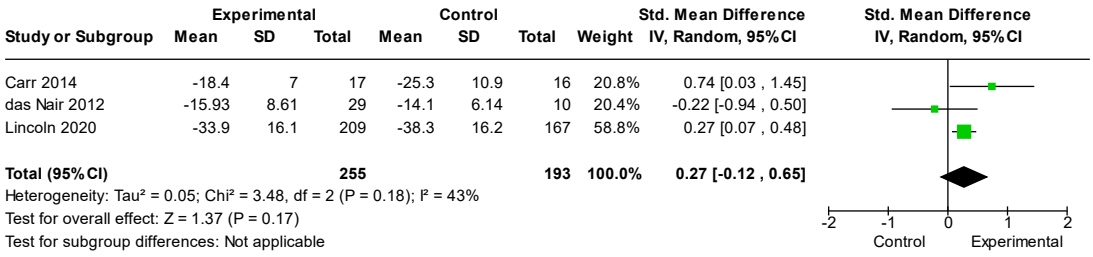


Figure 26 Meta-analysis for anxiety symptom measures at longer-term follow-up.

2.4.2.8 Outcome 8: Quality of Life (QoL)

Eleven studies included QoL measures. Eight of these studies provided immediate outcomes,[248,330,340,344,348,352,362,379] six of these studies provided intermediate outcomes,[244,248,260,319,338,352] five of these studies provided longer-term outcomes.[244,260,319,341,382] We found small to moderate between group differences for quality of life measures at immediate, intermediate, and longer-term follow ups: (SMD 0.42, 95% CI 0.15 to 0.68; 371 participants, high-quality evidence) (Figure 27), (SMD 0.30, 95% CI 0.02 to 0.58; 683 participants, high-quality evidence) (Figure 28), and (SMD 0.17, 95% CI 0.02 to 0.32; 687 participants, high-quality evidence) (Figure 29), respectively. The intervention group performed better than the control group at every follow-up.

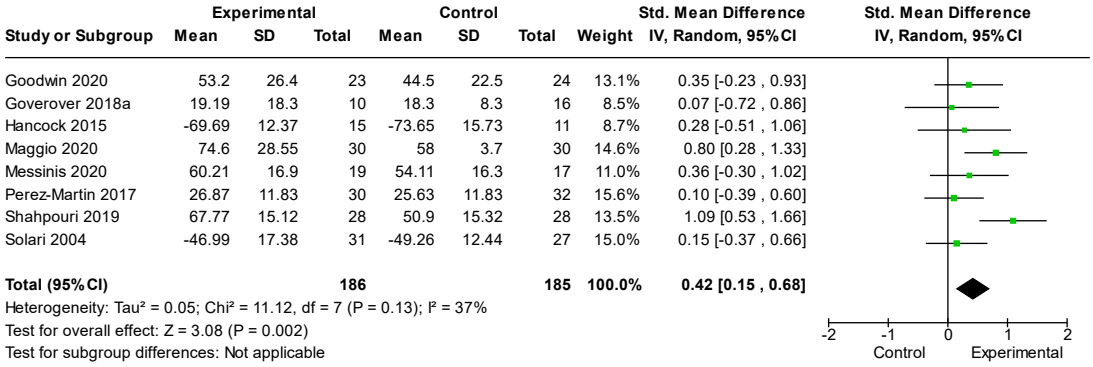


Figure 27 Meta-analysis for quality-of-life measures at immediate follow-up.

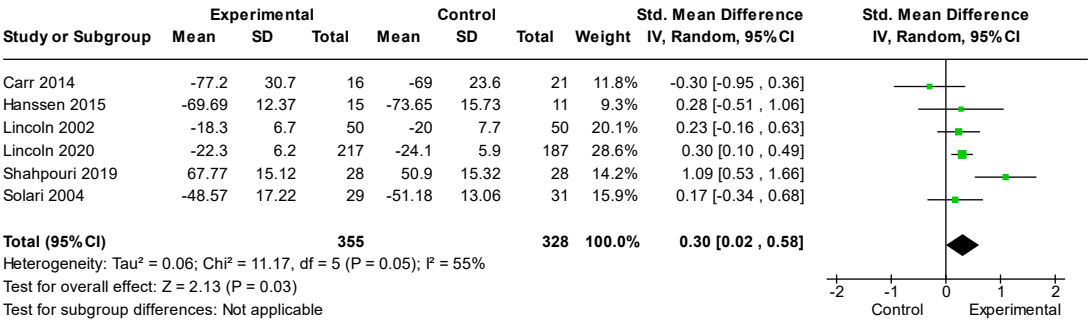


Figure 28 Meta-analysis for quality-of-life measures at intermediate follow-up.

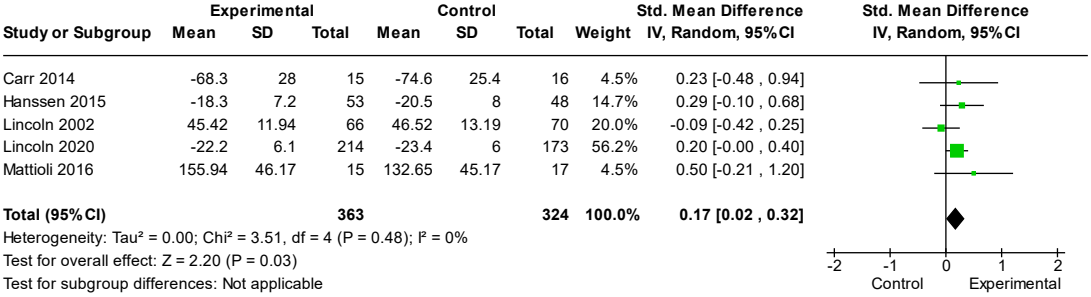


Figure 29 Meta-analysis for quality-of-life measures at longer-term follow-up.

2.4.2.9 Outcome 9: Functional abilities/Activities of daily living

Six studies included ADL measures of participants' daily functioning. Four of these studies provided immediate outcomes,[242,323,331,354] four of these studies provided intermediate outcomes,[242,336,354,362] and three of these studies provided longer-term outcomes.[336,338,354] We found little to no between group differences for ADL at immediate, intermediate, and longer-term follow-ups: (SMD 0.02, 95% CI -0.26 to 0.29; 265 participants, high-quality evidence) (Figure 30), (SMD -0.06, 95% CI -0.36 to 0.24; 400 participants, high-quality evidence) (Figure 31), and (SMD -0.11, 95% CI -0.49 to 0.27; 369 participants, high-quality evidence) (Figure 32), respectively.

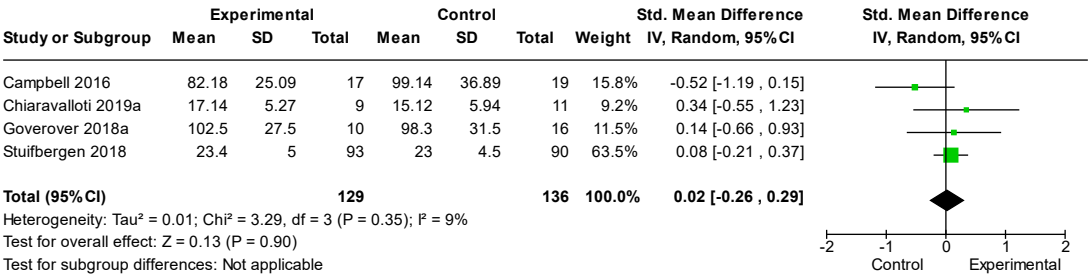


Figure 30 Meta-analysis for activities of daily living measures at immediate follow-up.

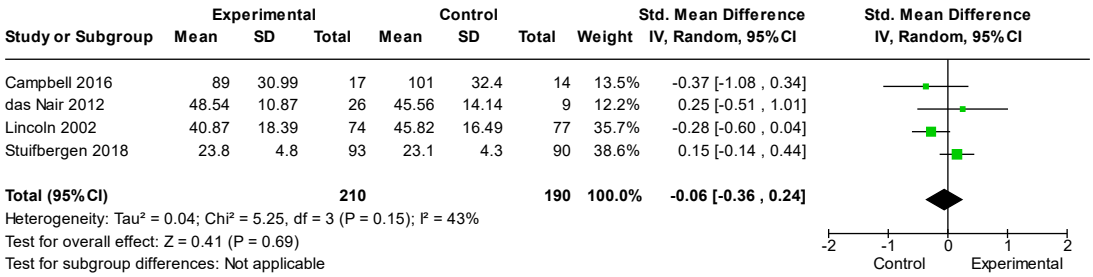


Figure 31 Meta-analysis for activities of daily living measures at intermediate follow-up.

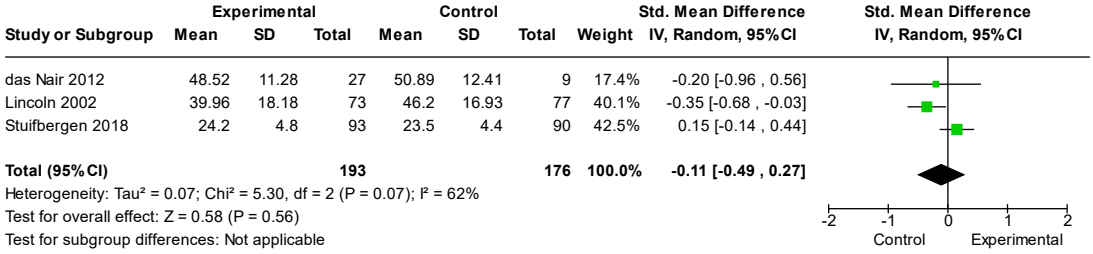


Figure 32 Meta-analysis for activities of daily living measures at longer-term follow-up.

2.5 Discussion

2.5.1 Summary of main results

In the last two decades, research groups globally have begun to address memory problems associated with MS. However, the literature base examining the effectiveness of memory rehabilitation for MS has been weak. While single-case and uncontrolled studies have found memory rehabilitation to be effective in reducing memory or psychological problems, these results had not been consistently replicated in RCTs. However, more recently, we have seen larger, more methodologically robust trials published in this area.

We included 44 RCTs or quasi-randomised trials in this review. These studies were either memory rehabilitation studies or cognitive rehabilitation trials with a specific memory component that included a memory intervention. These trials were mostly of relatively moderate quality, with many still not adhering to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[468] We included studies in the meta-analysis regardless of whether they met CONSORT guidelines to ensure a comprehensive assessment of the available evidence on cognitive rehabilitation in MS. Excluding these studies would have significantly reduced the sample size and potentially overlooked valuable data, which could impact the generalisability and robustness of the overall findings. Descriptions of the randomisation protocol, blinding, and content of treatment and control groups were

poor in approximately 50% of studies. Studies generally had modest sample sizes and used impairment-level outcome assessments to determine the effectiveness of the intervention.

Twenty-nine individual studies reported positive results on memory outcomes from their memory rehabilitation groups.[247,248,260,321,322,324–326,329,331,334,337,340–345,347–351,353–355,359,363,365] However, these results need to be interpreted in the context of the methodological limitations and the measures used to assess effectiveness, which may have influenced the outcome. In fact, most of the studies that reported a positive memory outcome for the participants in the intervention group were also rated as having a high or unclear risk of bias in at least one area, with the exceptions of four studies.[247,248,260,353] Despite the poor quality of many studies, the more recent trials have shown improvements in methodological rigor, suggesting a trend toward better quality research in the future.

The included studies displayed high heterogeneity in terms of the type of intervention, frequency of delivery, and mode of delivery. The high heterogeneity among the studies poses a challenge for reporting and synthesising the findings. It suggests that any pooled estimates of effect should be interpreted with caution, as the differences in intervention types, delivery frequencies, and modes could contribute to varying outcomes. This heterogeneity underscores the need for standardising intervention protocols in future research to allow for more meaningful comparisons and meta-analyses. However, there are positive implications for this also as the inclusion of diverse intervention types (e.g., computer-based training, therapist-led programmes) and their consistent positive outcomes across different settings support the robustness of the findings. This diversity indicates that various approaches to memory rehabilitation can be beneficial, enhancing the generalisability of the results.

Between group differences were found for quality-of-life outcomes in favour of the intervention group compared to the control group at each follow-up point, suggesting that memory rehabilitation can lead to positive change in the overall perception of quality of life of people with MS. It should be noted that this positive finding has not been observed in many other cognitive rehabilitation reviews for people with MS,[240] or reviews investigating cognitive rehabilitation in other cohorts such as post-stroke patients.[243] This could be due to more recent trials having a broader

focus on 'impact' of cognitive problems on MS, and therefore, likely to affect quality of life, while older trials mainly focused solely on memory impairments. It could also be that memory problems are more detrimental to the quality of life of people with MS compared to people with other neurological conditions and therefore, the tools to cope and self-manage their problems (that they are taught during memory and attention rehabilitation) lead to a greater improvement in their quality of life compared to other patient groups.

The results of this review suggest there is evidence to support the effectiveness of memory rehabilitation on subjective memory measures at immediate follow-up in favour of the intervention condition, and this result is sustained at intermediate and longer-term follow-ups of up to one year. This is a significant change compared to the previous version of this review, which found no evidence to support that memory rehabilitation had a positive effect on subjective memory measures. In this review, between group differences favouring the intervention group were also seen in the following outcomes: objective measures of verbal memory, both immediate and intermediate follow-ups; objective measures of visual memory at immediate follow-up; objective reports of working memory at immediate follow-up; information processing at immediate and intermediate follow-ups; mood measures of depressive symptoms at immediate follow-up; quality of life measures at immediate, intermediate and longer- term follow-ups. Little to no between group differences were found in activities of daily living measures or measures of anxiety.

Lincoln et al.[260] found a significant effect for memory outcomes at six- month follow-up but did not find evidence of this effect at 12- month follow-up, suggesting that the longevity or sustainability of the positive effects of the intervention cannot necessarily be expected in the long run. This supports the overall trend of these results in that, there were only two outcomes that maintained their significant effects at longer-term follow-up, suggesting that once the core intervention has been completed, maintenance plans (such as booster sessions) should be put in place to ensure the techniques learnt during the intervention are not forgotten or inconsistently used over time.

High heterogeneity (I^2>=50%) was seen in four statistically significant outcomes (working memory at immediate (I^2 = 62%) follow-up, quality of life at intermediate

(I^2=55%) follow-up, and information processing at immediate (I^2=77%) and intermediate (I^2=69%) follow-up) and thus, these findings need to be treated with caution and explored further. Firstly, there does not appear to be one or two primary studies contributing to the increased heterogeneity for working memory measures at immediate follow- up, therefore, this could be due to the wide variation in the type of intervention used by each study. Two studies used the same Memory Attention and Problem- Solving Skills in Multiple Sclerosis (MAPSS-MS) intervention,[353,354] whereas the other 10 studies all used different interventions from each other. We found a large variation in both the type of methods used, e.g., computerised versus face-to-face, and the frequency at which the intervention was delivered, e.g., ranging from four to 12 weeks in duration and from once to six times per week. These results suggest that variation in both type of intervention and frequency of delivery contributed to the high heterogeneity. This theory is supported by the sensitivity analysis which shows that the heterogeneity drops to 0% when all but the two studies that used the same intervention methods are removed.

Secondly, for the high heterogeneity for information processing outcomes measured at immediate follow-up, it appears that there are three main studies contributing towards this.[242,344,466] All three studies used RehaCom software for their interventions which took place at home and there was some variation in the frequency of sessions between each study. The type of intervention used in these studies may have contributed to the high heterogeneity however, without a meta-regression we cannot be certain of the cause and thus these results should be interpreted with caution.

Lastly, for the high heterogeneity seen in quality-of-life outcomes measured at intermediate follow-up, one study appeared to contribute towards this.[248] One possible cause could be that the outcomes were measured quote: "within 3 months after cognitive rehabilitation therapy" (p. 113). This suggests that some participants may have had their outcomes assessments immediately after treatment and others three months later, which could account for the large clinical variance in outcome scores.

However, these results must be viewed in relation to the quality of the evidence for this outcome, with the GRADE rating showing as low for information

processing at both immediate and intermediate follow-up, low for working memory at immediate follow-up but high for quality of life at intermediate follow-up.[469] Furthermore, improvements in outcomes are only maintained at follow-up for subjective memory measures and quality of life, which suggests that regular booster sessions of cognitive rehabilitation are necessary to maintain the improvements made and without them participants appear to revert to where they started. The degree to which this has the potential to generalise to everyday life, given the varying ecological validity of these tests, is questionable. However, it is important to note that the methodological quality of studies included in this review has improved compared to the previous review.

2.5.2 Overall completeness and applicability of evidence

The size of the literature-base examined in this review allowed us to address the research questions in as much depth as possible. The variety of outcomes in the trials enabled us to investigate domain-specific memory such as visual, verbal and working, thus this review not only shows the positive effects for general memory but also identified which domains are being improved by the rehabilitation intervention programmes and which of these improvements are maintained. This review fully investigated all types of studies, participants, interventions, and outcome measures as stated in the methods. The positive results in trials using computerised interventions have important implications for clinical practice, as delivering healthcare interventions virtually has become increasingly common following the Covid-19 pandemic. This review examined the evidence from RCTs and quasi-RCTs and found evidence to suggest that memory rehabilitation is effective in improving memory performance on subjective, objective (verbal, visual and working memory) assessments across immediate and intermediate follow-ups, and quality of life in the immediate, intermediate, and longer-term, and reducing depression (but only immediately after the intervention). However, this evidence should be interpreted in the context of the methodological quality as reported in the Summary of findings table (Table 19) before it is applied to a clinical setting.

2.5.3 Quality of the evidence

We identified 44 RCTs of memory rehabilitation for people with MS, and all but five had small sample sizes.[244,260,338,354,356] However, studies included in this review

were more methodologically sound than the memory rehabilitation RCTs included in systematic reviews of stroke or traumatic brain injury literature. Despite this, the CONSORT statement and guidelines were not always followed in these trials.

The randomisation protocol was inadequate and was poorly reported for 15 studies.[244,320,324,325,327,329,334,342,348–350,355,358,364,369] Gich et al.,[329] Hanssen et al.[244] and Tesar et al.[355] did not clearly mention how the randomisation list was created or what procedures were undertaken; Jønsson et al.[358] used closed envelopes but did not mention who created the random lists; Chiaravalloti et al.[320] used odd-even random allocation; and Hildebrandt et al.[334] and Pusswald et al.[349] used alternating allocation. These two latter forms of allocation are not always considered acceptable in RCTs,[470] but are classed by Cochrane as a quasi-randomised trial and were therefore included in this review. Mendozzi et al.[342] randomised only half the sample, with no stated random generation method. Twenty-seven studies reported their randomisation protocols adequately.[242,247,248,260,262,321–323,328,330,332,333,336–338,340,343–346,351–354,356,359,362] The 29 studies we have added in this update have improved in terms of quality of reporting of trials as far more of the trials added in this update were at low risk of bias than compared to previous studies. However, more work is needed to ensure that trialists follow the CONSORT statement.[468]

Furthermore, given that memory rehabilitation is a complex intervention, much more detail is required about what participants experience in both the intervention and the control arms of the trial. Indeed, the description of the interventions was adequate in most studies, however the control groups were much less well-described. Recently published guidelines such as the Template for Intervention Description and Replication (TIDieR) and the Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: revised guideline,[471,472] may help improve the quality of reporting of trials of complex interventions.

Given the complex nature of the intervention, it is important to determine whether the intervention was delivered as intended. Only four studies out of 44 reported whether a fidelity assessment was completed. Where it was assessed, authors found that the intervention was delivered with fidelity. The fact that 40 studies did not

assess fidelity has important implications for the robustness and validity of these findings. Fidelity assessment is crucial for ensuring that interventions are delivered as intended, which directly impacts the reliability of the study outcomes. Without rigorous fidelity checks, it is difficult to ascertain whether the observed effects are truly due to the intervention or influenced by variations in its implementation. This limitation highlights the need for future research to prioritize fidelity assessments to strengthen the evidence base and enhance the reliability of conclusions drawn from cognitive rehabilitation studies in MS. Future trials should consider including fidelity assessments.

Inclusion and exclusion criteria were relatively well-defined. While most studies described the flow of participants through the trial, Tesar et al.[355] did not, and only 14 of the 44 studies had flowcharts.[242,244,260,262,320,321,329,330,332,336,338,349,352,353]

Because MS is found in demographically diverse populations, we expected to see better description of the samples. Only five out of 44 papers described the ethnicity of the sample, while 38 out of 44 papers described the level of education. No studies reported whether participants were drawn from economically-disadvantaged groups or whether they had co-morbid conditions. While these factors could be balanced out through randomisation, we need to know whether the effects of the intervention are the same for these groups. This lack of clarity can lead to difficulties in comparing results across studies and in determining the applicability of the findings to the broader MS population. Moreover, inadequate sample descriptions hinder the ability to assess potential confounding factors that might influence the outcomes. To enhance the reliability and applicability of future research, it is essential for studies to provide comprehensive and detailed descriptions of their samples. Furthermore, while many studies recruited samples with people with different types of MS, we note that several studies only included people with relapsing remitting multiple sclerosis (RRMS). We recommend that future trials consider including people with other MS subtypes also, and outcomes described separately for each subtype.

Most trials opted to use impairment-level measures or tests with modest ecological validity and minimal chance of generalisation of treatment effects to activities of daily living. Fifteen studies used subjective measures of memory, which is a big

improvement from the five studies in the last update as these measures have some degree of ecological validity and were activity-level measures. However, these are prone to subjective reporting biases common to most Patient-Reported Outcome Measures (PROMs). Furthermore, the cultural appropriateness of outcomes has improved since the previous review, with more studies including translated and adapted assessment tools such as the GVLT which is the Greek adaptation of the California Verbal Learning Test (CVLT-II), used by one study in this review. Such adaptations have been validated in MS populations in the relevant countries before they were used in these studies, these adaptations involve translating these tests in the required languages while the content remains the same. Further details for the types of tests used by each study can be found in section 2.4.1.2.

There has also been a shift in focus in some of the more recent trials from assessing only cognitive outcomes to including other outcomes such as mood and quality of life. This, we believe, is a positive step forward in memory and cognitive rehabilitation. This review highlights the importance of not only including these quality-of-life measures as key outcomes. Only three studies assessed adverse events following memory rehabilitation.[260,321,322] While, the likelihood of such adverse events is remote, trials should assess them to be certain of this. Adverse events monitored included distress during the assessments or intervention, and more severe events such as hospitalisation and death. Any 'notable events' were recorded which included any event considered to be out of the ordinary. Lincoln et al.[260] included a safety outcome in which any participant who increased on the GHQ-30 by 30 points or more, were reported to the clinical teams.

Both parametric and nonparametric statistical tests were used to compare groups. Change scores were compared in six studies,[242,244,320,321,329,353] and all studies were concerned with significance testing. Contrary to the previous update of this review in 2016,[254] the majority of the newly included studies included P values in their reporting of outcomes as opposed to the seven that included them,[319,329,332,336,338,349,352] with many trials providing all P values in tables that were readily accessible in the papers and online as supplementary information. Most studies also mentioned confidence intervals and often reported the post-hoc

tests or statistical corrections or adjustments performed on their data. Eight studies used intention-to-treat analysis.[260,319,330,334,336,338,352,353]

During risk of bias assessment, we observed that some studies stated that they were "double-blind" studies without justifying how they were in fact double blind. This resulted in these studies being rated as high risk of bias. Such double-blind studies were typically those where computerised memory rehabilitation was the intervention being tested. Even in these situations where participants could potentially be blinded, it was not clear how different the computerised rehabilitation was from the computerised control group. Therefore, it was difficult to determine whether the participants were truly blinded. In some instances, the study authors reported that either participants or therapists delivering the intervention were blinded to group allocation, but from the study description, it was not always clear how this could have been the case. In future, we would strongly encourage authors to be more explicit in describing the blinding procedures used.

We conducted a separate sensitivity analysis for the studies where standard deviations were inputted and found no clinical differences between the sensitivity analysis and the primary analysis, suggesting that inputting the standard deviations had no significant effect. Only Lincoln et al.[338] had a large sample size and sufficient data available to complete a subgroup analysis. A subgroup meta-analysis based on type of MS will therefore need to be completed in a future review update when more studies become available.

2.5.4 Potential biases in the review process

Two of the review authors were lead investigators for three of the included studies,[260,336,338] and named authors on another included study,[319] but to mitigate bias, we had multiple review authors who independently appraised the methodological quality of these studies. As mentioned previously, I searched all abstracts, full texts, extracted the data from the included studies and carried out risk of bias assessments for all included studies. For each stage the abstracts, full texts and included studies were divided amongst the review authors so that all papers were reviewed by me and one other author. I also conducted all analyses and wrote the review up as a published manuscript. All review authors had the opportunity to review the manuscript once I finished the write up.

We only searched for papers in English, and we could only include mixed-diagnosis studies where separate data for those participants with MS were provided. Therefore, there may be more data available that we did not have access to. There were also potential overlaps between attention and memory retraining, where an intervention could be described as attention when it addressed memory, so we may have missed some trials. To mitigate this, we checked papers at full-text review to ensure that they were not excluded if a memory component was presented as part of the treatment. Finally, we searched GreyNet and the EThOS databases; however, we are not sure of the comprehensiveness of these, thus creating the possibility of further relevant grey literature that was not obtained via the searches.

2.5.5 Agreements and disagreements with other studies or reviews

This review complements the '*Psychological interventions for multiple sclerosis*' intervention review.[255] In one of their mini reviews, Thomas et al.[255] found quote: "some evidence of effectiveness of cognitive rehabilitation on cognitive outcomes, although this was difficult to interpret because of the large number of outcome measures used". Their interpretations have therefore been based on a narrative review of results from individual studies. Thomas et al. covered interventions that were not specific to 'memory rehabilitation', however, their findings related to effectiveness of interventions to help people with cognitive impairments were inconclusive.

Similarly, the Rosti-Otajärvi et al.[256] review found evidence that memory span, working memory, and delayed memory were significantly improved for the intervention compared with the control group. However, their review found no significant differences between intervention and control for emotional functions, whereas this review has found some significant differences, notably improved mood on depression scales and quality of life. Any discrepancies are likely due to the differences in inclusion criteria, as our review was specific to memory rehabilitation, or a cognitive rehabilitation with a memory component, whereas the Rosti-Otajärvi et al.[256] review evaluated a much larger breadth of neuropsychological interventions and outcomes.

The Goverover et al.[257] review found promising results to support cognitive rehabilitation for improving memory function and stated that there had been

substantial progress made in increasing the number of cognitive rehabilitation trials to allow for practise recommendations. However, they also suggest, like we do, there is still much work to be done to optimise cognitive rehabilitation potential by applying the most rigorous methodology to ensure the quality of evidence is as high as possible.

2.6 Limitations

One limitation of this review was that we could only obtain information on whether the studies used intention-to-treat or per-protocol analyses for eight studies,[260,262,334,336,338,352–354] therefore we could not complete a sensitivity analysis of intention-to-treat in comparison with per-protocol analysis. We were able to conduct a sensitivity analysis comparing studies judged to be at low risk of bias to all included studies, however, we were unable to run this analysis for four outcomes due to a lack of studies with low risk of bias in every area. This suggests that there could be a correlation between trials that measure their outcomes immediately post-intervention and high risk of bias within the methodology. Approximately a third of studies included in this review adhered to the CONSORT guidelines which notably impact the quality of the evidence. Our interpretation of the sensitivity analysis suggests that while the quality of the trials did not affect most outcomes, some differences were observed at immediate follow-up, with studies with higher risk of bias inflating the overall effect size estimates for these outcomes, and the test of overall effect changing from being statistically significant to not significant when studies at high risk of bias were excluded. This suggests that lower-quality studies may have positively influenced the outcomes, however, this could also be because only a few studies that measured immediate outcomes had low risk of bias in every area, and therefore, these results should be interpreted with caution. Furthermore, removing the studies with high risk of bias during this analysis often led to a reduction in heterogeneity. This could suggest an association between studies that have high risk of bias and increased heterogeneity. However, it is more likely that the heterogeneity was caused by wide variation in both type and frequency of intervention. There also appeared to be an association between studies that measure longer-term outcomes and low risk of bias.

2.7 Conclusions

2.7.1 Implications for practice

In the last two decades increasing attention has been given to memory problems as a frequent complaint for people with multiple sclerosis (MS). Memory rehabilitation programmes are offered to some people with MS, but their effectiveness has been questionable. Small studies using a mixture of internal and external memory aids, errorless learning, and environmental manipulation have yielded positive results with many of these using computer- delivered interventions. Large randomised controlled trials (RCTs) use mostly group-based and computer-delivered interventions and have also yielded positive results with improvements in outcomes seen in these trials often being maintained at follow-up. The positive results in trials using computerised interventions have important implications for clinical practice in the current COVID-19 pandemic, as cognitive rehabilitation may have to be delivered virtually for the foreseeable future. This review examined the evidence from RCTs and quasi-RCTs and found evidence to suggest that memory rehabilitation is effective in improving memory performance on subjective, objective (verbal, visual and working memory) assessments across immediate and intermediate follow-ups, and quality of life in the immediate, intermediate, and longer- term, and reducing depression (but only immediately after the intervention). Memory rehabilitation did not have an effect, at any time point, on activities of daily living or anxiety. There appeared to be no indication of harm caused by the interventions, but several studies did not routinely report adverse effects.

2.7.2 Implications for research

The research base from which to draw inferences for clinical practice regarding the effectiveness of memory rehabilitation for MS has improved since the previous review.[254] RCTs tended to be of modest sample size, and mostly used impairment-level outcome measures, which have limited value in assessing the functional effects of neurorehabilitation. These trials did not always adhere to the CONSORT guidelines,[473] which makes it difficult to get a full and true picture of the studies, and therefore limits the reader from making an informed decision regarding the fidelity of their conclusions. Missing information from such reports also make collating information for a meta- analysis difficult. Furthermore, results from 'positive' trials may be difficult to implement in clinical practice if

sufficient details about the actual intervention are not clearly spelt out. The TiDieR checklist and other more specific guidance for reporting of memory rehabilitation trials may help improve the quality of reporting trials of complex interventions.[474,475] Given that memory rehabilitation is a complex intervention, and only four studies assessed the fidelity of the intervention, we would encourage trialists to consider intervention fidelity assessments in future memory rehabilitation trials. The results of this review indicate that more research is required to arrive at a definitive answer as to whether memory rehabilitation for MS is effective in reducing activity limitations or restrictions to participation. It also highlights the need for more well-conceptualised, executed, and reported RCTs of memory rehabilitation that take into consideration the issues raised in this review.

In this chapter we demonstrated that there is evidence to support the effectiveness of cognitive rehabilitation for people with MS, however it is important to consider the limitations described above and how the quality of evidence may have impacted the conclusions that may be drawn. We were able to show that people with MS improved significantly in their cognition, quality of life and mood following cognitive rehabilitation. We were also able to show that these improvements could be sustained long term for quality of life and subjective measures of memory. However, not all people with MS appear to benefit from cognitive rehabilitation uniformly, therefore, the potential reason for this variation is what I explore further in Chapter 3.

Chapter 3: Determining who benefits most from cognitive rehabilitation for multiple sclerosis: A secondary data analysis.

3.1. Chapter overview

The findings of Chapter 2 highlighted evidence in support of the effectiveness of cognitive rehabilitation, such that the improvements made in subjective cognitive measures and quality of life were sustained long-term (6-24 months post-intervention).

This chapter presents a secondary data analysis exploring the possible factors such as demographics and clinical characteristics related to the likelihood of benefitting from cognitive rehabilitation compared to other groups. As the symptoms of people with MS vary significantly (in terms of number, type, and severity of symptoms), it is logical to assume that the degree to which people with MS benefit from cognitive rehabilitation would also vary. This theory was supported by our Chapter 2 findings, where we observed that not everyone with MS benefitted uniformly from cognitive rehabilitation. We, therefore, investigated whether we could predict how likely a person with MS was to improve or not improve in terms of their cognition, mood and quality of life outcomes following cognitive rehabilitation.

3.1.1. The CRAMMS trial

The data used in this study came from the Cognitive Rehabilitation for Attention and Memory in Multiple Sclerosis (CRAMMS) trial, which investigated the clinical efficacy and cost-effectiveness of a group-based cognitive rehabilitation programme for people with MS.[260]

In short, 449 participants were randomised into the cognitive rehabilitation programme (*n*=245) or the usual care group (*n*=204). To evaluate the clinical effectiveness, the participant's memory, attention, mood, levels of fatigue, and quality of life were assessed using objective and subjective measures at 6- and 12-months post-randomisation; this assessed both immediate and long-term effects of the intervention.

The cognitive rehabilitation consisted of 10 group sessions, each approximately 90 minutes long, with four to six people with MS per group. The intervention involved both restitution strategies to retrain impaired memory and attention functions and compensatory strategies to enable people to cope with these memory and attention

problems. However, as improving memory function was the primary focus, the intervention focused mostly on compensatory strategies with two weeks dedicated to attention training and restitution strategies which included psychoeducation around how attention processes work and some pencil-and-paper tasks designed to improve attention. Compensatory strategies included internal memory aids, rehearsal strategies, category grouping, mnemonics, and external memory aids as ways of coping with cognitive problems in daily life.

Baseline assessments were conducted to determine the participants' cognitive abilities. Each session was then tailored according to the needs of the participants in each group. The control group received their usual clinical care, which included general advice from MS specialist nurses and occupational therapists on how to manage cognitive difficulties, as this was the standard NHS care pathway, but they would not have received any specific interventions for cognitive problems.

Of the participants randomised, 214 intervention group participants and 173 control group participants were included in the primary analysis. The primary outcome of the CRAMMS trial was the Multiple Sclerosis Impact Scale-Psychological subscale (MSIS-Psy) (20) at 12 months. No significant effect was found between groups for this outcome (adjusted difference in means -0.6, 95% confidence interval -1.5 to 0.3) p=0.20). However, the study did find a significant effect for the MSIS-Psy at 6 months (adjusted difference in means –0.9, 95% confidence interval –1.7 to -0.1; p=0.03). Furthermore, significant between group effects were found for the Everyday Memory Questionnaire-participant version (EMQ-p), Everyday Memory Questionnaire-Relative version (EMQ-r) and 30-item General Health Questionnaire (GHQ-30) at 6 months and 12 months.

3.2 Rationale

Despite the effectiveness of cognitive rehabilitation highlighted by the systematic review, the degree to which people with MS benefit from this intervention appears to vary. This could be due to extremely broad inclusion criteria in terms of socio-demographics and clinical characteristics. Variability in benefit could also be due to type of cognitive rehabilitation and different modes of delivery, however, in this case we are focusing on the degree to which people with MS benefit from the same type of cognitive rehabilitation in the same study. Therefore, there is a need to determine

which subgroups of people with MS benefit most from cognitive rehabilitation, because this will help clinicians decide to whom this intervention is offered.

Clinical prediction tools help make such decisions, matching patients to treatments to yield the optimum outcomes/benefits, in line with the principles of precision medicine.[476] This (i) helps optimise Health Service resources in an efficient way (currently, very few centres offer cognitive rehabilitation due to limited number of clinicians available to offer the intervention), and (ii) avoids offering unnecessary interventions to those unlikely to benefit (reducing unnecessary travel to the therapy sessions, and any frustration of having participated in a treatment that does not benefit patients). There appears to be no developed clinical prediction tools to determine who would benefit most from group-based cognitive rehabilitation. We therefore aimed to close this research gap within this study.

3.3 Aims and objectives.

The primary aims of this study were to identify who benefitted most from the CRAMMS trial and create statistical models that can predict the likelihood an individual will benefit from cognitive rehabilitation. Understanding the groups of people with MS who are most likely to benefit from this intervention will allow the intervention to be targeted to those with a higher chance of improvement.

3.4 Methods

3.4.1 Study sample and design

This is a secondary data analysis of the Cognitive Rehabilitation for Attention and Memory in Multiple Sclerosis (CRAMMS) trial, the largest Phase III randomised controlled trial that evaluated the clinical and cost-effectiveness of a group-based cognitive rehabilitation programme for people with MS, involving 449 patients. For a detailed description of this trial please see CRAMMS monograph.[260] To ensure our results can be considered with their context, we have included a description of the CRAMMS trial sample below (Table 1).

Table 1 Description of CRAMMS trial cognitive rehabilitation group taken from Lincoln et al.[260] manuscript.

Characteristics	Cognitive rehabilitation group (N=245)
Age at randomisation	
Mean (SD)	49.9 (9.8)
Minimum, maximum	18, 69
Gender, n (%)	

Men	67 (27)
Women	178 (73)
Ethnicity	
White	237 (97)
Black	3 (1)
Asian	3 (1)
Mixed	2 (1)
Marital status, n (%)	
Single/divorced/widowed	81 (33)
Married/with partner	164 (67)
Participant reported time since diagnosis (years)	
Mean (SD)	12.1 (8.0)
Minimum, maximum	0, 36
Type of MS	
Relapsing-remitting	159 (65)
Primary progressive	22 (9)
Secondary progressive	64 (26)
Number of relapses in the previous 6 months, n (%)	
0	186 (76)
1	47 (19)
2	5 (2)
3	7 (3)
Relapses between baseline and randomisation, n (%)	
No	220 (90)
Yes	24 (10)
Not known	1 (<0.5)
Years of education	
Mean (SD)	14.2 (3.4)
Minimum, maximum	10, 35
Employment status, n (%)	
Retired	80 (33)
Not employed or in education	82 (34)
Employed part time	44 (18)
Employed full time	31 (13)
Any employment (full or part time)	75 (31)
Living arrangements	
Lives alone	49 (20)
Lives with others	196 (80)

3.4.2 Statistical analyses

For the current analyses, we explored all outcome measures in which improvement was observed in the CRAMMS trial.

Directed acyclic graphs (DAGs) were built to determine potential confounding factors for individual regression analyses. DAGS are graphical representations used to

illustrate and analyse the relationships between variables, particularly in the context of causal interference. In a DAG, nodes represent variables, and directed edges (arrows) indicate the direction of causal influence. A separate DAG was used for each dependent variable and all possible predictors to identify the possible causal relationships (see Figure 33). The DAGs were used to identify which predictors could potentially influence whether an individual is likely to improve in each dependent variable. This method also allowed me to identify potential confounding variables, which was essential as confounding variables have the potential to mask the true relationships between variables making it harder to identify the true predictors of improvement. These predictors were then included in the regression models and any identified confounding variables were controlled for accordingly. Confounders were defined as variables that were associated with both the exposure (cognitive rehabilitation) and the outcome (improvements in cognitive function or psychological wellbeing) but were not part of the causal pathway.

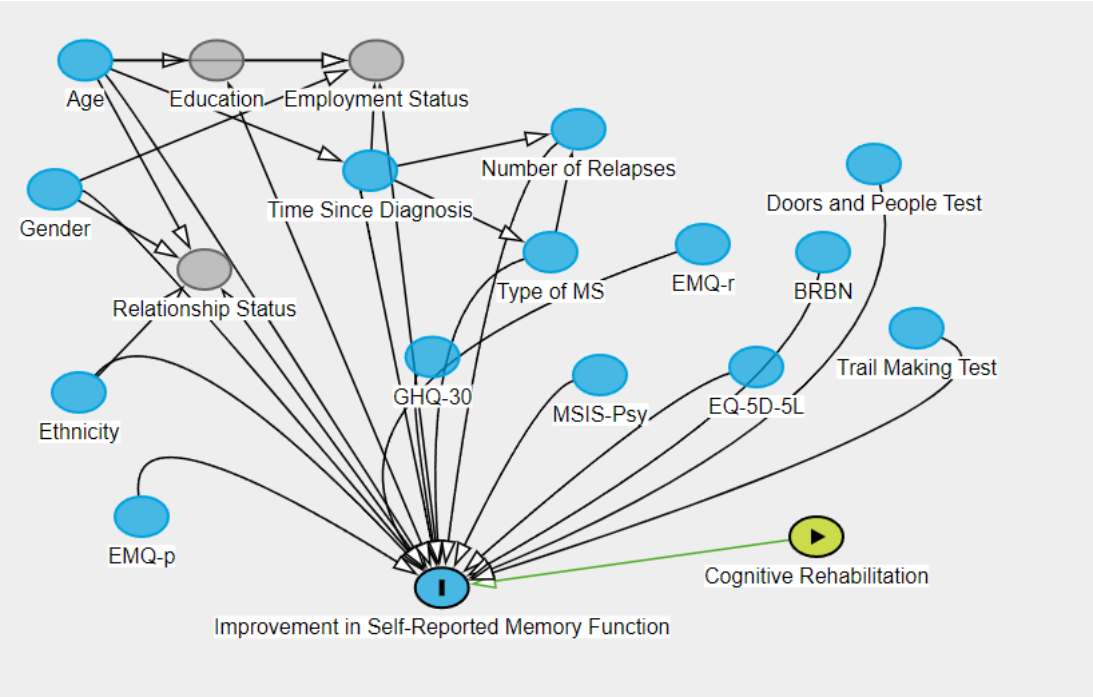


Figure 33 Directed acyclic graph showing relationships between predictors, cognitive rehabilitation and improvement in self-reported memory function.

The DAG highlights potential causal pathways and confounding relationships among the variables. For instance, we posit that cognitive rehabilitation directly influences improvement in self-reported memory function. Moreover, variables such as employment status, education, and gender are interconnected and may confound the

relationship between cognitive rehabilitation and memory function improvement. By visualising these relationships, we gain insights into potential pathways through which cognitive rehabilitation may impact memory function, informing the design and interpretation of regression models aimed at assessing the effectiveness of the cognitive rehabilitation programme.

Akaike information criterion (AIC) was used to ensure the final model was the best fit for the data. We calculated Nagelkerke's pseudo R^2, which indicates the explanatory power of the model (i.e., how much of the total variability of the dependent variable is explained by the model). This value ranges from 0 to 1, with scores of 0.75, 0.5 and 0.25 indicating substantial, moderate, and weak explanatory power of the model, respectively.[477]

To explore the presence of potential predictors of change in the outcome measures, univariate descriptive statistics of baseline demographics, clinical variables, self-report cognitive symptoms and objective neuropsychological test performance (Table 2) were used to create graphs to identify any interesting breaks in the distributions, including very high or very low values. This also allowed us to understand how each potential predictor related on its own, to each outcome measure, and other potential predictors.

Table 2 Primary categories of possible predictors.

Predictor category	Predictors
Socio-demographics	Age Gender Education Ethnicity Employment status Relationship status
Clinical variables	Number of years a person has been diagnosed Type of MS Number of relapses six months prior to initial assessment Number of relapses within six months of starting the intervention
Self-reported cognitive symptoms	Everyday Memory Questionnaire-participant version (EMQ-p)

	Everyday Memory Questionnaire-relative version (EMQ-r) 30-item General Health Questionnaire (GHQ-30) Multiple Sclerosis Impact Scale-Psychological subscale (MSIS-Psy) European Quality of Life five-level version (EQ-5D-5L)
Objective neuropsychological test performance	Brief Repeatable Battery of Neuropsychological tests (BRBN) Doors and people test Trail making test

The dependent variables were the difference in scores of self-report cognitive measures and neuropsychological tests between baseline and 6-month follow-up (Table 3). We used this to determine whether a participant improved or not. Each dependent variable was dichotomised to include participants that improved and did not improve following cognitive rehabilitation. From the final models, we were able to understand which predictors contributed significantly to the improvement in each cognitive area following cognitive rehabilitation.

The classification of improvement following cognitive rehabilitation is a critical aspect of our study methodology. While we acknowledge potential concern regarding measurement error and variation, our decision to dichotomise the dependent variables based on any improvement versus no improvement was made after careful consideration of several factors.

Firstly, my choice to dichotomise improvement was influenced by the practical implications of our research question. I aimed to evaluate the effectiveness of cognitive rehabilitation in producing clinically meaningful changes in cognitive function, which is often assessed using dichotomous outcomes in clinical practice. By dichotomising the outcome, I aimed to capture whether participants experienced any noticeable improvement in cognitive function following the intervention, regardless of the magnitude of change.

Secondly, the decision to use a dichotomous classification was based on the sensitivity of the outcome measures. Some of the self-report cognitive measures and neuropsychological tests used in our study may have limited sensitivity to detect

subtle changes in cognitive function. Dichotomising the outcomes allowed me to focus on identifying participants who demonstrated any degree of improvement, which may still be clinically relevant even if it falls below a more stringent threshold.

Furthermore, it is worth noting that some outcome measures used in my study, such as self-report cognitive measures, may lack clear cutoffs for meaningful improvement. Without established thresholds for clinically significant change, there was no obvious way to classify improvement based on specific cut-off points. Therefore, my approach of dichotomising the outcomes provided a pragmatic solution for evaluating improvement in the absence of clear criteria for meaningful change.

While I acknowledge that using a more stringent threshold for improvement could potentially yield a more conservative estimate of treatment efficacy, I believe that this approach strikes a balance between sensitivity and clinical relevance. By including participants who showed any degree of improvement, I aimed to capture a broader range of treatment effects and provide a comprehensive assessment of the impact of cognitive rehabilitation on cognitive function.

Table 3 Neuropsychological and subjective cognitive measures.

Neuropsychological tests		
BRBN	Brief Repeatable Battery of Neuropsychological test (1) +	A cognitive screening battery that mainly assess memory and attention and takes motor into account
	Symbol Digit Modalities Test	Sustained and divided attention and information processing.
	Selective Reminding Test Total recall (0-72) Delayed recall (0-12)	Verbal learning and memory
	10/36 Spatial Recall Total correct (0-30)	Visuospatial memory
	Paced Auditory Serial Addition Test (PASAT) Easy total correct Hard total correct	Auditory information processing speed and working memory
Doors and people test	Overall age-scaled score + Verbal total score + Non-verbal total score + Total forgetting score +	Visual and verbal recall and recognition
Trail Making test	Part B – Part A (0-20) +	Visual attention and task switching
Subjective cognitive measures (questionnaires)		
EMQ-p	Everyday Memory Questionnaire-participant version ++ (0-112)	Everyday memory
EMQ-r	Everyday Memory Questionnaire-relative version ++ (0-112)	

MSIS-Psy	Multiple Sclerosis Impact Scale-Psychological subscale +++	Psychological wellbeing
GHQ-30	30-item General Health Questionnaire ++++ (0-90)	General health over the past few weeks

+ Higher scores indicate better cognitive function.
++ Higher scores indicate more frequent memory problems.
+++ Higher scores indicate a greater negative impact of MS.
++++ Higher scores indicate higher levels of psychological distress.

The analyses were performed on the available data, i.e., if values were missing, no imputation of missing data such as intent-to-treat was performed.

3.5 Results

The exact number of participants included in each model (out of the 245 participants who were randomised to receive the cognitive rehabilitation) varied depending on how many people completed the 6-month follow-up outcome measures. A substantial number of participants improved in cognition and psychological wellbeing outcomes following cognitive rehabilitation (Table 4). For discussions regarding whether the below results were what I expected, please see section 3.6.

Table 4 Frequency of improvement after cognitive rehabilitation for people with MS.

	Frequency	%	*N* total
EMQ-p			214
Improved	152	71.02	
Not improved	62	28.98	
MSIS-Psy			215
Improved	172	79.78	
Not improved	43	20.22	
SDMT			220
Improved	168	76.33	
Not improved	52	23.67	
PASAT3			217
Improved	150	68.98	
Not improved	67	31.02	
PASAT2			217
Improved	165	75.92	
Not improved	52	24.08	
S10/36			217
Improved	138	63.67	
Not improved	79	36.33	

EMQ-p: Everyday Memory Questionnaire-Participant; MSIS-Psy: Multiple Sclerosis Impact Scale-Psychological; SDMT: Symbol Digit Modalities Test; PASAT3: Paced Auditory Serial Addition Test-3 second; PASAT2: Paced Auditory Serial Addition Test-2 second; S10/36: 10/36 Spatial Recall Test.

3.5.1 Everyday memory

The final model (model $\chi^2(9) = 168.665$, $p<.001$) that predicted improvement in Subjective Memory following cognitive rehabilitation included predictors from all

categories (Table 5). A Nagelkerke's pseudo R^2 of .580 indicates a moderate explanatory power of the model. The final model correctly classified 79.8% of participants. The odds of improvement were 2.16 times greater for those 'living with others' compared to those living alone, however this was not statistically significant (*p*=.098). The odds of improvement increased as age decreased (p=.606) and education increased (p=.210), however, this was not significant.

The odds of improvement decreased as participants' baseline scores in the Everyday Memory Questionnaire (EMQ-p) increased (p<.001), suggesting that those who scored in the mild to moderate range of the questionnaire are more likely to benefit from cognitive rehabilitation than those who score severe. When mild, moderate, and severe groups were added into the model separately, both mild and moderate groups predicted improvement when compared to the severe group, confirming these results. However, this post hoc analysis was not significant.

The odds of improvement decreased as participants' baseline scores on the Doors and People test increased (p<.001). During post hoc analysis, we found that participants that scored mid-range (5-8) in their total forgetting scores were more likely to improve compared to those scoring high (9-13) and low (0-4). This supports the finding that those with mild to moderate cognitive problems are most likely to benefit from cognitive rehabilitation.

3.5.2 Psychological wellbeing

The final model (model $\chi 2(6) = 108.523$, *p*<.001) predicting improvement in Psychological Wellbeing following cognitive rehabilitation included type of MS (*p*=.042), relapses experienced in the six months prior to receiving the cognitive rehabilitation (*p*=.086) and baseline Multiple Sclerosis Impact Scale (MSIS-Psy) scores (*p*=.005). The odds of improvement were 1.016 times greater for people with RRMS (*p*=.972) and .158 times lower for people with PPMS (*p*=.021), when compared to those with SPMS. A Nagelkerke's pseudo R^2 of .513 indicates a moderate explanatory power of the model. The final model correctly classified 86.6% of participants. The odds of improvement in psychological wellbeing were 2.139 times higher for those who had experienced relapses in the six months prior to receiving cognitive rehabilitation (*p*=.086).

3.5.3 Sustained and divided attention

The final model (model $\chi^2(12) = 70.322$, $p<.001$) predicting improvement in the sustained and divided attention scores between baseline and 6-month follow-up following cognitive rehabilitation included younger age ($p<.001$), higher education ($p=.137$), baseline MSIS-Psy scores (p=.011), type of MS (p=.011), baseline SDMT scores ($p<.001$) and baseline verbal recall scores (p<.021). A Nagelkerke's pseudo R^2 of .391 indicates a low to moderate explanatory power of the model. The final model correctly classified 80.9% of participants.

For type of MS, the odds of improvement were 2.617 times higher for people with RRMS ($p=.039$) and 2.237 times higher for people with PPMS ($p=.278$), compared to people with SPMS. The odds of improvement over time increased by 1.094 times per year of education. The odds of improvement decreased by .917 per year of age, suggesting that younger participants were more likely to benefit from cognitive rehabilitation.

3.5.4 Processing speed

The final model (model $\chi^2(14) = 76.847$, $p<.001$) predicting improvement in processing speed following cognitive rehabilitation included younger age ($p=.990$), higher education ($p=.815$), baseline EMQ-p scores ($p=0.321$), baseline Doors and People test scores ($p=003$) and baseline PASAT-2 scores ($p<.001$). A Nagelkerke's pseudo R^2 of .420 indicates a moderate explanatory power of the model. The final model correctly classified 79.3% of participants.

For the Doors and People baseline scores, the odds of improvement decreased by .338 and .273 per point scored on the non-verbal recall ($p=.008$) and recognition subtests ($p=.003$), respectively. The odds of improvement decreased by .990 per year of age and increased by 1.014 per year of education, however, this was not significant. The odds of improvement were .827 times lower for participants who has experienced one or more relapses six months prior to receiving the cognitive rehabilitation, however, this was not significant.

3.5.5 Verbal memory and recall

The final model (model $\chi^2(9) = 97.490$, $p<.001$) predicting improvement in verbal memory and recall between baseline and 6-month follow-up following cognitive rehabilitation included younger age ($p=.048$), higher education ($p=.409$), baseline SRT-s scores ($p<.001$), baseline SDMT scores ($p=.093$), baseline s10/36 scores

(p=.476), and baseline doors and people scores (p=.007). A Nagelkerke's pseudo R^2 of .305 suggests low to moderate explanatory power of the model. The model correctly classified 71.2% of participants as.

The odds of improvement over time decreased by .972 per year of age, suggesting that younger participants were more likely to improve their verbal memory following cognitive rehabilitation. The odds of improvement decreased by .904 per point scores on the SRT, suggesting that participants who scored lower were more likely to improve. The odds of improvement increased by 1.203 per point scores on the overall-aged score subset of the Doors and People test.

Table 5 Logistic regression models.

Model	χ^2	*df*	*p*	R^2(Nagelkerke)	Variables in the model	B	*SE*	Wald	*df*	Sig.	Exp(B)	95% CI for Exp(B) lower	upper
Improvement in Subjective memory	168.665	9	<.001	.580	Age	-.010	.018	.267	1	.606	.910	.974	1.047
					Education	.071	.056	1.573	1	.210	.932	.834	1.041
					Living w/ others	.772	.466	2.737	1	.098	2.163	.867	5.397
					Time since diagnosis	-.035	.023	2.369	1	.124	.965	.923	1.010
					Relapses	.583	.370	2.484	1	.115	1.791	.868	3.696
					EMQ-p	-.031	.009	11.009	1	<.001	.969	.951	.987
					MSIS-Psy	.000	.033	.000	1	.995	1.000	.937	1.068
					SDMT	-.006	.015	.159	1	.690	.994	.966	1.023
					Doors and people test tfs								
					Constant	-.187	.052	13.021	1	<.001	.829	.749	.918
						24.814	4774.872	.000	1	.996	5.977E+10		
Improvement in Psychological wellbeing	108.523	6	<.001	.513	Living w/ others	.303	.460	.433	1	.511	1.354	.549	3.337
					Time since diagnosis	-.031	.026	1.395	1	.238	.970	.922	1.020
					Relapses	.760	.442	2.957	1	.086	2.139	.899	5.089
					MS Type			6.359	2	.042			
					RRMS	.016	.454	.001	1	.972	1.016	.418	2.471
					PPMS	-1.842	.798	5.331	1	.021	.158	.033	.757
					MSIS-Psy	.096	.033	7.901	1	.005	1.101	1.029	1.177
					Constant	-17.501	3270.966	.000	1	.996	.000		
Improvement in Sustained attention and Information processing	70.322	12	<.001	.391	Age	-.087	.026	11.535	1	<.001	.917	.872	.964
					Education	.090	.061	2.213	1	.137	1.094	.972	1.233
					Relapses	-.022	.471	.002	1	.963	.979	.389	2.462
					MS Type			4.490	2	.106			
					RRMS	.962	.465	4.276	1	.039	2.617	1.052	6.515
					PPMS	.805	.742	1.177	1	.278	2.237	.522	9.577

					MSIS-Psy	.093	.036	6.535	1	.011	1.097	1.022	1.178
					Doors and people test								
					Oass								
					Vrecalls	.779	.425	3.367	1	.067	2.180	.948	5.012
					Nvrcogs	.266	.115	5.364	1	.021	1.304	1.042	1.633
					Vts	.155	.102	2.317	1	.128	1.168	.956	1.427
					nvts	-.569	.272	4.388	1	.036	.566	.332	.964
					SRT-s	-.336	.279	1.446	1	.229	.715	.413	1.236
					SDMT	-.028	.016	3.007	1	.083	.973	.942	1.004
					Constant	-.132	.025	28.240	1	<.001	.876	.834	.920
						5.951	2.523	5.565	1	.018	384.263		
Improvement in Processing speed	76.847	14	<.001	.420	Age	-.010	.024	.183	1	.669	.990	.943	1.038
					Education	.014	.058	.055	1	.815	1.014	.904	1.136
					Relapses	-.190	.455	.175	1	.676	.827	.339	2.016
					Time since diagnosis	-.016	.028	.303	1	.582	.985	.932	1.041
					MS Type			1.966	2	.374			
					RRMS	-.590	.506	1.358	1	.244	.554	.205	1.495
					PPMS	.950	.792	1.438	1	.230	.387	.082	1.826
					MSIS-Psy	-.039	.043	.815	1	.367	.962	.885	1.046
					EMQ-p	-.012	.012	.985	1	.321	.988	.966	1.011
					Doors and people test								
					Oass								
					Nvrecall	.096	.016	.844	1	.358	1.101	.897	1.352
					Nvrcogs	-1.084	.409	7.026	1	.008	.338	.152	.754
					Nvts	-1.297	.434	8.943	1	.003	.273	.117	.640
					Pasat2	1.775	.681	6.792	1	.009	5.899	1.553	22.411
					SRT-s	-.113	.025	20.264	1	<.001	.893	.851	.938
					Constant	-.012	.016	.557	1	.456	.988	.957	1.020
						9.469	2.893	10.713	1	.001	12954.01		
Improvement in Verbal Recall	97.490	9	<.001	.305	Age	-.028	-0.28	3.909	1	.048	.972	.946	1.000
					Education	.033	.040	.681	1	.409	1.033	.956	1.116
					EMQ-p	-.004	.006	.386	1	.534	.996	.985	1.008
					SRT-s	-.101	.012	65.833	1	<.001	.904	.882	.926
					SDMT	.021	.012	2.823	1	.093	1.021	.997	1.046
					S10/36	.020	.028	.509	1	.476	1.020	.965	1.079
					Doors and people								
					Oass	.185	.068	7.330	1	.007	1.203	1.052	1.376
					Vrecalls	.087	.065	1.762	1	.184	1.091	.960	1.240

	vts	-.083	.074	1.244	1	.265	.921	.796	1.065
Constant		2.304	1.250	3.394	1	.065	10.011		

*Relapses refers to relapses that were experienced in the six months prior to receiving memory rehabilitation.

EMQ-p: Everyday Memory Questionnaire-Participant; MSIS-Psy: Multiple Sclerosis Impact Scale-Psychological; PASAT2: Paced Auditory Serial Addition Test – 2 second; SDMT: Symbol Digit Modalities Test; SRT-s: Selective Reminding Test-Long Term Storage; S10/36: 10/36 Spatial Recall Test; Oass: Overall Age Scaled Score; Vrecalls: Verbal recall; Nvrecalls: Non-Verbal Recall Score; Nvrcogs: Non-Verbal Recognition Score; Nvts: Non-Verbal Total Score; Vts: Verbal Total Score; Nvts: Non-Verbal Total Score.

3.6 Discussion

This study investigated the participant characteristics that predicted neuropsychological improvement in people with MS six months after 10 weeks of cognitive rehabilitation. Almost 80% of the intervention group improved in at least one of the six neuropsychological tests domains measured by both subjective measures of cognition and objective neuropsychological tests. Four categories of predictors of improvement in neuropsychological test performance were examined at the univariate level and, subsequently, in the context of a hierarchical logistical regression model.

Of all of the variables examined, the most frequently occurring significant predictors of neuropsychological improvement were (i) age and education, from the sociodemographic category; (ii) type of MS and relapses experienced in the six months prior to receiving the cognitive rehabilitation, from the clinical category; (iii) baseline everyday memory scores and psychological wellbeing scores, from the self-report cognitive symptoms category; and (iv) baselines scores on the Doors and People Test, PASAT scores, and Selective Reminding Test scores, from the neuropsychological test category. Our findings were consistent with expectations based on existing literature from other clinical populations such as stroke and schizophrenia. In the following paragraphs, I compare our results with these studies and provide potential explanations grounded in cognitive theories and clinical evidence.

Participants with RRMS were more likely to report improvement of their psychological wellbeing, processing speed and sustained attention over time when compared to those with SPMS. Participants with PPMS were less likely to report improvement in their psychological wellbeing but were more likely to report improvement in processing speed and sustained attention when compared to those with SPMS. Participants who had a relapse in the six months prior to receiving cognitive rehabilitation were less likely to cognitively improve, but perhaps as anticipated, as the relapse symptoms presumably improved, the participant noticed some improvement of their psychological wellbeing. In outcome studies of patients with acquired brain injuries (without interventions specifically aimed at treating cognitive deficits), medical injury severity has been predictive of functioning.[18,19] Cognitively, relapses might have caused further damage to the areas of the brain

responsible for cognitive processes tested. There is evidence that cognition is notably more impaired during and immediately after an active relapse in people with MS compared to stable patients,[20] so it is possible that patients immediately following a relapse may be slower to improve. A recent review posited that cognition declines acutely during a relapse and that cognitive impairment in people with MS may result from incomplete recovery of these relapses.[21] However, there is a lot we still do not understand about the neuropathology driving cognitive relapse and recovery; thus, these results need to be interpreted with caution.

We found that younger participants were more likely to improve compared to older participants. This could be due to the nature of the cognitive rehabilitation programme. A significant part of this programme is teaching and encouraging participants to use external aids to help manage their cognitive difficulties. While a range of external aids are discussed, many focus on technology such as smartphones, mobile apps, smart home devices (e.g., Alexa), and online shared calendars. Using this technology may have come more naturally to those of a younger age, therefore, this may have contributed to the improvement in subjective measures of memory.

It is possible that age may play a significant role in predicting cognitive resilience or improvement linked to cognitive reserve.[22] Higher levels of cognitive reserve in people with MS can protect against disease-related cognitive decline and younger adults tend to have higher cognitive reserves compared to older adults.[23] Studies have suggested that age can not only influence initial cognitive abilities but may also play a moderating role in the improvement of cognition during rehabilitation.[24,25] Langbaum et al.[24] investigated how healthy adults responded to memory training and concluded that higher education and higher baseline cognitive functioning were predictors of cognitive improvement, with age providing a moderating effect.

Age at diagnosis may also predict cognitive improvement with recent evidence suggesting cognitive impairment is more severe for people with MS who are diagnosed earlier.[26,27] As a progressive disease, MS symptoms experienced gradually accumulate and worsen over time. Disease duration has been found to have a negative impact on both processing speed and working memory.[28]

Although education was repeatedly found to be a notable factor in predicting improvement in several of the models, it did not contribute significantly. The

literature suggests that higher education is predictive of improvement or faster recovery of cognition in older healthy adults and could be protective against MS associated cognitive deficits.[24] Furthermore, the cognitive rehabilitation programme teaches the use of internal aids such as mnemonic strategies (e.g., visualisation, categorisation, chunking, repetition, etc.), and the ability to self-generate these mnemonic strategies is associated with higher education, which could lead to improved memory and better performance on memory tasks.[29,30]

Education may be a predictor of improvement in cognition mediated possibly through employment. Highly educated people with MS being more likely to remain in work compared to those with a lower education.[31] Being employed may make people with MS more motivated to engage in cognitive rehabilitation effectively, which could influence performance on the cognitive tests performed after cognitive rehabilitation.

In terms of socio-demographics, we found that people with MS living with others were more likely to experience improvement in their memory than those living alone. This could be explained as the partner or family might be able to provide emotional support to the participants during the intervention period as well as helping with some of the technical aspects of using external memory aids.

Baseline neuropsychological tests, such as lower verbal recall and recognition test scores, were a significant factor in predicting improvement. Although no participants were performing at ceiling and therefore, all participants had room for improvement, it is plausible that those who scored lower simply had more room for improvement. Post hoc analysis provided some support for this explanation as, when we examined the mean gain improvement scores in those that scored below the mean on the EMQ-p at baseline, greater improvements were seen compared to those that score above the mean.

Based on these findings, we created the following algorithm or 'predictive model'. People with MS who are aged 49 or younger, are educated to at least a high school level or above, have not experienced any relapses in the six months prior to starting the cognitive rehabilitation programme, are living with others such as a partner, friends, or family members, and scored in mild to moderate range in all cognitive screening and baseline assessments are most likely to benefit from group-based cognitive rehabilitation. For the BRBN, scoring 1 SD below the norm is considered to

be evidence of mild cognitive impairment, we considered 2 SD below the mean to be moderate impairment and 3SDs below the mean to be severe impairment. For the subjective measures of memory, cut-offs are not currently established although groups such as the NEuRoMS project are making progress towards establishing mild, moderate and severe impairment cut-offs for people with MS which will allow this predictive model to be refined. Further investigations are needed to refine and test this algorithm before it can be used to target cognitive rehabilitation to those who may benefit most.

3.7 Limitations

One of the strengths of this study, owing to the large sample size of CRAMMS, is that we were able to consider several predictor and outcome variables. Of course, the main limitation of this post hoc analysis is that our findings are based on retrospective data. Therefore, findings from this study should be confirmed using a prospective research design, which we are currently undertaking.

3.8 Conclusions and implications

Improvement in some cognitive domains is more predictable than improvement in others. For instance, predicting improvement in subjective measures of memory and psychological wellbeing appear to be more accurate and accounts for greater variance than predicting improvement in sustained attention and verbal memory. This could be due to the mechanism driving improvement in cognition being more complex for neuropsychological tests. We also must note that the models vary in the amount of variance associated with improvement that they account for. However, the final models were able to correctly predict between 71.2% and 86.6% whether participants improved or did not improve following cognitive rehabilitation. This has significant clinical implications as one of the key reasons cognitive rehabilitation programmes are not routinely offered is due to there not being the resources and staff to offer it to everyone with MS. However, if we can identify those that are more likely to benefit, and the results of this study suggest that we may be able to do just that, then we can target the cognitive rehabilitation to those most likely to benefit and design (and offer) other interventions for those who are less likely to benefit.

In this chapter, we demonstrated that we were able to develop an algorithm that could predict what characteristics or groups of people with MS were more likely to show significant improvement in cognitive function and psychological wellbeing following

group-based cognitive rehabilitation. This algorithm will form the basis of a clinical prediction tool that could be used in clinical practice by clinicians to help them determine if their patients are likely to benefit from group-based cognitive rehabilitation or not. However, before this can be implemented into clinical practice, it must be tested. This is the focus of Chapter 4 in which I investigated both the feasibility and acceptability of delivering his group-based cognitive rehabilitation remotely and whether there were early signals of efficacy of the algorithm developed in this study.

Chapter 4: Who benefits most from cognitive rehabilitation for multiple sclerosis: A feasibility randomised controlled trial.

4.1 Chapter overview

Chapter 3 demonstrated that the algorithm developed could predict whether a person with MS was likely to improve or not improve in their neuropsychological test scores following group-based cognitive rehabilitation, with up to 86% accuracy.

This chapter presents a feasibility randomised controlled trial (RCT), which aimed to determine the feasibility and acceptability of delivering group-based cognitive rehabilitation online. This could allow people with MS to access this treatment regardless of their location. Furthermore, this trial aimed to determine whether there were preliminary signals of efficacy for the algorithm to determine whether it could be used as a clinical prediction tool to aid clinicians in deciding who best to target group-based cognitive rehabilitation to.

4.2 Rationale

Our Cochrane review, described in Chapter 2, investigated the effectiveness of memory rehabilitation for people with MS.[478] Results of this systematic review provide evidence to support the effectiveness of memory rehabilitation in improving memory performance and other outcomes including quality of life and mood at various follow-up times such as immediate (up to one month after the intervention) and intermediate (up to six months after the intervention). Furthermore, in subjective memory and quality of life, these improvements were found to be maintained at longer-term follow-up (after six months). The number of RCTs investigating cognitive rehabilitation has increased dramatically over the last five years and thus allowed us to gain a clearer understanding surrounding the efficacy of cognitive rehabilitation and the key areas of cognition in which significant improvement can be found. This review, together with our secondary data analysis of the CRAMMS trial described in Chapter 3, has given us insight into which factors/characteristics may make an individual most likely to benefit from cognitive rehabilitation.

Clinical prediction tools have a role to play in helping make such decisions about matching patients to treatments to yield the most optimum outcomes/benefits.[479] However, there is currently no clinical prediction tool available to use in clinical

practise to determine who benefits most from group-based cognitive rehabilitation for MS or any other neurological condition.

4.3 Study design

This was a mixed-methods feasibility RCT to compare online group-based cognitive rehabilitation plus usual care for people with MS, compared to usual care only. As this study was conducted remotely, we were able to recruit participants from across the United Kingdom (UK).

The primary aim of this study was to assess the feasibility of conducting a Phase III RCT to investigate the clinical effectiveness of an online group-based cognitive rehabilitation programme for people with MS.

Objectives:

1. To assess the feasibility and acceptability of the online group-based cognitive rehabilitation for people with MS.
2. To identify the necessary parameters to undertake a clinical effectiveness analysis in a definitive trial.
3. To gather detailed qualitative feedback interviews on the intervention and the study procedures.
4. To prospectively test our developed algorithm to understand preliminary signals of efficacy for predicting who is most likely to benefit from group-based cognitive rehabilitation.

While feasibility studies are not powered to detect statistical significance or test hypotheses, my preliminary hypothesis was that it would be both feasible and acceptable to people with MS to deliver group-based cognitive rehabilitation online.

This study was given favourable opinion by Health Research Authority [East Midlands – Derby Research Ethics Committee] Research Ethics Committee (Reference number: 22/EM0051) (see Appendix E and Appendix F).

4.4 Participants

4.4.1 Inclusion criteria

We recruited people with MS who:

- Were 18 or over and under 70 years of age. The lower age limit is because MS is usually diagnosed in adulthood and treatment strategies tend to be different

for children. People aged 70 and over may start to encounter age-related cognitive problems, which may confound the effects of cognitive problem due to MS. Also, most tests are standardised on this adult age group.

- Had MS, diagnosed at least 3 months prior to the baseline assessment contact with the study team, to allow for adjustment to diagnosis. This diagnosis was confirmed using the patient's medical records.
- Had cognitive deficits, defined as performance below the 25th percentile on the Brief Repeatable Battery of Neuropsychological Tests (BRBN).[295]
- Were able to speak English sufficiently to complete the cognitive assessments and take part in group sessions.
- Had access to a mobile device that supports Microsoft Teams.
- Gave informed consent.

4.4.2 Exclusion criteria

Participants were excluded if they had:

- Vision or hearing problems, such that they were unable to complete the cognitive assessments.
- Had concurrent severe medical or psychiatric conditions which would prevent participants from engaging in treatment, if allocated.
- Were involved in other psychological intervention trials.

4.5 Recruitment

Participants were recruited through the neurology service at Nottingham University Hospitals (NUH) NHS Trust, branches of the MS Society, and our Patient and Public Involvement (PPI) group. Recruited participants were requested to nominate a friend or relative who knew them well enough to complete a relative version of one of the outcome measures.

1. Nottingham University Hospitals

Potential participants who attended routine MS clinic visits were introduced to the study by a member of their MS clinical team (e.g., their neurologist or MS nurse). If patients did not wish to have further information, no contact was made by the researchers. If they were interested, the clinical team provided them with the Participant Information Sheet (PIS) (see Appendix G) and requested verbal consent to pass on their contact details to the research team. Participants contact details were

then passed on securely via email to a dedicated email address for this study (only research team members had access to this email address). We then provided these potential participants with more information about the trial. The clinical team recorded the date and time when verbal consent was obtained to pass on contact details.

2. Public and Patient Involvement (PPI)

We identified potential participants within our Nottingham MS Research Group PPI lists and invitation letters were sent out. This invitation letter included study information and research team details. If interested, people with MS replied to this email communication declaring their interest in the study and we then send out the PIS. If after reading the PIS, participants were still interested in taking part then we arranged a screening assessment with them at their earliest convenience.

3. Posters/self-referral

Posters were displayed at NUH in areas commonly visited by patients to advertise the study (see Appendix H). Advertisements were also placed with local MS Society branches, local therapy centres, and on the MS Society website in the form of a blog post. The study was also advertised using social media channels, twitter accounts and our PPI newsletters, thus people with MS had the opportunity to self-refer to the study. Offering this self-referral route was only possible because we chose to deliver the study remotely, so that we could reach a more varied population while also assessing the feasibility of delivering a group-based cognitive rehabilitation remotely. In these instances, people could contact me for further information using the contact details in the advertisements. I sent out the PIS to anyone with MS who responded to the advertisement expressing their interest in participating by email and offered a phone call during which any questions they had could be answered to ensure they fully understood the study. Following this, I then arranged screening appointments with anyone who wanted to participate in the study.

Prior to booking the screening appointments, I sent out a list of pre-screener questions to ensure that the participant was eligible to participate. These questions focusing on ensuring that the person with MS met the inclusion criteria listed above. If participants were found to be eligible at this point, I scheduled in their screening assessments. Prior to the screening assessment, I sent out consent forms to be

completed prior to the screening assessment (see Appendix I). I used e-consent for this study, in that participants were required to complete the consent form online and email it back to me completed. If participants struggled with this, I gave them the option to complete the consent form with them at the beginning of the screening assessment or to post it out with a stamped return envelope so that they had a paper copy to complete. For anyone who did not meet the inclusion criteria or did not pass the screening or baseline assessments, I gave them an overview of their test scores and explained why they were not eligible to take part in this study, and therefore, they would not be invited to continue to the next step.

For this study, recruitment continued until 36 people with MS passed the screening assessments. We opted for a sample size of 36 because it should be sufficient to address the research questions, it is the average sample size of cognitive rehabilitation trials in MS, and samples between 24 and 50 were recommended for such studies.[480,481] Furthermore, practical considerations such as recruitment feasibility and resource availability were also considered. Given the specific population of interest and the intensive nature of the cognitive rehabilitation program, recruiting a larger sample might have been challenging and could have compromised the study's feasibility.

4.6 Group allocation

Participants were randomly allocated to either the intervention plus usual care group or the usual care only group on a 3:1 ratio in favour of the intervention group. This ratio was chosen to gauge the intervention-feasibility of our target group and whilst a 1:1 ratio provides a greater power for tests of effectiveness trials; it is often preferable to use an uneven ratio for intervention trials.[482]

A member of the research team not directly involved with intervention delivery used a remote, internet-based randomisation system to obtain allocations for each participant. This member of the team was blinded to the participants recruited and created the randomisation schedule in REDCap (Research Electronic Data Capture). All study data were collected and managed using REDCap electronic data capture tools hosted at University of Nottingham. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing, 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulating and export procedures; 3) automated export procedures of seamless data downloads to

common statistical packages; and 4) procedures for data integration and interoperability with external sources.[483]

Participants were not blinded to whether they were participating in the cognitive rehabilitation or usual care only, however, participants in the cognitive rehabilitation sessions were blinded whether the algorithm predicted them to be most or least likely to benefit.

4.7 Intervention

Online cognitive rehabilitation was offered remotely via Microsoft Teams to groups of four to six people with MS who were experiencing cognitive difficulties for 10 sessions over 10 consecutive weeks. Each session was up to 1.5 hours long. The intervention delivered was the manualised group-based cognitive rehabilitation programme developed for the CRAMMS trial, mentioned previously in Chapter 3. For a detailed description of the CRAMMS trial please see.[242]

The intervention manual was originally developed as part of a programme of research on cognitive rehabilitation for people with neurological disabilities. The initial version of this manual was developed for the REMIND (rehabilitation of memory in people with neurological disorder) trial.[484] This trial showed that participants who received training in restitution and compensatory strategies used significantly more internal memory aids than those in the self-help control group.

The manual was later revised combining restitution and compensatory strategies into a single intervention which was more reflective of how cognitive rehabilitation was being delivered in clinical practice. The manual was adapted to address the unique cognitive challenges faced by individuals with MS. It focuses on MS-related issues such as memory, processing speed, and attention, incorporating strategies to manage cognitive fatigue and providing additional support and education tailored to the MS population. An RCT comparing those who received this combined intervention to those who received their usual clinical care only (REMIND-MS) found that those who received the combined cognitive rehabilitation improved significantly in their mood compared to the control group 8-months post-randomisation.[319]

Following these studies, the REMIND-MS cognitive rehabilitation programme was evaluated in a large scale multicentre RCT for people with MS which was named the CRAMMS trial.[260] The CRAMMS trial showed that people with MS who received

this intervention improved in the everyday memory scores and mood compared to the control group. Participants also stated during feedback interviews that they found the intervention strategies helpful and valued working with other people with MS who had similar memory problems to them.

In this feasibility RCT, we used the latest version of the manual as used in the CRAMMS trial. This manual is freely available online and can be accessed at https://www.nottingham.ac.uk/research/groups/longtermconditions/cognitive-impact/cramms/.

This intervention included teaching people with MS how to use a variety of compensatory strategies and providing them with psychoeducation so they could understand how their MS was impacting their cognition as well as how various cognitive processes work. The strategies taught during this intervention were compensatory strategies, including mnemonics (such as first letter cues and rhymes), other internal memory aids such as associations, visual imagery and categorisation, external memory aids such as diaries, smartphones, and calendars. The intervention focused on a different topic each week:

- Week 1: Introduction
- Week 2: Memory and memory problems
- Week 3: Attention I
- Week 4: Attention II
- Week 5: Introducing internal memory aids
- Week 6: Internal memory aids II
- Week 7: Internal memory aids III
- Week 8: Introduction to external memory aids and diaries
- Week 9: External memory aids II
- Week 10: Review of the programme and fine-tuning

The emphasis was on identifying the most appropriate strategies to help individuals overcome their cognitive problems and in providing participants with a range of techniques, which they can adapt and use according to their needs. In total, I led five groups a week for 10 weeks, under the supervision of a clinical psychologist. As much as possible, the programme was tailored to the individual needs of the group,

and the participants were grouped according to similar levels of cognitive functioning as identified during screening and baseline assessments.

We chose to test the intervention via an online platform instead of face-to-face, as it was originally designed for the CRAMMS trial,[260] following the Covid-19 pandemic. Conducting the intervention online has several advantages: fewer resources are required, which subsequently reduces costs, and the treatment can be delivered regardless of geographical distances, creating more opportunities for patients to join (especially those with mobility problems).

To adapt the cognitive rehabilitation manual for the online format of the intervention, I converted the paper inserts into electronic versions that could be shared on screen during sessions. This ensured that all materials were accessible and easily viewable by participants in a virtual setting. Additionally, I incorporated interactive elements to enhance engagement and made use of digital tools to facilitate real-time feedback and collaboration. These adaptations maintained the integrity of the original manual while optimising it for an effective online delivery.

All sessions were recorded for fidelity but also to allow participants to catch up on any missed sessions. If a participant missed a session, they were sent to recording to review along with the notes from that week's session and an overview of the take home activity, including where to find the relevant pages in their participant work booklet.

4.8 Usual care

This trial involved a usual care group. All participants, regardless of group assignment, received their usual clinical care. Usual care may include the provision of information on cognitive problems, but they were unlikely to be offered cognitive rehabilitation. Most people with MS with cognitive problems do not get any treatment for these difficulties following diagnosis. Other clinical services may include referral to employment rehabilitation services, self-help groups, or support from specialist charities, such as the MS Society.

4.9 Flowchart

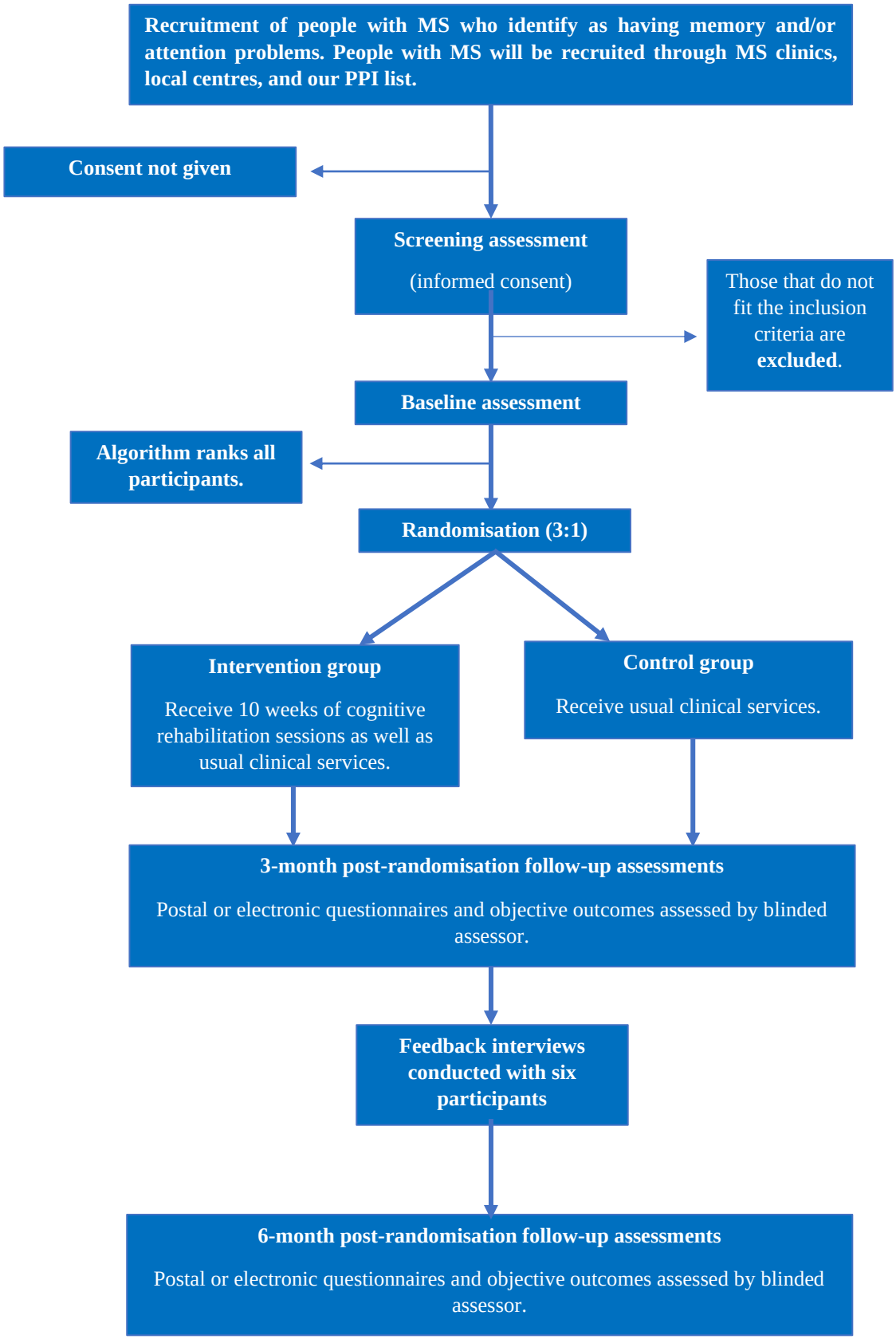


Figure 34 Participant flow through the study.

4.10 Assessments

4.10.1 Screening assessment

The screening assessment was carried out to determine participants' eligibility to take part in the study. I made it clear to all potential participants that the purpose of screening assessments was to check that each participant met the inclusion criteria and to also obtain baseline data for those who were eligible.

Demographic information recorded included gender, date of birth, ethnicity, level of education, living arrangements, relationship status, and current employment status. Clinical characteristics were also recorded such as subtype of MS, date of diagnosis and number of relapses in the past six months, if any. Following the collection of this data, the Brief Repeatable Battery of Neuropsychological Tests (BRBN) was performed with all potential participants.

4.10.1.1 The Brief Repeatable Battery of Neuropsychological Tests

The BRBN is one of the most sensitive and commonly used batteries for detecting cognitive impairment in MS.[485] This is a brief screening battery of tests to objectively assess cognitive problems in people with MS. This battery assesses various cognitive domains including sustained attention/concentration (the Paced Auditory Serial Addition Test, the Symbol Digit Modalities Test), verbal learning and delayed recall (the Selective Reminding Test), visuospatial learning and delayed recall (10/36 Spatial Recall Test), and semantic retrieval (Word List Generation).[295] The Word List Generation test is an optional addition that we chose not to include in our screening assessment to reduce the burden on participants.

The order of administration for this test is very specific and detailed in the BRBN manual.[295] The order of the tests is as follows:

1. Selective Reminding Test (SRT)
2. 10/36 Spatial Recall Test (10/36)
3. Symbol Digit Modalities Test (SDMT)
4. Paced Auditory Serial Addition Test (PASAT)
5. Delayed recall of the SRT
6. Delayed recall of the 10/36

The SRT is a verbal list-learning test that distinguishes between retrieval from working memory and long-term memory. The SRT also examines consistency of

retrieval from long-term memory. The SRT is a validated measure of verbal learning and delayed recall in MS populations.[486,487]The version of the SRT included in the BRBN involves six learning trials, this was shortened than the original 12 learning trials due to previous research indicating that six trials yield equivalent data to 12.[488–491] During this test, participants are read a list of 12 different words and are then asked to recall the words back immediately. The participants are then prompted on the words they did not say and the trial resets. This is repeated until all six learning trials are completed. [452,453]

The scoring of the SRT is presented in Appendix J. As mentioned above, the SRT measures recall from long-term memory which is defined as any word that is spontaneously recalled without prompting or reminding and is identified as two spontaneous recalls in a row. If a word is spontaneously recalled on all subsequent trials, then this is consistent long-term retrieval. Scores are provided for total number of words recalled, Long Term Storage (LTS), Consistent Long-Term Retrieval (CLTR) and total number of words recalled after the delay period.

The 10/36 spatial test was adapted from the 7/24 and is a more difficult version of this test.[492,493] The 10/36 spatial test measures visuospatial learning and delayed recall. During this test, the participant is presented with a 6x6 checkerboard and given 10 checkers. The participant is then shown a picture of a 6x6 checkerboard with all the 10 checkers placed in a specific pattern. The participant is given 10 seconds to look at the checkerboard before it is taken away and then participant is asked to recreate the pattern on the completed checkerboard from their memory using their checkers and checkerboard to the best of their ability. This is then repeat twice more, for three trials in total. Between each trial, the participants are asked to move the checkers off the board so that each trial is a genuine attempt. At the end of the test, participants are asked again to recreate the pattern on the checkerboard that they were shown previously, but the completed checkerboard is not shown again so that delayed recall can be assessed. The scoring for this test is the number of correct checkers added up for each of the three trials to give a total recall score and then a separate number of correct checkers is recorded for the delayed recall.

The SDMT is the most widely used assessment of cognition in MS and it is widely accepted to be a measure of information processing speed.[303] However, the cognitive

processes underlying the SDMT are likely multifarious with the SDMT manual describing it as a measure of visual processing and learning,[302] and the BRBN manual describing it is a measure of sustained attention.[295] Recent research in MS populations suggests that the SDMT measures multiple cognitive processes, with memory, information processing speed and rapid automatised naming (lexical access speed) contributing to SDMT performance.[494] This may explain the high degree of sensitivity the SDMT has to cognitive changes in MS.

For the BRBN, the oral version of the SDMT is used. For this test, the participant is presented with a sheet of paper, on which there is a key at the top of the page which has a row of symbols and a row of numbers. Each symbol has a number that corresponds to it. Underneath this key, there are several rows of symbols, and it is the participant's job to match each symbol with its corresponding number using the key. First, a practise round is conducted to ensure the participant understands what is being asked of them and then the participants are given 90 seconds to correctly identify as many numbers as possible. The total number of correctly identified numbers matching to the symbols is recorded for the final score. The highest possible score on this test is 120.

The PASAT measures multiple cognitive domains, the details of which vary depending on the research. The BRBN manual states that, like the SDMT, the PASAT measures sustained attention/concentration while the National MS Society states that the PASAT assesses auditory information processing speed and flexibility, as well as calculation ability. However, more recent research suggests that the PASAT is a measure of both attention and working memory due to the extensive load the PASAT places on working memory capacity.[495] This has been supported by functional magnetic resonance imaging (fMRI) studies which have found that when completing the PASAT test, participants show activation in their prefrontal cortex,[496] which is the region of the brain thought to play a critical role in working memory.[497]

The PASAT test involves playing a recording to the participant, on which a series of numbers are spoken. The participant is tasked with adding the first two numbers together and then telling the assessor the answer. The participant is then required to add the next number they hear to the one they heard previously and so on. There are two versions of this test which involve the numbers being read out at two different

speeds, one every two seconds or one every three seconds. The test is scored by calculating the number of correct answers with a maximum of 60. For the purposes of this study, the three second version was used as it is the easiest.

To enable the remote administration of the BRBN without compromising the validity of the assessments, several adaptations were made. A screening materials packet was created and mailed to participants, containing all necessary items for the tests. I adhered to the original BRBN manual including using the materials developed by Rao et al.295 and ensured that all adaptations aligned with the in-person delivery. Similar neuropsychological test batteries have been validated for remote delivery, finding similar test scores in participants between face-to-face and remote delivery.530

The SRT was the only test that required no adjustments for remote administration. It was conducted online in the same manner as an in-person test according to the BRBN manual. On the other hand, for the s10/36 test, participants were tasked with arranging checkers to match a specific pattern on a checkerboard. Normally, a physical checkerboard and pieces would be provided. To adapt for remote administration, a laminated version of the checkerboard was included in the screening materials pack. Black circles of the correct size, representing the checkers, were printed, laminated for durability, and shared with participants. This replicated the environment of the face-to-face test.

During the test, a PowerPoint slide of the completed checkerboard was displayed for 10 seconds, then hidden for each trial. However, assessing the results remotely posed a challenge as participants could not show their boards on camera due to image flipping. To address this, participants were asked to take a photo of their arrangement using their smartphone and send it for scoring. Alternatively, participants could verbally communicate the placement of each checker. For the SDMT, the oral version of this was used. A scoring sheet was printed and included in the screening pack provided to participants.

Age and education matched normative data has been developed for all measures included in the BRBN.[295] To be eligible for this study, participants were required to score at least one standard deviation below their age and education matched norm on at least one of the tests (Table 6). Participants who did not meet this criterion were thanked for their interest in the study and given the option of receiving a lay report of

their test scores. Participants who met this criterion were informed that they were eligible for the study and invited to complete the baseline questionnaires.

Table 6 BRBN cut-off scores stratified by age and education using the criteria of 1 SD below the mean value HC in each test.[295]

	Age		
Education	<35 years	35-49 years	>49 years
≤8 years (low level)			
SRT-S (LTS)	38	40	28
SRT-R (CLTR)	34	32	25
SRT-D	8	8	7
10/36	12	12	12
10/36D	4	4	4
SDMT	32	31	24
PASAT3	24	24	24
PASAT2	19	19	19
WLG	15	15	15
9-12 years (middle-low level)			
SRT-S (LTS)	40	41	33
SRT-R (CLTR)	34	32	25
SRT-D	8	8	7
10/36	15	15	15
10/36D	5	5	5
SDMT	33	36	33
PASAT3	35	35	35
PASAT2	26	26	26
WLG	21	21	21
13-16 years (middle-high level)			
SRT-S (LTS)	43	46	37
SRT-R (CLTR)	34	32	25
SRT-D	8	8	7
10/36	16	16	16
10/36D	5	5	5
SDMT	45	36	36
PASAT3	40	40	40
PASAT2	30	30	30
WLG	22	22	22

	Age		
Education	<35 years	35-49 years	>49 years
≥17 years (high level)			
SRT-S (LTS)	50	49	44
SRT-R (CLTR)	34	32	25
SRT-D	8	8	7
10/36	19	19	19
10/36D	7	7	7
SDMT	55	39	40

Notes. SRT-S, Selective Reminding Test Long-Term Storage; SRT-R, Selective Reminding Test Long-Term Retrieval; SRT-D, Selective Reminding Test Delayed Recall; 10/36, 10/36 Spatial Recall Test; SDMT, Symbol Digit Modalities Test; PASAT 2-3, Paced Auditory Serial Addition Test 2 and 3 seconds; WLG, World List Generation; SD, Standard Deviation.

4.10.2 Baseline assessment

The baseline assessments involved completing a series of questionnaires that aimed to understand the participant's memory difficulties, fatigue levels and the impact MS has on their daily life. The questionnaire pack contained four questionnaires: Everyday Memory Questionnaire participant version (EMQ-p), Multiple Sclerosis Impact Scale (MSIS), Fatigue Severity Scale (FSS), and EuroQol-5 item-5 level (EQ-5D-5L) Questionnaire (see Appendix K). Completing these questionnaires took participants approximately 15-20 minutes. The questionnaires could either be sent out via email using a REDCap link or via post according to participant preference. All participants were also asked to nominate a relative or friend to complete the Everyday Memory Questionnaire-relative version (EMQ-r) on their behalf, which allowed us to understand the participant's cognitive difficulties from their relative/friend's perspective, although this was not mandatory.

4.10.3 Rationale for using the baseline questionnaires

4.10.3.1 Everyday memory questionnaire

The EMQ is a self-report rating scale to assess participants' attention and memory difficulties in daily life.[498] This questionnaire consists of 28 items, each describing a different everyday activity that may involve memory difficulties. The questionnaire asks participants to think about how often they experience each memory problem with five possible answers: once or less in the last month/never, more than once a month but less than once a week, about once a week, more than once a week but less than once a day, or once or more a day. These responses were scored on a scale of 0-4,

respectively. Scores on the EMQ range from 0-112 with higher scores indicating more frequent memory problems.

The items included in this questionnaire cover a range of types of memory such as episodic memory, procedural memory, and prospective memory. Examples of these items include "Forgetting where you have put something. Losing things around the house" and "Finding that a word is 'on the tip of your tongue'. You know what it is, but you cannot quite right it". The relative version of this questionnaire includes the same items but instead asks them to think about how often their relative/friend experiences these problems.

The EMQ was created as a subjective assessment of memory impairment in everyday life. The EMQ was created when Sunderland et al.[498] began questioning the validity of lab-based memory tests to evaluate the outcomes associated with therapy programmes. The list of 28 items in the questionnaire includes a wide range of everyday scenarios that could be associated with memory difficulties such as 'finding a television story hard to follow'. Initially, this questionnaire was developed for people who had experienced traumatic brain injuries, but it was later refined and validated to be used with MS populations.[499]

The EMQ has strong face validity, assesses situations that occur in everyday life and is frequently used in clinical practice.[500] Concurrent validity has been established between the EMQ and the Subjective Memory Questionnaire, the Wechsler Memory Scale and the Rivermead Behavioural Memory Test.[501]

4.10.3.2 Multiple Sclerosis Impact Scale-29

The Multiple Sclerosis Impact Scale (MSIS-29) is a self-report scale used to assess the perceived physical and psychological impact of MS.[311] This questionnaire comprises two scales: the physical impact scale (Phys) and the psychological impact scale (Psy). The physical impact scale includes 20 items that relate to physical function and includes two leading prompts. The first prompt is 'in the past two weeks, how much has your MS limited your ability to…' and then items such as 'do physically demanding tasks?'. The second prompt is 'in the past two weeks, how much have you been bothered by…' and then lists items such as 'problems with your balance?' and 'spasms in your limbs?'. The psychological impact scale includes nine items that relate to psychological function using the prompt 'in the past two weeks,

how much have you been bothered by…' and then lists items such as 'worries relating to your MS?', 'feeling depressed?' and 'feeling mentally fatigued?'. Participants are given four response categories to these items: not at all, a little, moderately, or extremely, with these items being scored on a 1-4 scale, respectively. These scales can be split into two separate scores. The MSIS-Phys scores range from 20-80 with higher scores indicating greater physical impact of MS. The MSIS-Psy scores range from 9-36 with higher scores indicating greater psychological impact of MS.

The MSIS-29 has strong validity and reliability to other measures. The MSIS-Phys correlates well with other measures of disability in MS such as the Expanded Disability Status Scale and the MS Functional Composite. The MSIS-Phys is more responsive than the EDSS,[502–504] the 36-item Short Form Survey (SF-36),[505] and the Functional Assessment of MS Instrument,[503,506] suggesting that the MSIS-Phys may be a useful measure of physical function in clinical settings. The MSIS-Psy is highly correlated with the SF-36 mental health subscale, the Functional Assessment of MS (FAMS) emotional wellbeing subscale and General Health Questionnaire (GHQ) scales.[507]

4.10.3.3 Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a self-report scale to assess severity of fatigue with fatigue being defined as a lack of energy or total body give-out.[508] This scale is frequently used in clinical trials of interventions for fatigue and other symptoms in people with MS.[509] Participants are given the prompt 'during the past week I have found that…' and then five items are listed which relate to fatigue: 'I am easily fatigued', 'fatigue interferes with my physical functioning', 'fatigue causes frequent problems for me', 'fatigue interferes with me carrying out certain duties and responsibilities', and 'fatigue interferes with my work, family, or social life'. Participants are asked to rate how much they agree with each fatigue statement on a scale of 1-7, with 1 indicating strongly disagree and 7 indicating strongly agree. Scores ranges from 5-35, with higher scores indicating a greater impact of fatigue.

The FSS has high reliability in the MS population with a Cronbach's alpha value of 0.93.[510] Cronbach's alpha values are a measure of scale reliability with a value above 0.7 considered to indicate high reliability.[511] The FSS and the Modified Fatigue Impact Scale (MFIS) scale are highly correlated. The FSS is a shorter scale than the MFIS however, and while the four-week recall period of the MFIS may be more

accurate than the one-week recall period of the FSS,[512] for the purposes of this study, understanding how fatigued people with MS felt at the time of baseline and follow-up assessments was adequate to address the research questions.

4.10.3.4 EQ-5D-5L

The EuroQol five-dimension (EQ-5D-5L) scale is a generic health-related quality of life measure which was developed by the Euroqol group. The scale is often used for health economic and clinical evaluations. The EQ-5D-5L consists of five dimensions: mobility, self-care usual activities, pain/discomfort, and anxiety/depression. Participants are asked to score these on a Likert scale of 1-5 and each option is worded similarly. For example, for the anxiety/depression dimension the responses are: 'I am not anxious or depressed', 'I am slightly anxious or depressed', 'I am moderately anxious or depressed', 'I am severely anxious or depressed', or 'I am extremely anxious or depressed'. This questionnaire also includes a visual analogue scale which asks participants to rate their overall health on a scale of 0 to 100, with score of 0 indicating the 'worst health imaginable' and a score of 100 indicating the 'best health imaginable'.

The EQ-5D-5L is recommended by the National Institute for Health and Care Excellence (NICE), and it is validated in several patient populations.[513]

4.10.4 Follow-up assessments

All screening assessments and baseline assessment were repeated at 3- and 6-months post-randomisation (this included the BRBN and the questionnaire pack) to assess immediate and medium-term efficacy of the online group-based cognitive rehabilitation.

After the intervention was completed, I sent out the questionnaire pack for participants to complete via a REDCap link (unique to each participant) which was delivered to them via email. I sent all participants a separate email with a request to arrange the follow-up assessment at their earliest convenience. These assessments consisted of the BRBN, they took approximately 20 minutes each and were carried out via Microsoft Teams. If participants did not respond to this request, then I sent a follow-up email after three days of no response, and then again after six days of no response. If the participant did not respond to either of these follow-up emails, then they were considered to be lost to follow-up.

4.11 Feedback interviews

Qualitative feedback interviews were conducted with six participants from the intervention group. The semi-structured interviews were conducted to capture participants' perspectives and experiences, to understand the acceptability of the online cognitive rehabilitation programme, and to inform further improvements to the programme. This interview was used to gather information regarding any additional benefits or improvements the participants may have experienced following the cognitive rehabilitation and understand any parts of the programme that they either did not like or did not find beneficial.

During each baseline assessment, I asked participants if they were willing to participate in the feedback interviews. I explained the purpose of the interviews and the approximate time requirements. I made it clear that only six participants would be selected for interview, but all participants were asked because we wanted to ensure that as much as possible, the participants interviewed were representative of those included in the trial and I wanted to ensure diversity in the sample. The six participants from those who expressed their interest in taking part in the feedback interviews were selected using maximum variation sampling considering age, type of MS, gender, level of cognitive abilities and intervention group.

An assistant psychologist (AP), who was not involved in any other aspect of this study, conducted the interviews. The interviews were scheduled for a time that was convenient for the participants. At the start of the interviews, the AP completed the informed consent form with the participants with a separate consent form (see Appendix L). The participants at the beginning of the interview were reminded that they were free to withdraw from the interview at any time without giving a reason.

The questions included in the interview were open-ended, with the aim of gathering as much information from the participants as possible and ensuring they were free to talk about their experiences in a way that was meaningful to them. The semi-structured schedule is detailed in Appendix M.

All participant interviews were conducted using Microsoft Teams. All interviews were video, and audio recorded using the recording feature in Microsoft Teams. These videos were then converted into mp3 files and transcribed verbatim using the University of Nottingham automated transcription service. All transcriptions were

anonymised and checked for accuracy by the AP before being sent back to the research team for analysis.

4.12 Data analyses

I carried out the statistical analyses using IBM SPSS Statistics version 28, Stata version 17 and NVivo version 14.

4.12.1 Baseline

The data were split into data from the intervention group and data from the usual care group so that the demographic and clinical characteristics could be compared. Categorical variables were reported using exact numbers and percentages while continuous variables were reported using mean, standard deviation, and range. The distribution of baseline data was assessed for normality using the value of the skewness statistic, where this value was greater than twice the value of its standard error then non-parametric procedures were applied. Parametric statistics were used if most variables included in the analyses were normally distributed. Participants were randomly allocated to either the intervention group or the usual care group so any differences between groups were due to chance, therefore, I did not use a statistical test to determine whether the differences were due to chance.

4.12.2 Feasibility

As this is a feasibility trial, the feasibility measures were the primary outcomes. The number of referrals and recruitments from each recruitment pathway and the percentage of referrals converted to participants were reported. All known reasons for exclusions, withdrawals and dropouts were described. The number and percentages of completed outcome measures were calculated. The number of sessions attended by intervention group participants was reported, as well as the reasons for missed sessions.

We pre-specified success criteria for these feasibility outcomes to guide our evaluation:

- Recruitment Success: Achieving a minimum recruitment rate of 70% of the target sample size within the designated recruitment period.
- Retention Success: Maintaining a retention rate of at least 80% from baseline to follow-up.

- Adherence Success: Ensuring that at least 75% of participants adhered to the intervention protocol (attended scheduled sessions and completed assigned tasks).
- Acceptability Success: Achieving a satisfaction rating of at least 80% (participants reporting the intervention as acceptable or highly acceptable).

4.12.3 Effectiveness of the intervention

The statistical analyses conducted in this study are exploratory in nature. Given that this is a feasibility trial, the primary objective is not to establish the efficacy of the cognitive rehabilitation intervention but to explore potential trends and gather preliminary data that will inform the design of future, larger-scale studies. Consequently, all reported p-values are uncorrected for multiple comparisons. This approach is suitable for an underpowered feasibility study where the focus is on assessing feasibility outcomes and generating hypotheses for further research.

The distribution of follow-up data was assessed for normality using the skew statistics. Where the skew statistic was lower than twice the standard error, means, standard deviations and ranges were reported. Analysis was conducted according to randomised group, regardless of the number of treatment sessions attended, and without imputation for missing data (i.e., modified intention to treat).

I used paired t-tests to compare the differences in scores from baseline to 3-month follow-up for all participants. I chose to use t-tests as the primary statistical analysis method for this study due to their relevance and appropriateness for examining the research questions and the nature of the data. T-tests are widely recognised for their utility in comparing means between two groups or conditions, making them a suitable choice for assessing the significance of differences in the context of this research. In this study, I was specifically interested in comparing the means of the intervention group and the control group to evaluate whether there is a statistically significant difference between them. This aligns with the fundamental purpose of t-tests.

Furthermore, t-tests are especially well-suited for relatively small sample sizes, which characterise our dataset. This is crucial because it allows for a rigorous analysis of the available data while avoiding the potential limitations associated with more complex statistical methods that might require larger samples. The application of t-tests in our

analysis ensures that we can draw meaningful conclusions from the data, considering the sample size constraints.

A significant improvement from baseline to follow-up on all outcome measures was determined as $p<0.05$. Effect sizes were also estimated using Cohen's d, by calculating the mean difference divided by the standard deviation of the difference. Effect sizes were classified small, moderate, and large for values equal to or greater than 0.2, 0.5 and 0.8, respectively.

The statistical analyses conducted in this study are exploratory in nature. Given that this is a feasibility trial, the primary objective is not to establish the efficacy of the cognitive rehabilitation intervention but to explore potential trends and gather preliminary data that will inform the design of future, larger-scale studies. Consequently, the p-values reported in Tables 12-14 are uncorrected for multiple comparisons. This approach is suitable for an underpowered feasibility study where the focus is on assessing feasibility outcomes and generating hypotheses for further research.

Furthermore, I performed a subgroup analysis to examine between-group differences within the intervention group of those predicted to be most likely to benefit and those predicted to be least likely to benefit to assess the (previously developed) algorithms' effectiveness. I divided the cognitive rehabilitation group into those who were predicted to be most likely to benefit according to the algorithm and those predicted to be less likely to benefit according to the algorithm. To put it simply, I put all the participants who met all the criteria for being most likely to benefit outlined in chapter 3 in one group, and all participants who did not meet these criteria is the second group. I conducted an independent t-test to compare the differences in scores at 3-months post-randomisation between these two groups.

4.12.4 Feedback interviews

The qualitative data obtained during the semi-structured feedback interviews were coded and analysed thematically. I used NVivo 14 for Windows to organise and store the data.

For the qualitative data, we opted to use framework analysis because it is an atheoretical form of thematic analysis, which has become an increasingly popular approach in medical and health research.[514] Framework analysis is similar to thematic

analysis in that it's focus is to identify commonalities and differences in the data, then focuses on the relationship between difference parts of the data to create themes.[515] In framework analysis, the data from the transcripts are mapped onto a predefined framework. I used the analytic framework developed from the CRAMMS study to map the new data onto this framework and determine whether there are any similarities and differences.[339]

I followed the structured and systematic approach outlined by Yardley et al.[516] which is designed to provide a robust and comprehensive method for qualitative data analysis. This method involved a rigorous and iterative process, encompassing several key steps.[517,518] Firstly, data familiarisation was achieved through the thorough review and immersion in the collected qualitative data, enabling a deep understanding of the context and content. Subsequently, a clear and systematic indexing system was developed, ensuring the data were effectively organized and categorized. The process of charting was then carried out, involving the transformation of data into a clear and coherent framework, emphasising patterns and themes that emerged during the analysis.

This framework was based on the framework matrix developed for the CRAMMS trial. The framework analysis method allowed for a systematic exploration of qualitative data, ultimately facilitating a comprehensive and structured approach to understanding and interpreting the findings of the research. We used the framework matrix developed for the CRAMMS trial and explored whether there were similarities and differences.

I followed the procedure for framework analysis reported by Gale et al.[514] in which seven stages are outlined: (1) transcription of the interview recordings, (2) familiarisation with the transcripts, (3) coding, (4) developing an analytical framework, (5) applying the analytical framework, (6) charting data into the framework matrix, and (7) interpreting the data. However, I did deviate from stage four due to using a pre-existing framework matrix as mentioned above.

Once the initial coding was complete, I entered these data into the framework and determined the fit to the matrix. Any new data that did not fit the matrix were considered again to see whether a new thematic structure was needed to include such data.

Themes were defined as a pattern that captures a significant aspect of the data that related to the research purpose and in this case, the interview questions.[519] Deductive coding was used as some codes were pre-defined in line with the interview questions, however, inductive coding was used where appropriate to allow for unexpected perspectives. I coded the transcripts using the developed framework matrix and themes from the CRAMMS trial, these were then checked by the AP who led the interviews to ensure credibility and to also ensure that the coding was unbiased.

4.13 Results

4.13.1 Recruitment

Fifty-seven people with MS were either referred to this study by neurologists at Nottingham University Hospitals NHS Trust (NUH) or expressed interest in taking part (see Table 7). People with MS had the option of self-referring to this study as it was conducted remotely which allowed people from across the UK to take part. We advertised the study on Twitter and through the MS Society, both in their magazine and on their website as a blog post.

Table 7 Referral, expressions of interest and inclusion figures by recruitment method.

Recruitment method	Number of referrals/expressions of interest	Number of participants included in the study	Percentage of referrals/expressions of interest included
Nottingham University Hospitals NHS Trust referrals	14	10	71.4%
Patient and Public Involvement Group	7	6	85.7%
Self-referrals (e.g., advertisements on twitter or MS Society website/magazine)	36	20	55.6%
Total	57	36	63.2%

Most participants in this study came through the self-referral route. The Patient and Public Involvement (PPI) Group had the highest conversion rate, meaning that this group had the most expressions of interest that converted into participants. Referrals from neurologists at NUH were the second largest group for this study.

4.13.2 Description of sample

Thirty-six people with MS were recruited between August 2022 and March 2023 to participate in a feasibility RCT to assess the feasibility and acceptability of conducting an online group-based cognitive rehabilitation.

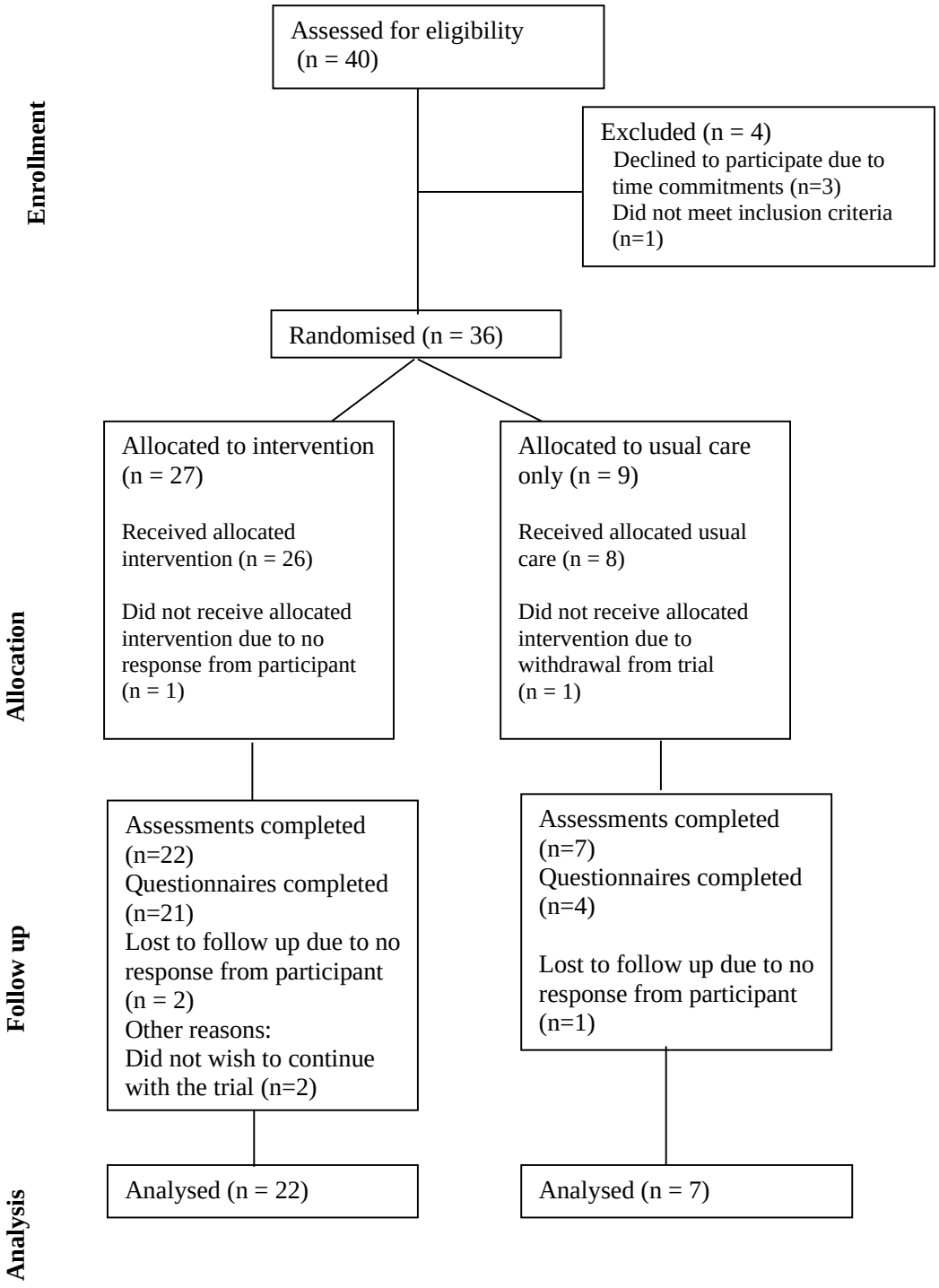


Figure 35 CONSORT diagram to show the flow of participants through the study.

The demographic and clinical characteristics of the sample are described in Table 8.

Table 8 Baseline characteristics.

Characteristic	**Cognitive rehabilitation (n=27)**	**Usual care (n=8)**
Age (years)		
Mean (SD)	50.89 (9.13)	55.13 (9.16)
Minimum, maximum	35, 69	40, 67
Gender, *n* (%)		
Men	5 (18.5)	4 (50)
Women	21 (77.8)	4 (50)
Non-binary	1 (3.7)	
Ethnicity, *n* (%)		
White	26 (96.3)	7 (87.5)
Mixed	1 (3.7)	1 (12.5)
Marital status, *n* (%)		
Single/divorced/widowed	8 (29.6)	1 (12.5)
Married/with partner	19 (70.4)	7 (87.5)
Living arrangements, n (%)		
Living with others	22 (81.5)	7 (87.5)
Living alone	5 (18.5)	1 (12.5)
Years of education		
Mean (SD)	15.08 (2.43)	16.13 (3.36)
Minimum, maximum	12, 18	12, 22
Employment status, *n* (%)		
Not employed	9 (33.3)	3 (37.5)
Retired	6 (22.2)	2 (25)
Employed full-time	5 (18.5)	1 (12.5)
Employed part-time	7 (25.9)	2 (12.5)
Time since diagnosis		
Mean (SD)	13.07 (7.71)	14.38 (9.94)
Minimum, maximum	1, 29	3, 32
Type of MS, *n* (%)		
Relapsing-remitting	19 (70.4)	4 (50)
Secondary-progressive	7 (25.9)	3 (37.5)
Primary-progressive	1 (3.7)	1 (12.5)
No. of relapses in six months previous, assessed at screening, *n* (%)		
0	22 (81.5)	7 (87.5)
1	2 (7.4)	0 (0)
2	2 (7.4)	0 (0)
Not known	1 (3.7)	1 (12.5)

The intervention group and the usual care group were comparable for most of the descriptive and clinical characteristics. The usual care group had a higher average age, a slightly higher number of years of education and years since diagnosis. The sample is skewed towards women, although this is considered representative of the MS

population as MS is three times more common in women compared to men, it is still important to consider this when drawing conclusions.

4.13.2 Feasibility outcomes

4.13.2.1 Return of outcome measures

Error! Reference source not found. demonstrates outcome measure return as well as the number of withdrawals and dropouts from the study. The cognitive rehabilitation group had a higher completion rate of all outcome measures overall, with two members of the control group not completing the follow-up questionnaires.

4.13.2.2 Cognitive rehabilitation session attendance

The mean number of sessions attended by participants is presented in see Table 9.

Table 9 Summary of attendance at cognitive rehabilitation sessions.

Sessions attended	**(*n* = 27)**
Mean	8.04
Median	8.5
Number of sessions attended, *n* (%)	
0-4	3 (11%)
5-7	9 (33%)
8-10	15 (56%)

The reasons that participants did not attend cognitive rehabilitation sessions is shown in Table 10. Two participants withdrew from the trial once it had begun and missed a total of 17 sessions. The most common reasons for missing a session were either a holiday (22%) or a hospital appointment (22%). One participant attended the first session and then was unable to attend the next several sessions due to family circumstances. This participant requested to move to another group at a more convenient time but did not attend any further sessions despite several attempts to contact them.

Table 10 Reasons cognitive rehabilitation sessions were missed.

Reason scheduled session missed	**Total number of sessions**	**Total number of participants**
Withdrawal from trial at intervention stage	17	2
Unable to contact	9	1
Forgot to attend	3	3
Unwell	8	4
Hospital appointment	6	6
Holiday	10	6

Work commitment	5	4
Family commitment	4	3
Undisclosed	2	1

All participants were given access to the recordings of the session to ensure they could catch up in their own time. Participants were also sent a summary sheet each week which summarised the contents of the discussions that took place during each session (see Appendix N).

4.13.2.3 Attrition

After all participants had been randomly allocated, one participant withdrew from the study due to a family bereavement. Another participant in the intervention group was considered to have dropped out after I was unable to contact them to organise the timing of the cognitive intervention sessions.

After the intervention started, one participant withdrew from the study as they missed the first two intervention sessions due to other health related appointments. This participant expressed concern that they would not be able to properly catch up and dedicate the appropriate time to the study as they had upcoming appointments with their mental health team which overlapped with the cognitive rehabilitation sessions that they have been booked in for. These appointments were booked in after I asked all participants allocated to the intervention group what their availability would be for the cognitive rehabilitation sessions. This participant was offered the opportunity to move to a different group, but they felt that they were already too far behind, and it would cause them too much stress.

Another participant decided to withdraw after receiving four cognitive rehabilitation sessions. The reasons they gave were that they felt that their diagnosis of secondary progressive MS separated them from the group as they expressed that their main concern was linked to mobility issues.

After the intervention period, three participants were lost to 3-months follow-up after we were unable to contact them to complete the outcome measures. This attrition rate was in line with the attrition rate from the CRAMMS trial.

4.13.3 Baseline characteristics

All baseline scores had normal distributions, therefore we used parametric statistics. Descriptive statistics of neuropsychological tests are reported below in Table 11 and Table 12.

Table 11 Scores on baseline neuropsychological tests prior to randomisation.

Assessment	Cognitive rehabilitation group, (n=27)		Usual care group, (n=9)	
	Mean (SD)	Range	Mean (SD)	Range
BRBN				
Selective Reminding				
Total recall	41.26 (8.02)	28, 60	43.38 (6.86)	32, 52
Long-term storage	31.81 (13.17)	10, 61	36.63 (13.09)	8, 50
Consistent long-term retrieval	19.74 (12.86)	2, 59	21.5 (10.41)	4, 40
Delayed recall	5.77 (2.14)	2, 12	7.25 (1.58)	6, 10
10/36 Spatial Recall				
Total correct	18.78 (5.28)	8, 30	21.63 (4.69)	16, 28
Delayed recall	6.04 (2.33)	1, 10	7.63 (2.39)	4, 10
Symbol Digit Modalities	44.48 (8.60)	21, 61	49.50 (14.36)	26, 65

Notes. BRBN, Brief Repeatable Battery of Neuropsychological Tests. Selective Reminding Test, Total recall: minimum 0, maximum 72; long-term storage: minimum 0, maximum 72' consistent long-term retrieval: minimum 0, maximum 72; and delayed recall: minimum 0, maximum 12. 10/36 Spatial Test, total correct: minimum 0, maximum 30; delayed recall: minimum 0, maximum 10. Symbol Digit Modalities Test: minimum 0, maximum 110.

Small differences were noted between randomly allocated groups, as anticipated.

Table 12 Scores on baseline cognitive questionnaires prior to randomisation.

Questionnaire	Cognitive rehabilitation group, (n=27)		Usual care group, (n=7)	
	Mean (SD)	Range	Mean (SD)	Range
MSIS-Phys	47.52 (13.22)	22, 72	60.75 (16.48)	46, 76
MSIS-Psy	21.74 (6.47)	13, 36	22.75 (5.06)	17, 27
EMQ	35.04 (21.72)	6, 75	22 (16.55)	6, 43
EMQ (Importance scores)	83.74 (11.65)	60, 103	80.75 (11.15)	69, 93
EQ-5D	60.77 (15.95)	30, 90	48.75 (24.62)	25, 70
Mobility	2.89 (1.25)	1, 5	3.75 (1.50)	2, 5
Selfcare	2 (1.13)	1, 5	2.25 (1.26)	1, 4

	Usual activities	2.77 (1.14)	1, 5	3.00 (1.41)	2, 5
	Pain/Discomfort	2.85 (.97)	1, 4	2.75 (1.26)	1, 4
	Anxiety/Depression	2.31 (1.26)	1, 5	2.25 (.96)	1, 3
FSS		27.29 (8.06)	9, 35	28.75 (6.50)	20, 35

Notes. MSIS-Phys, Multiple Sclerosis Impact Scale-Physical subscale; MSIS-Psy, Multiple Sclerosis Impact Scale-Psychological subscale; EMQ, Everyday Memory Questionnaire; FSS, Fatigue Severity Scale. MSIS-Phys: scores range from 20 to 80, higher scores indicate greater physical impact of MS on everyday life; MSIS-Psy: scores range from 9 to 36, higher scores indicate greater psychological impact of MS on everyday life; EMQ: scores range from 0 to 112, higher scores indicate more frequent memory problems; EQ-5D: scores range from 0 (worst health a participant can imagine) to 100 (best health a participant can imagine); EQ-5D subscales (mobility, selfcare, usual activities, pain/discomfort, anxiety/depression): scores range from 1 to 5, with a higher score indicating a greater impact of MS; FSS: scores range from 5 to 35, with higher scores indicating greater impact of fatigue.

Both the intervention and usual care groups were comparable across baseline questionnaires scores.

4.13.4 Quantitative outcomes

We found significant differences between the intervention group and the usual care group (Table 13). There was a significant difference between groups for the SRT, favouring the cognitive rehabilitation group. We found a large effect size for the SRT for both the total recall and consistent long-term recall sub-scores indicating that the cognitive rehabilitation programme had a large effect on verbal learning and recall. We also found moderate effect sizes for the SDMT, the MSIS-psychological scale, the FSS, the EQ-5D VAS score and the mobility and pain scales. This indicates early trends that the intervention may lead to improvements in cognition, psychological wellbeing, fatigue and quality of life.

Table 13 Comparison of cognitive scores at 3-months post-randomisation between the cognitive rehabilitation group and the usual care group.

	Mean difference	**SE difference**	**t-value**	**df**	**p-value**	**Cohen's d**
SRT-TR	7.89	3.25	2.428	28	.01*	1.048
LTS	5.05	4.69	1.076	28	.14	.464
CLTR	11.5	5.34	2.154	28	.02*	.930
SRTD	1.19	.91	1.307	28	.10	.564
s10/36	-1.37	1.90	-.720	28	.23	-.311
S10/36d	-.32	.76	-.425	28	.33	-.183
SDMT	4.92	4.98	.988	28	.16	.426
MSIS-Phys	-14.23	8.33	-1.708	23	.05*	-.932
MSIS-Psy	-2.48	3.05	-.813	23	.21	-.443

EMQ	5.39	9.35	.575	23	.28	.314
EMQ (IS)	.11	6.97	.015	23	.49	.008
EQ-5D VAS score	8.63	10.70	.806	23	.21	.440
Mobility	-1.04	.78	-1.328	23	.09	-.724
Selfcare	-.30	.72	-.415	23	.34	-.227
Usual activities	-.43	.69	-.618	23	.27	-.337
Pain/discomfort	-.46	.57	-.816	23	.21	-.445
Anxiety/depression	-.20	.66	-.306	23	.38	-.167
FSS	-3.09	.412	-.834	23	.21	-.412

Note. *p<.05

We used our predictive algorithm to split the intervention group into 'most likely to benefit' and 'less likely to benefit'. Descriptive statistics for both groups are shown below in Table 14.

Table 14 Descriptives statistics for the 'most likely to benefit' group and 'less likely to benefit' as predicted by the predictive algorithm.

Characteristic	**Most likely to benefit (n=11)**	**Less likely to benefit (n=16)**
Age (years)		
Mean (SD)	42.86 (8.03)	53.19 (9.37)
Minimum, maximum	35, 49	40, 69
Gender, *n* (%)		
Men	2	3
Women	8	13
Non-binary	1	0
Ethnicity, *n* (%)		
White	10	16
Mixed	1	0
Marital status, *n* (%)		
Single/divorced/widowed	3	5
Married/with partner	8	11
Living arrangements, n (%)		
Living with others	11	11
Living alone	0	5
Years of education		
Mean (SD)	15.1 (2.56)	14.94 (2.54)
Minimum, maximum	12, 18	12, 18
Employment status, *n* (%)		
Not employed	1	3
Retired	2	6
Employed full-time	4	4
Employed part-time	4	3
Time since diagnosis		
Mean (SD)	10.55 (5.77)	13.93 (8.80)

Characteristic	Most likely to benefit (n=11)	Less likely to benefit (n=16)
Minimum, maximum	1, 20	1, 29
Type of MS, *n* (%)		
Relapsing-remitting	11	8
Secondary-progressive	0	7
Primary-progressive	0	1
No. of relapses in six months previous, assessed at screening, *n* (%)		
0	11	12
1		3
2		1
Not known		

We found preliminary signal of efficacy between people with MS who were predicted to be more likely to benefit compared to those predicted to be less likely to benefit on the SRT, EMQ and EQ-5D, favouring the most likely to benefit group (Table 15). A large effect size was found for all these tests. These results could indicate that the cognitive rehabilitation programme has a greater effect for those predicted to be most likely to benefit compared to those predicted to be less likely to benefit.

Table 15 Sub-group analysis of cognitive rehabilitation group comparing cognition scores at 3-months post-randomisation between participants predicted to be most likely to benefit and participants predicted to be less likely to benefit.

	Mean difference	SE difference	t-value	df	p-value	Cohen's d
SRT-TR	6.53	3.08	2.118	21	.02*	.891
LTS	8.53	4.69	1.820	21	.04*	.765
CLTR	7.93	5.50	1.443	21	.08	.607
SRTD	1.45	.93	1.570	21	.06	.660
s10/36	.62	1.86	.332	21	.37	.140
S10/36d	.90	.74	1.217	21	.12	.512
SDMT	5.58	4.49	1.242	21	.11	.522
MSIS-Phys	-7.49	6.54	-1.146	21	.27	-.501
MSIS-Psy	.15	2.52	.058	21	.48	.025
EMQ	17.41	6.61	2.633	19	.008*	1.151
EMQ (IS)	4.47	5.74	.779	19	.22	.340
EQ-5D VAS score	19.89	7.06	2.817	19	.01*	1.231
Mobility	-.79	.61	-1.297	19	.11	-.567

Selfcare	-.67	.57	-1.176	19	.13	-.514
Usual activities	-.33	.55	-.590	19	.28	-.258
Pain/discomfort	.22	.45	.486	19	.32	.212
Anxiety/depression	-.28	.55	-.509	19	.30	-.222
FSS	4.05	3.19	1.267	19	.11	.533

Note *p<.05

We also found moderate effect sizes for the s10/36, SDMT, MSIS, FSS which could indicate potential trends that those we predicted were most likely to benefit improved in visual memory, processing speed, and fatigue following cognitive rehabilitation compared to those we predicted to be less likely to benefit.

Table 16 Comparison of cognitive scores at 6-months post-randomisation between the cognitive rehabilitation group and the usual care group.

	Mean difference	**SE difference**	**t-value**	**df**	**p-value**	**Cohen's d**
SRT-TR	12.00	4.79	2.501	15	.014*	1.337
LTS	12.57	6.89	1.823	15	.047*	.974
CLTR	13.71	9.14	1.500	15	.080	.802
SRTD	2.00	1.06	1.894	15	.311	1.012
s10/36	.57	3.44	.166	15	.435	.089
S10/36d	.43	.85	.505	15	.311	.270
SDMT	4.57	6.56	.708	15	.246	.378
MSIS-Phys	-10.10	9.09	-1.111	20	.141	-.625
MSIS-Psy	-4.05	3.83	-1.056	20	.153	-.594
EMQ	-.83	12.06	-.069	20	.473	-.410
EQ-5D VAS score	18.60	12.43	1.496	20	.076	.884
Mobility	-.83	.87	-1.017	20	.162	-.572
Selfcare	-.18	.82	-.225	20	.412	-.127
Usual activities	-.33	.78	-.423	20	.339	-.238
Pain/discomfort	-.48	.64	-.761	20	.229	-.428
Anxiety/depression	-.25	.73	-.342	20	.368	-.192
FSS	-.71667	4.82	-.148	20	.442	-.084

Note *p<.05

At 6-months post randomisation, the significant differences between the cognitive rehabilitation group and the usual care group for the SRT are maintained (We also found moderate effect sizes for the s10/36, SDMT, MSIS, FSS which could indicate

potential trends that those we predicted were most likely to benefit improved in visual memory, processing speed, and fatigue following cognitive rehabilitation compared to those we predicted to be less likely to benefit.

Table 16). Furthermore, we also found large effect sizes for delayed SRT score and the EQ-5D VAS score, indicating that the group-based cognitive rehabilitation programme may have some effect on the quality of life of people with MS.

4.13.5 Qualitative outcomes

Feedback interviews were carried out with six participants from the intervention group, and their demographic characteristics are presented in Table 17 below. All participants consented to being recorded and to anonymised quotes being used in research papers. I aimed to get a sample of participants across multiple cognitive rehabilitation groups to ensure that we did not only interview participants from one group. I asked all participants if they were willing to be interviewed and then selected six participants across the groups from those that gave verbal consent. At the beginning of the interview, the AP carried out e-consent with the participants, completing the consent form with them.

Table 17 Demographic characteristics of participants in feedback interviews.

Participant	Age	Gender	Type of MS	Years since diagnosis	Ethnicity	No. of sessions attended
1	47	Woman	RRMS	1	Mixed	7
2	61	Woman	SPMS	9	White British	10
3	51	Man	RRMS	14	White British	10
4	40	Woman	RRMS	1	White British	9
5	45	Woman	RRMS	7	White British	9
6	58	Woman	RRMS	9	White British	8

Note. RRMS, Relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis.

Five themes were derived: (1) management of cognition before the trial, (2) online format of the intervention, (3) perceived cognitive changes, (4) perceived mechanism of change of cognitive function, and (5) possible improvements to the intervention. I initially coded this data, using the framework matrix developed for the CRAMMS trial as a guide and made adaptations to align with the studies aims (Appendix O). Overall, a lot of the themes were similar which is encouraging as it suggests that delivering the group-based cognitive rehabilitation online did not negatively impact the overall effectiveness of the intervention.

The main difference is that we have included an additional theme for the online format of the intervention as one of the main aims of this RCT was to understand whether delivering the intervention online was feasible and acceptable for people with MS. Themes, sub-themes and sub-theme categories are summarised in (Table 18).

Table 18 Theme summary.

Theme	**Sub-theme**	**Sub-theme categories**
Management of cognition before trial	Cognitive difficulties	Memory
		Brain fog
		Concentration
		Invisible symptoms
	Advice received	None
		Information about MS on websites/booklets
		Information about this trial from consultant
	Self-generated strategy use	
Online format of intervention	Positive impact of online format	Effective and convenient
		Group dynamic
		Understanding the instructions given
	Negative impact of online format	Missed sessions
		Comprehension of tasks
Perceived cognitive changes	Improved	
	Impacted everyday life	Increased awareness of cognitive problems
		Increased confidence
Perceived mechanism of change of cognitive function	Increased strategy use	Effectiveness of strategies
	Psychoeducation	Acceptance of cognitive problems
		Theoretical understanding of cognition
		Inspired to learn more
	Effect of group format	Sharing experiences and ideas
		Being understood
		Social aspect
	Positive appraisal of psychologist skills	Knowledgeable
		Managed the group well

Theme	Sub-theme	Sub-theme categories
		Communication skills
	Workbook	Useful
		Not useful
Possible improvements	Update memory aids	
	Psychoeducation included throughout the intervention	
	Additional workbook content	

Themes are explored below with excepts from the transcripts, which highlight participants' experiences.

Theme: Management of cognition before trial

Sub-theme: Cognitive difficulties

Memory

One of the most commonly described cognitive difficulties participants described experiencing prior to starting in this trial was memory problems. This would often lead to the participants forgetting to attend events or forgetting vital information.

"I - I found at times I'd forget that I had meetings even though I had like my Teams calendar and stuff. So, I – I'd end up being late to some of those meetings." (ID 02)

"My ability to remember instructions and appointments is very, very unreliable now. You know, you couldn't say I'll see you in the pub Thursday night because unless it's written down, unless I use a prompt or whatever, I wouldn't be there." (ID 09)

These accounts underscore the profound impact of memory impairments on daily functioning and the need for effective cognitive rehabilitation interventions.

Brain fog

Some participants also mentioned the concept of brain fog. So, rather than noticing they were forgetting a lot of information, the participants explained that they often felt like they were not as cognitively sharp as they used to be, or it took them longer to process information or they felt a bit fuzzy.

"I think last year I had a bit of a relapse; I think. I think and one of the things that came out of it is I just don't feel as sharp as I did if that makes sense." (ID 18)

"Well, generally speaking, um I've noticed they've sort of slowing up and deterioration in the speed at which I can work. And the speed at which I can understand things, and certainly my ability to remember things, places, names, experiences, detailed stuff." (ID 09)

Concentration

Some participants felt that they now struggled to concentrate either on one task or many tasks at once.

"And also multitasking, which is something that I did used to do a lot of in my work and now I have to concentrate on the one thing in hand and have a simple set of instructions to follow." (ID 04)

One participant expressed that their main concern was with receiving emails for work, especially if these were quite long and detailed:

"I think it's just my, my brain just goes - I think it just - everything just goes fuzzy, and I just can't concentrate on - on stuff like that." (ID 19)

Invisible symptoms

Some participants mentioned specifically struggling with invisible symptoms both with the symptoms themselves such as cognitive processing but also with people who may not understand their symptoms because they are invisible:

"And I looked, you know, that awful phrase that everyone always comes up with, the way you look so well, you know, you – you look normal. I am normal, but I like to think I am and but um, you're struggling, because of the invisible symptoms." (ID 04)

Sub-theme: Advice received

None

The majority of participants had not received any advice about managing their cognitive difficulties from their clinical teams:

"I don't think so." (ID 04)

"No. No." (ID 19)

"But no, no, not from the MS nurse or - or neurologist or anything though." (ID 27)

Some participants mentioned that they felt when they brought up their cognitive difficulties it was dismissed or brushed off as a normal part of the ageing process:

"No, no it's and it, it's still something that that isn't really acknowledged by the – the team really, it's kind of dismissed but kind of kind of like well you know you're on treatment now and - and you know, you should see improvements and there's been no seriousness taken to it really. And yet I know that that it's affected my quality of life and my ability to do things that are pleasurable to me." (ID 02)

"No, not really. I've mentioned it a few times to my neurologist. Um, sometimes to my MS nurse. Umm. And it was very broad brush, sort of advice and kind of. It was never put in this way, but I came away with thinking I'm just getting old." (ID 09)

Participants also felt that other symptoms were the focus of the appointment and because they are short appointments and you only get one a year, cognitive difficulties were not prioritised:

"Because you only see the consultant face to face once a year, and obviously you've only got that tight time slot. And he's obviously doing a lot of tests in that time slot. So, like walking and like whacking you on the knee with stuff. So yeah, he's doing all that. And then he just says, have you noticed any changes? So, when I said yes about what I just told you, yeah, he said, ohh, yeah, there's some studies coming up. And that was kind of it really. And it's like, yeah, it's, I think it's quite a lot for him to sort of time slot." (ID 18)

Information about MS on websites/booklets

A few participants mentioned that while they had not received any advice from their clinical team, they could recall reading something about memory on the MS Society website:

"No, no, I mean I think I may have read something on the - the MS Society, but I probably read it, didn't take it and forgot it." (ID 27)

Information about this trial from their consultant

A few participants stated that when they expressed concerns of their cognitive difficulties to their consultant, they advised that there were some studies that may be helpful (including this feasibility RCT):

"So, when I said yes about what I just told you, yeah, he said, ohh, yeah, there's some studies coming up. And that was kind of it really." (ID 18)

"The support that [the consultant] gave me was like, ohh, I'm gonna speak to somebody and see what we can do for you…So he was quite, you know, like, um, supportive in their way, straight away to something. Right. Let's see what I can do for you. And then from there the study came." (ID 19)

Sub-theme: Self-generated strategy use

When asked about any strategies that they were using before starting the trial, a few participants mentioned using external aids such as calendars and diaries.

"But yeah, like my friends take the mick, I've got like a paper-based diary on my desk. I always have done, and they take the mick and ohh God, if she's not got it in that [redacted] diary, it's not gonna happen. And I've got literally everything in there." (ID 18)

"I'm very heavily reliant on Outlook and my to do lists on my phone and in my emails." (ID 09)

Theme: Online format of intervention

Sub-theme: Positive impact of online format

Effective and convenient

The majority of participants found the online format and delivery of the intervention to be very effective and convenient.

Some participants expressed that they found participating online to be very convenient for them as it took less time out of their day due to not having to travel:

"I'm quite biased because I work online anyway, think if it was, say, for me, it was easy because, and I think for some of the other [participants] it was easy too, because you just log on like now at like 2 minutes to 10 and you log off, you're done, aren't you? You can be in your kitchen making a cup of tea."

"Fabulous. If it - if it was for me to go anyway because I work from home which to me it's just like a godsend." (ID 19)

"And all through COVID we did. We took to zoom for our committee meetings, for our, uh, social gatherings and everything. So, you know, I - I'm totally comfortable with it." (ID 27)

A few participants also expressed that if it was not online, they did not feel that they could have participated:

"And it's not taken up a lot of your day, where I think realistically going into the hospital for 10 weeks would be a bit much. And I don't think my boss would have gone for that either." (ID 18)

"But at the same time, if I was asked to go to a meeting, even if it was 5 miles down the road in [redacted], my first initial thought is - will I be tired by the time I get there? And then I've got to get through the meeting. Whereas if you asked me to join the meeting at 3:00, click in. I've literally pulled over at the side of the road. I'm sitting in a very nice place, so those [online] meetings are nowhere near as exhausting." (ID 09)

"I know I'm home. I don't need to be commuting. So, it's fine. And it works for me. Um. So, if these things had to happen outside, I don't think I would have been able to participate. So, I think this, this is fab. Yeah. It's really good." (ID 19)

Some participants expressed that they felt the online format enabled them and others to feel more comfortable during the sessions due to being in their home environment:

"I think it would have impacted not just myself I think it would have impacted everybody else. I think everybody feels a little bit more relaxed online than being in an [unfamiliar] environment where you're in person. I think when you're in person you feel a bit more withdrawn to - to start a conversation or I don't know that maybe that's just me now." (ID 19)

"[…] I could put more energy into it, into the meeting. Yeah, I found some of the sessions. I couldn't tell you which ones were sort of part way through. They were quite tiring. I thought the end of it I - I think I would have a lie down. Which if it had been a face to face, I wouldn't have been able to. Yeah, it was good. That was nice." (ID 09)

"It fitted in really easy. Everyone was lovely. It was. You can, like you say, you could sit and eat and drink and have like a lot of the time. I had my breakfast while she was doing it and [intervention provider] was really friendly as well." (ID 18)

One participant expressed that offering the intervention online may encourage people who are typically more introverted to be encouraged to try new other online meetings which could lead to improvements in quality of life:

"But it but it really did bring [name] out of their shell, you know. I think [name] felt supported by it and everything. So I think, I think it might encourage people who are not necessarily technically savvy and not normally into that sort of thing because you're asking direct questions and they've done their homework and they're - they're feeling an improvement that they may even then do more online and maybe even start meeting people with MS and - and maybe even join the MS societies local groups and do stuff you know…You know, because if you start using your brain more and you start being social, yeah, it may even prove to [have an] even wider impact than just memory." (ID 27)

Some participants expressed that the online format of the intervention meant that it was easier to catch up on missed sessions due to each session being video recorded:

"Yeah, [intervention provider] would. She would send it to us with - with everything on it and all the information and the recording and everything that we that we spoke about. So yeah, everything was easy to find, and you could - you could use it. So that was fine because it felt like as if I didn't miss anything." (ID 19)

"She [intervention provider?] actually sent me the, the full thing [video recording]. So, I watched the whole thing." (ID 27)

Group dynamics

Participants spoke positively about the group dynamics and expressed that they got on well with other members of the group and felt they were able to share their experiences even though they were not face-to-face:

"I have to say, and the cameras, and we very much did engage it was quite a - well, I wouldn't say chatty but well, you know what I mean. We did engage with each other, especially as the course progressed." (ID 04)

"I felt um engaged with it. I felt I could join in. I didn't feel sort of out on a limb." (ID 09)

"You say, oh my God, yeah, that's happened to me. And that was really nice, I think. And then obviously by the end of the sessions, like group - I think it was session 10, everyone - like it's - it's just like talking to friends really." (ID 18)

"…it was a lovely group and I think we were very supportive of each other, and we got on well and - and I personally I like the group situation, I like people, I like talking I'm happy online." (ID 27)

Participants also expressed that they were able to get their point across and were all given equal opportunities to speak:

"I thought [intervention provider] was very good at making sure that everybody was equally heard, and she was very good at steering the group to make sure that nobody went - nobody had too much dominance in the group, and nobody went too far off. And when we did, and we when we all collectively inevitably did, she was very good at sort of drawing us gently back onto topic." (ID 09)

"The group members were so nice. They were really, really nice so and - and [intervention provider] she was - she was fab as well. I mean the way she - she engaged with everybody she - she kept everybody in in engaged in the conversations you know what I mean? […] she was really good. […] and the group participated well. So, it was really nice. Yeah." (ID 19)

One participant expressed that they thought the online format allowed people to connect with each other that may not necessarily get the chance otherwise:

"And also, it connects people, you know, I mean. Particularly if it got rolled out nationally. I mean, yeah, I think it's nice." (ID 27)

However, one participant expressed that they felt the group was mixed in terms of cognitive ability, in that some participants had higher levels of education than others which led to some negative feelings about the group dynamic:

"We - we had a very, very mixed group." (ID 27)

"So, say like most of us are here [gestures at her shoulder with flat hand to indicate level] and then we drop and then [they, they've] dropped to way above what we

maybe started from [gestures to above her head to indicate level]. So, it was a little bit, sort of intimida-, I don't mean they're [another participant] intimidating but [they] didn't mean to be." (ID 27)

Understanding the instructions given

The majority of participants felt that the instructions given throughout the sessions were easy to understand:

"I didn't have any problem at all with the explanation of what was required and – and the group tasks. We were very clearly spoken through them, yes." (ID 04)

"I think so, yeah. Yeah. Yeah, I don't think I can remember any incident where I didn't understand what it was, I was supposed to be doing." (ID 09)

Sub theme: Negative impact of online format

Two of the participants also expressed some negative feelings about the online format of the intervention, with some frustration around technology sometimes not working for them:

"I think the - the only thing that it impacted me negatively and I don't know whether others have experienced this - is it is just so frustrating when my links don't work. And it is such an effective way, I – I do believe, of doing all these things now through teams and zoom calls and whatever, but when your technology is just playing up, it's even more frustrating than worrying." (ID 04)

"I wasn't keen on it being online if I'm honest." (ID 02)

One participant expressed that they would have preferred it to be face-to-face, but they could see the value of it being online for those that would potentially struggle to access the intervention otherwise:

"I think I'm a person that that learns by getting up and about and - and doing things and moving around. So, I didn't necessarily kind of value that, but I could see that there's a lot of benefit because some of the other participants that were on the - the course – they wouldn't have been able to attend and physically I don't imagine and - and we're in different geographical areas as well so. I think I appreciate that, but I think I could have got more value out of it from being a face to face." (ID 02)

Missed sessions

A few participants expressed that they felt as though they missed out on key learning if they missed a session due to not being able to actively participate in the discussions:

"Yeah, it just if you hadn't attended the session, it felt like you - you kind of missed out on key learning." (ID 02)

"But yeah, no, I think that was, making sure that I made it every week was - was quite important to me because I feared that I wouldn't catch up in the rest of the week. Because life is, wee bit too busy for me at the moment." (ID 09)

Comprehension of tasks

One participant expressed they sometimes struggled to comprehend the tasks they were asked to do, particularly in reference to the take home activities and would have benefitted from the instructions from being shared on the screen:

I: And what's the information then, for like the instructions of activities? Was that shared on the screen to you or is it all, was it verbal?

P: No, I think it was verbal, I think, yeah. Yeah, I think it was verbal. So actually yes, that having the - a visual there of a slide might - might have been - been helpful." (ID 02)

Theme: Perceived cognitive changes

Sub-theme: Improved

The majority of participants felt that they had improved in their cognitive abilities since they started the intervention:

"I don't feel entirely hopeless and - and despondent […] the internal dialogue has changed from I can't do this there's no point in doing this to let's see what tools I've got that I can - I can try and see if it makes a difference if that makes sense." (ID 02)

"I've certainly got a lot out of it. So yeah." (ID 09)

"This has helped me improve and I have learned a lot with it." (ID 19)

"But I - I can now picture and remember names of faces and I know how to keep them in there. But that's, that's absolute vast improvement, you know." (ID 27)

Sub-theme: Impacted everyday life

Increased awareness of cognitive problems

Many participants, both during the sessions and during the interviews felt that they now had an increased awareness of their cognitive problems, both in terms of what they were experiencing but also in terms of how their behaviour or symptoms such as fatigue was impacting their cognitive problems:

"I realised how little attention I was paying. I'd given up I just stopped paying attention. I was just like I can't do this I – I [had] just given up." (ID 27)

"And I got to the point that I thought actually I'm - I'm not losing it and I'm not thick. I think it's just um, think it's sometimes how you feel. If I'm feeling tired, uh - uh yeah. So, it - it put me a bit more ease." (ID 19)

"I think part of it is that I'm gonna have good days and bad days that there is internal cognitive tools [to help] and - and also the external ones." (ID 02)

Increased confidence

When participants were asked by the AP whether they felt more confident now in manging their cognitive difficulties, the majority agreed that they did feel more confident:

"I'd like to think so, yeah. Yeah, I do. I do. I do think." (ID 09)

"Yeah, yeah, yeah, yeah, totally, totally." (ID 19)

"Absolutely. Yeah, definitely." (ID 27)

One participant expressed that they felt confident that they could look back on the work booklet and remind themselves about the strategies:

"…if I you know I want to view the contents again [for] learning strategies to improve attention, well, I would certainly go back to that thing and then that would remind me and that would trigger my, my brain." (ID 04)

Participants also expressed that they felt more positive now:

"And I've come away like I say, maybe like a bit more positive, like what's that called placebo effect where you. I've done my course. I should be better now. Like it. Yeah. So hopefully that might help me with my exam that I'm doing."

Theme: Perceived mechanism of change

Sub-theme: Increased strategy use

All participants in the intervention group reported that they were using significantly more internal strategies because of participating in the cognitive rehabilitation programme and that they were applying tips learned in the sessions to use their external aids more effectively.

Effectiveness of strategies

Many participants reported being surprised at how effective the internal memory aids were for them:

"I've certainly taken some of the techniques away from it that I was surprised were so effective. The things like grouping the things like making up a little story to remember things, categorising - kind of knew about them already. But I hadn't realised how powerful they were and why they worked so well. So yes, I've most definitely taken a lot, but those are my key learning points from it." (ID 09)

Many participants spoke about which strategies were most effective for them:

"... there's several tools that, that - that I use. I think one of the ones that that really stick out is kind of the 5W's and - and the H, when - when you're getting a lot of information." (ID 02)

"P (ID 04): There are one or two exercises I can remember and stick out, and things like and - and actually things that I was already doing and now, that's embellished a bit more. So, things like what? I think it's called clunking or chunking?

I: Chunking?

P: Yes! Now that's one that's certainly has stayed with me."

"There was the grouping together of things so like if you've got like 20, I don't know. Different names and numbers and bits. Group them together into categories. Yeah, that's definitely helped work as well." (ID 18)

Some participants felt that all the strategies were important as they were all effective in different situations:

"You know what? I think they're all important They're all important really, because I think uh, in my day-to-day I think I use all of them in in a certain way. So, I think to - to me everything that we learnt is important to me and I'll use them nearly all the time because even when I use them at work, I'm like, ohh yeah, this is something that you spoke about. So, I think all of them were - are important to me." (ID 19)

Some participants also spoke about the strategies they did not feel were most effective for them or that they wouldn't use every day:

"And of course, there was the story one where we had to make up a story and then - so we could remember things. Would I use that in everyday? I'm not sure I would." (ID 04)

Sub-theme: Psychoeducation

Acceptance of cognitive problems

Acceptance was a recurring theme among participants. Many participants expressed that prior to the programme they felt like they were going 'crazy' or that they were 'a bit thick' or just 'stupid'. But since the programme some participants expressed that they felt they had accepted themselves because they feel more at ease with who they are and how their MS is affecting their cognition:

"Like I say after – after all this, even people that don't have MS probably the feel the same as we do. So, it's – it's like I say we're not on our own. So, it's not just me. We are, you know, I felt a little bit more um, at ease and not so under pressure and not so you know upsetting myself so much like thinking that I'm um, you know really losing it. You know what I mean? So, I think it's just yeah, I felt a bit better I felt more relieved and a bit more confident in myself that that OK. It's not just me and it's I'm – I'm all right. Yeah." (ID 19)

*"Yeah, when you're struggling because you can go well, you know this. This isn't you being crap, or s*it or - or thick. The MS has done this to your brain." (ID 02)*

Theoretical understanding of cognition

Many participants stated that they really enjoyed learning about the science and the theories behind cognition and how the different processes work as well as how MS is affecting their cognition:

"The more I understand about an issue and the problem I'm having, once I've recognised it, once someone said, yeah, that's - that's the issue that you've got. The more I understand it, the more it relaxes me, calms me down. I realise it's not that major deal and the more interested I get into it." (ID 09)

"I like all of that and I said because my job and stuff I do like the - like the theory behind things. So, to me that was I like that bit of it. And I thought that's actually really interesting, and it makes sense." (ID 18)

"How the layers work, that you have to try and get things in deeper for them. Just like, yeah, to remember that. I found that really interesting and I thought I didn't expect her [intervention provider] to go into that level of, but that was quite - I thought that was really interesting when she did that. Ohh, so the talking about like shallow and deep processing and then bringing in the kind of the biology and the aspects of cognition and how it - how it functions. And from that was that useful to then incorporate why the strategies worked." (ID 18)

Inspired to learn more

Some participants expressed that after the sessions or after the programme they had done further reading into the topics discussed in the sessions:

"… it's been a very worthwhile exercise. I found it fascinating. I've started doing some reading around the whole science and memory and all that and that. So that's been brilliant. [intervention provider]'s obvious enthusiasm in the subject. It kind of enthused me to go off and read a wee bit more into it. And it's - it's a fascinating subject. I can see why people like [intervention provider] want to get PhD's out of it now." (ID 09)

Sub-theme: Effect of group format

Sharing of experiences and ideas

All participants reported that they found the group format of the cognitive rehabilitation programme to be incredibly beneficial to them. Participants expressed

that being able to share their experiences with other people with MS who could not only empathise with them but could also understand and relate to their experiences was very comforting. Participants shared that they felt relieved that there were others who were experiencing the same difficulties as them, and everyone was happy to share their experiences because they knew they would be understood.

Participants really valued being able to share their experiences with the group and to hear the experiences from other people that were very similar to their own. As well as sharing experiences, participants also shared advice with each other and tips to help with cognition problems and with other aspects of MS:

"[I felt] Quite reassured that I wasn't alone. Loads of little stories that other people in the group about this and the other like Blimey I'm thought I thought I was the only person who did that, or you know other people had come up with coping strategies. Independent to this from a long time ago though, so yeah, I've kind of done that as well, which was reassuring to know that." (ID 09)

"Things that I learned with it was, you know, the tips and stuff from - from everybody because it was quite interesting how people deal with different things in different ways. It was quite interesting steps that people use, you know, little tricks." (ID 19)

"It was like they shared what worked for them and that's what I tried to get from that other group, but it wasn't that. But this group was, it was somebody sharing like - I'm really into like Alexa and I'd be saying about Alexa, and someone didn't like Alexa and you know you can switch that feature off etc. Ohh, I didn't know that. So, they [another participant] had gone away and got an Alexa. So, it was quite nice to sort of like swap and change different bits that we all use." (ID 18)

Being understood

A common theme through the intervention sessions was that participants felt very understood by other members of the group:

"Hearing the stories of three or four other people that you don't know from Adam. You know, and - and actually they've - they've got similar things. It is quite reassuring. And you know, I - I think, oh my God, I just thought it was me that was doing that and - and oh God, that really is a thing. So, I think that there's some power in in in the conversation of the group with - with that." (ID 02)

"Like the group overall was like really good to know it's not just you that's going sort of like crazy on your own. And it was really good. Everyone's on the same wavelength so they all kind of get it." (ID 18)

Social aspect

Participants enjoyed the opportunity the group provided to connect with people who had similar experiences as them:

"I think it was good to have the consistency of the same team, group members attending the group and it was good that it was always [intervention provider] because we kind of built up a rapport with - with [intervention provider]." (ID 02)

"Um, I think we got to know each other. So, we were quite open about, yes, about, you know, the deficits that we were coming across and - and whatever. So yes, we were quite open, I felt, with each other." (ID 04)

One participant talked about how they are still in touch with members of their group and spoke about a time recently when another participant in that group shared their success story of using one of the strategies they learned in the programme and then every member of the group shared theirs also:

"We still maintain contact. And then they were giving they was speaking about stuff and tips that they learned, and they was telling us that they used it, and it was like, that's really good news. You know what I mean? That you - you managed to use that and - and it helped you. So yeah, we still maintain contact, which is really good." (ID 19)

Another participant mentioned that they did not expect the group to be as positive as it was due to previous experiences in other groups:

"Everyone was really nice. So, I - I wasn't probably expecting that. And yeah, positive. Sort of like it was really positive. I wasn't really. I thought, oh God, there's bound to be one that brings the whole group down. But there wasn't." (ID 18)

This same participant was also surprised that the group got on so well:

"So yeah, I don't know what you did to actually get people grouped, but it was everyone like got on." (ID 18)

Sub-theme: Positive appraisal of psychologist's skills

Participants commented on the skill with which the psychologist delivered the intervention and the support they received throughout.

Knowledgeable

Participants expressed that they felt the psychologist was very knowledge able the topics they were discussing during the intervention:

"She clearly knows an awful lot about her subject matter. Because she can get across really complex issues but at the same time make them sound simple and understandable for the likes of me, anyway. So, I was - I was very impressed with that." (ID 09)

"She was, um, very good at explaining things. So, she just made it so easy to be there. Um, you wouldn't even feel like it was an hour in. And I think now in 15 minutes or hour and a half or whatever it was, you wouldn't even think that she would be there for so long. It she - she was really good. She really helpful. Really. She made you understand what was going on." (ID 19)

"But no, I felt very supported by [intervention provider], and I really did think she was excellent and perfectly trained for this and you know she very, very skilled." (ID 27)

Managed the group well

Many participants commented on how the psychologist managed the group throughout the intervention, often noting that they were able to keep the group on track with topics:

"I've chaired in the past. I used to chair technical working groups in this and the other. but I struggle with them. They are hard work. I know they are hard work, but she made it look easy. I'm sure she was exhausted after every session, but she did make them look really easy." (ID 09)

"And [intervention provider] was very good at that because we'd all go up, back up like go off track and we'd all be talking about dogs or something. And she's very good at then drawing you back on and going, come on ladies, we've got to got to do this." (ID 18)

"I just think she - she handled everyone perfectly yet say like being one of the lads. Probably rambled on a little bit too much, but she allowed it within reason. The beginning occasionally got off topic, but she - she brought - brought us back without make us feel stupid." (ID 27)

Communication skills

Some participants commented on the psychologist's ability to remain professional throughout the intervention whilst also being friendly and ensuring everyone was comfortable:

"I know she was lovely, like, you cannot fault her like at all, super friendly. And it was, it was fun in that way that it wasn't too formal. But no, she did it really well and it was really sort of really - she was really professional, but she was really friendly at the same time." (ID 18)

"To be quite honest, I think [intervention provider] was - was on it the whole time. She was always supportive, even if it wasn't on the session, out the session, she was always there. She would always respond straight away to your e-mail. So, she was really, really good. She was very easy to um; I think she made the group at ease." (ID 19)

"I do think that she was very good [intervention provider], she was, she was brilliant in the way in which she presented, and she spoke very clearly actually and clarified what was required." (ID 04)

Sub-theme: Workbook

Participants gave feedback on many elements of the intervention, including the work booklet. This work booklet was used throughout the intervention, allowing the participants to complete tasks both during the intervention and after. Participants were also free to keep their work booklets which means that they can be used to refresh their memories on everything learned during the intervention.

Useful

Participants seemed to have mixed feelings about the workbook, some thought it was very useful for following along during the sessions, for referring to after sessions and useful as a reminder on some of the strategies in the future:

"The book is really, really nice in the way it's - it's, you know, broken up in - in phases or stages or do you know what I mean? Chapters, you want to put it that way. And it's just like, like I say, it's not like an e-mail, it's like not like an essay written. There were no, it's something that you can just look, comprehend and that's what you need to do. I think it was really good, really straightforward." (ID 19)

"And like you said, it's easy to go back and just actually it's nice to have them sort of like all in place, isn't it, That you can just, yeah. In the future, go back and refer to." (ID 18)

"I'll definitely want to sort of read it. I don't know, every six months or every year just to again to remind myself about why and how." (ID 27)

One participant commented that they felt the work booklet would be useful to trigger memories of the strategies if they could not quite remember how to use a specific one:

"I think it triggers it would - it would act as a trigger having the workbook." (ID 04)

One participant commented that they were concerned when the work booklet arrived in the post because it was so big, but they were pleasantly surprised at how fast they got through it:

"When it first arrived, I was a wee bit like, wow, that's a lot of material It did look a wee bit intimidating. But I guess by the second or third or maybe the 4th session, you could see how quickly you were getting through it. That kind of settled me a little bit more, but it did look enormous and uh, it was going to be a lot of very dry reading to us sort of thing. But it wasn't at all." (ID 09)

Not useful

A few participants felt that the work booklet was not as useful as they potentially hoped it would be. One participant commented on the work booklet and how they felt it was too simple and as such undermined the enormity of MS:

"Yeah, I - I just didn't really value the - the booklet itself. It felt a little bit simplistic in terms of its, its layout and I think that kind of umm, devalued. I think devalued [is] not the word, but like the - the enormity of these cognitive issues that we're all experiencing and then the – what - what's in in the book, it didn't necessarily kind of reflect that I think. Yeah, and I think that again it's - it's difficult because people have

got different levels of cognition and - and it - it needs to be in plain English. I think I just expected more from - from the booklet really to - to help us along." (ID 02)

Theme: Possible improvements

Participants were given the opportunity to recommend about improvements that they felt could make the intervention more effective.

Sub-theme: Update memory aids

Some participants commented that they felt the work booklet was a bit outdated in terms of references to certain external memory aids such as Dictaphones and Filofaxes and was missing newer technology such as Alexa:

"Only thing that I would criticise if I was going to criticise anything. The book is quite old, so it's got stuff like Dictaphones in it. We're like, yeah, maybe 10-15 years ago we did use Dictaphones and I can remember using those at work but now we don't. And there was no sort of mention of like and like - like iPhones or anything like that in there. There was no mention of like Alexa or the artificial intelligence that you use. There was no mention of just all those kinds of things. You could tell the book was probably like 10 years, so out of date, say. So, there was a few pages that I thought, well, actually you could do with getting rid of that page and just, yeah, getting rid of say, the Dictaphone bit and calling it maybe like a voice note or using the language that we use now." (ID 18)

"I mean I think the, I think we all said the - the book needs updating because it's not you know it's - it's got things like Dictaphones and Filofax and stuff like that and then sort of her calendar and mobile phone and sort of they're integrated and so you need to yeah it needs updating with to the to the - the modern world." (ID 27)

This booklet was published in 2018 and while that is only six years ago, some participants felt it needed updating. We have taken these comments on board and are now in the process of updating this booklet, this included adding comments to help with remote delivery such as suggesting that the inserts are scanned so they can be shared on screen during the groups.

Sub-theme: Psychoeducation included throughout the intervention

A few participants mentioned that they would have liked for the psychoeducation and the scientific theories to be included throughout the intervention rather than primarily focused at the beginning:

"[the science behind how MS affects cognition] It was covered in the first and second sessions, but I would have liked it to be more layered, interwoven." (ID 02)

Sub-theme: Additional work booklet content

Some participants gave some examples of improvements they felt could be made to the intervention of work booklet, often surrounding additional information that they would have liked to have received:

"I think it would have been helpful just to have more focus on kind of work-based skills and like they - they were quite lifestyle tools really for - for kind of living your life. But I think some of these - the tools weren't relevant to or applicable to the workplace in the in the way that I needed them to be." (ID 02)

Participants suggested that the intervention and manual would be more beneficial if they incorporated more work-based skills. This feedback highlights the practical needs of individuals with MS, who often face cognitive challenges in their professional lives. By integrating strategies and exercises tailored to work-related tasks, the intervention could become more relevant and effective in improving participants' daily functioning and job performance. This suggestion underscores the importance of aligning cognitive rehabilitation programs with the specific contexts in which participants experience difficulties.

One participant commented about how they would have liked some specific strategies focused on word finding as that was a main concern for them:

"If we - we talked very much about learning stuff new and then and then putting it in and - and then and then remembering to retrieve it. But if it's already in there, you know something I've learnt? Retrieving all that stuff, that's the only thing that I don't think we covered...But [intervention provider] did say if you start using your brain more and practising using it more, it may be just that, you know, that might come a bit better."

4.14 Discussion

The aim of this study was to assess the feasibility and acceptability of an online group-based cognitive rehabilitation. The study presented in this chapter has provided promising results to support the feasibility and acceptability of providing the group-based cognitive rehabilitation programme online.

We discuss our findings based on the study objectives and endpoints and guidance for progression criteria to definitive trials and consider the traffic light system recommended by Avery et al.[520] of green, amber, and red indicating go, amend, stop, respectively in determining whether this trial was feasible (see Appendix P). Based on this criterion we believe that this trial highlighted that online cognitive rehabilitation is feasible and largely acceptable to people with MS to reduce cognitive decline and improve overall quality of life and therefore a full trial is warranted to understand whether this is effective. The suggestions for improvements to the work booklet that participants made during the feedback interviews should be considered before a full trial is conducted.

The recruitment target was met. However, as it took longer than expected to recruit the required number of participants, I submitted a non-substantial amendment to the Health Research Authority (HRA) to extend the recruitment period to extend the recruitment period. Extending the recruitment period allowed the recruitment target of 36 to be met.

Initially we had planned for a recruitment period of six months but needed eight months to reach the target. This delay could have been due to the number of studies that were being recruited to at Nottingham University Hospitals NHS Trust. There were three additional cognitive research studies for MS patients open for recruitment during this study's recruitment period. This was positive for people with MS as it meant that not only did they have the opportunity to receive support with their cognitive difficulties, but they also had the opportunity to choose which study best suited them. However, it also meant that the recruitment process took longer.

During the study recruitment period, the Neuropsychological Evaluation and Rehabilitation in MS (NEuRoMS; www.neuroms.org) project was also being carried out at Nottingham University Hospitals NHS Trust. As part of this project, all MS patients were sent a letter containing a link to an online cognitive screening

assessment to complete prior to their clinic appointment. This screening assessment measures both the subjective and objective cognitive abilities of the patient as well as their fatigue and mood. This screening tool made identifying potential participants easier because all patients that were experiencing cognitive difficulties (according to pre-approved cut-off scores) were followed up by the clinical team and offered information about the cognitive research studies available to them. I feel this enabled the recruitment process to be much more streamlined as the clinical team could identify potential participants that were experiencing cognitive difficulties directly and reach out to start these important conversations, rather than waiting for patients to express their concerns of this during clinic appointments.

Due to delays caused by the Covid-19 pandemic, recruitment began later than intended in August 2022. August is typically a quieter month in the hospital with fewer clinics which meant that there were fewer participants to recruit. This also meant that the recruitment process overlapped with the Christmas period which is a difficult time to recruit. Advertising for the study so that people with MS could self-refer was more difficult than I imagined. The MS Society for example, has a specific way in which they support the recruitment process and while they were incredibly supportive throughout, it took three months for the study to be advertised via the MS Society magazine and six months for it to be advertised via the MS Society website.

Calculating the response rate was difficult as we do not know exactly how many people saw the advertisement on twitter. Based on the number of expressions of interest received, the conversion rate was between 55 and 85% depending on the recruitment pathway with the PPI group having the highest conversion rate. Our PPI group is well established in Nottingham and most people with MS in this group are very engaged in MS research which could explain the high conversion rate. Based on these findings, we deduced that the recruitment strategy was effective. However, for a definitive trial a longer recruitment period (or more sites) may be required which would be a minor change to the current protocol. Therefore, we gave this criterion an amber rating.

There was no indication from the findings that participants objected to being randomised and no participants withdrew from the study due to being allocated to the control group. Therefore, the randomisation method was given a green rating.

However, it is important to note that this is based on a 3:1 randomisation ratio rather than the typical 1:1 ratio of large scale RCTs.

Despite the commitment of being involved in a 10-week cognitive rehabilitation programme, 44% of participants in the intervention group were employed either full or part time whereas in previous studies, this was higher than in the CRAMMS trial (34%).[260] Furthermore, no one dropped out of the intervention because they felt that it was too time consuming. This could indicate that the remote format of the cognitive rehabilitation programme made it more accessible to a wider group of people with MS as this was easier to fit around work and home life compared to similar in person programmes that require travel to and from a clinical setting.

Findings from the feedback interviews indicated that the online format did not negatively impact the effectiveness of the intervention and there was good acceptability of the intervention being delivered remotely via Microsoft Teams, which is in keeping with current literature. A recent systematic review comparing online cognitive behavioural therapy (CBT) with face-to-face CBT in 17 studies, found no significant differences between the two groups for patient satisfaction.[521] Participants expressed that they enjoyed being able to participate in the intervention from the comfort of their own home and they felt it was very convenient for them as they could fit it around their work and home life. Some participants expressed that if the intervention had been in person, they may not have been able to participate. These findings support the growing trend that online rehabilitation programmes or 'telerehabilitation' may be beneficial to people with MS and provide a suitable alternative method to delivering services.[522]

Two participants withdrew from the intervention after it had started. The first participant expressed that they were struggling with their mental health and subsequently had emergency appointments that were booked in with the mental health team by their general practitioner (GP). These appointments were booked in after the days and times for the intervention groups had already been decided based on when participants stated that they were free. The participant's appointments coincided with the intervention group that they had been allocated to and they therefore missed the first two sessions. I offered for the participant to join a different group instead, but

they felt that they had to prioritise their mental health first and expressed that they would become too stressed trying to catch up on the sessions they had already missed.

This raises an important issue regarding participants being mentally fit to participate in the cognitive rehabilitation programme and this is something that could be screened for and included in the eligibility criteria in future studies. However, as this was only the case with one participant further studies should be conducted before any conclusions can be drawn. Currently, cognitive rehabilitation studies often screen for diagnosed psychiatric illness or medications affecting psychiatric status,[523–525] but do not typically include screening for undiagnosed mental health disorders.

The second participant withdrew from the intervention after attending four cognitive rehabilitation sessions. This participant expressed via email that they felt their diagnosis of SPMS separated them from the group as they expressed that their main concern was linked to mobility issues. Due to this being a feasibility trial, the sample size of this study was small. This meant that I was limited in terms of how I could group the intervention participants whilst accommodating all schedules. The primary focus when organising these groups was to ensure that, as much as possible, the groups included people with MS who had similar levels of cognitive ability.

However, the feedback from this participant raised an important point that in the future, similar trials and interventions should potentially ensure that people with MS are grouped together with those who have similar levels of physical ability as well as cognitive ability. EDSS scores were not measured for the purposes of this intervention, but this could be used to help group participants together for future studies in addition to few simple questions regarding physical ability. Although there are no recent cognitive rehabilitation studies which have grouped participants with MS according to physical ability, some studies have used cut-off EDSS scores in their inclusion/exclusion criteria when recruiting participants. For instance, Shahpouri et al.[526] used an EDSS cut-off of 5.5 and Mattioli et al.[527] used an EDSS cut-off score of 4, however, no justification was given for this. Similarly, Migliore et al.[528] used an EDSS cut-off of 2.5 to ensure they were only recruiting participants with MS with very mild levels of physical disability.

Overall, all participants appeared to understand the study design and were all willing to be randomised to either the intervention group or the usual care group. The

retention rate was 92% for those who received the intervention and 89% for those who were randomised to the intervention group. Bevens et al.'s[529] systematic review reported the pooled attrition rate for digital health interventions across 32 RCTs was between 14.7% and 15.6%. The attrition rate of the current study was 8%, therefore, attrition was given a green rating.

The outcome measures selected were based on those used and deemed acceptable for people with MS in the CRAMMS trial. However, as this study was delivered remotely, I investigated the feasibility and acceptability of using the outcome measures remotely. For screening assessment, I carried out the Brief Repeatable Battery of Neurological Tests (BRBN). The BRBN encompasses four tests which have been described in detail earlier in this chapter. This battery of tests was originally designed to be conducted in person with patients therefore, adaptations had to be made to enable me to conduct them remotely including creating screening materials packs that were sent out to every participant.

I had no difficulties delivering the majority of the BRBN, however, the Paced Auditory Serial Addition Test (PASAT) posed significant challenges when conducted remotely. Typically, this test involves playing tape recordings to participants during in-person assessments. Attempting to do this remotely proved difficult, as participants frequently reported difficulties in hearing the recordings despite various methods being employed, such as playing them aloud from a phone or embedding them in a PowerPoint slide. As a result of the inconsistent success in conducting the PASAT remotely, the scores from this test were not included in the final analysis.

The study suggests that future research could focus on finding more effective methods to administer the PASAT remotely, given the challenges encountered in ensuring consistent and accurate administration of the test under remote conditions. However, due to the undue levels of anxiety and frustration reported by participants during the PASAT in previous studies,[530] the PASAT may not the most appropriate measure of cognition and therefore, should not be included in a future large-scale trial.

The cognitive rehabilitation group had a high completion rate of all outcome measures overall, with several members of the control group not completing the follow-up questionnaires. No participants reporting any issues in completing the questionnaires online. However, a common problem with outcome measures is that they often cannot

capture the nuances of participant experiences or the unexpected benefits. The feedback interviews provided valuable information about patient experiences during the cognitive rehabilitation programme. The participants reported improved confidence in managing their cognitive difficulties, increased awareness of their cognitive difficulties, increased compensatory strategy use, an increased understanding of how MS affected their cognition and an acceptance of their cognitive difficulties.

Of the participants who completed the intervention, 96% completed the outcome measures. This indicates that the outcome measures were feasible to deliver remotely to people with MS, although further adaptations are needed for the PASAT and therefore, appropriateness of outcome measures was given an amber rating.

The between group analyses showed some promising results for the use of online cognitive rehabilitation programme for people with MS, with the cognitive rehabilitation group showing more favourable results than the usual care group. The analyses showed large effect sizes for the SRT which suggests positive trends that may suggest group-based cognitive rehabilitation could lead to improvements in cognitive function. These findings contrast with the CRAMMS trial that found no evidence of improvement in objective test scores following group-based cognitive rehabilitation, however, this was measured 6-months post-randomisation rather than 3-months which could explain this difference. However, these findings are supported by Mani et al.[245] who showed significant improvements in both subjective and objective measures following group-based cognitive rehabilitation. Although the tests used in this study were different, the cognitive domains measured were the same.

In interpreting the results of this feasibility study, it is essential to recognize the exploratory nature of the statistical analyses conducted. The p-values presented in Tables 12-14 are uncorrected, and therefore, any observed differences should be interpreted with caution. This is particularly important given the feasibility study's limited sample size and underpowered nature, which inherently reduces the study's ability to definitively establish efficacy.

For example, while the analyses showed significant differences in the SRT with a large effect size, these findings should be considered preliminary. The uncorrected p-values indicate that these results might be subject to Type I error (false positives), and

thus, they should be viewed as initial indications rather than conclusive evidence of the intervention's effectiveness. Further research with larger, adequately powered samples and corrected p-value analyses will be necessary to confirm these preliminary findings.

In summary, the exploratory analyses provided valuable insights and potential trends that will guide future research, but care must be taken not to overstate the significance of these results. The primary aim of this feasibility study was to assess the practicality of the intervention and gather data to refine future studies.

Interestingly, the sub-group analysis showed large effect sizes for the SRT, EMQ and EQ-5D VAS scores at 3-months post-randomisation between those predicted to be most likely to benefit and those predicted to be less likely to benefit according to the algorithm developed in study 2. Shahpouri et al.[248] found a similar improvement on the EMQ following group-based cognitive rehabilitation. Lincoln et al.[531] found significant differences between the intervention and usual care group on the EMQ-p and MSIS-Psy at 6-months post-randomisation.

In the initial analysis of the feasibility RCT, we found few large effect sizes for cognitive function outcome measures. This may have been due to heterogeneity of the sample which is a common problem in RCTs in clinical research. This is supported by the sub-group analysis which indicated that once the cognitive rehabilitation group was split into those most and less likely to benefit using our developed algorithm, the large effect sizes become more apparently with many differences being statistically significant. Furthermore, the large effect sizes found at 3-months post-randomisation were also found at 6-months post-randomisation. Therefore, we considered the signal of efficacy to have a green rating.

These findings could be supportive of the evidence found in study 2 in which we concluded that it was possible to predict which people with MS were most likely to improve in their cognitive symptoms following the group-based cognitive rehabilitation plan. However, we must acknowledge that this was a small sample size and larger RCTs are required before this algorithm could be used in clinical settings, but it is a promising finding with the potential for strong clinical impact in the future.

Participants attributed the improvement in their cognitive difficulties to several factors which were consistent with previous literature in MS.[532–534] One reason for this was

due to an increase in strategy use, including both internal and external aids.[531] This increase in strategy use was due to participants feeling that the strategies were effective and applicable to everyday life. Participants spoke positively about the group format and reported that they enjoyed having the opportunity to speak with other people with MS that understood what they were experiencing as it made them feel less alone. Participants felt that the groups offered them an opportunity to connect socially, with some commenting that towards the end of the group it felt like talking to friends. These findings could be explained by social support theory which underscores the importance of social relationships in promoting well-being.[535] Participants' comments about the group feeling like talking to friends and the intervention provider being friendly and easy to talk to point to the significance of social support. Social connections and a positive therapeutic alliance with the intervention provider can enhance participants' emotional and psychological well-being.[536]

Participants generally enjoyed the psychoeducation involved in the intervention, expressing that they enjoyed learning about how their MS affects their cognition and cognitive processes. They associated this learning with an acceptance of their cognitive difficulties, and it encouraged them to use the strategies as they understood why and how they helped them. Participants spoke positively about the intervention provider, commenting that they were highly skilled in facilitating the group, very knowledgeable about MS and very friendly and easy to talk to. This could be explained by the self-determination theory which is a psychological framework that explores human motivation and the factors that drive individuals to engage in specific behaviours.[537,538] This theory proposes that there are three basic psychological needs that, when satisfied, lead to greater intrinsic motivation and wellbeing: autonomy (learning about how MS affects the participant’s cognition may have empowered participants by giving them more autonomy in managing their condition), competence (participants associated their learning with an acceptance of their cognitive difficulties and the use of cognitive strategies, which demonstrates that they felt competent in using strategies) and relatedness (the positive rapport with the intervention provider likely created a sense of relatedness, making participant feel comfortable and encouraged to engage in the intervention).[539,540]

While all participants felt that the intervention was effective, some had ideas and suggestions about how to potentially improve the intervention. They felt that the workbook was somewhat outdated in that it included some external aids that are not typically used anymore and did not include some newer technologies such as smart home devices. Participants enjoyed the psychoeducation during the intervention and commented that they would have liked this to be more interwoven through the programme rather than focused on the beginning. While participants felt that the strategies were very useful, some felt that they would have liked to see some strategies that were specifically designed to be used in the workplace also. Therefore, we considered the patient work booklet to have an amber rating.

In this chapter we demonstrated promising results supporting the feasibility and acceptability of delivering cognitive rehabilitation for people with MS online. The study's objectives were evaluated using the traffic light system, which indicated that this trial was feasible and largely acceptable to people with MS. The study highlighted the accessibility and convenience of the remote format, with no adverse effects on the effectiveness of the intervention. Participants showed strong retention and completion rates for outcome measures, suggesting that the measures were feasible for remote administration, although further adaptations may be needed for some tests. The results indicated that the cognitive rehabilitation program had a positive impact on participants' cognitive difficulties, which they attributed to increased strategy use and social support within the group. While the study demonstrated promising outcomes, some participants offered suggestions for improvement, such as updating the workbook, incorporating workplace-specific strategies, and integrating psychoeducation more throughout the program. In chapter 5, we will gather insights garnered from the previous chapters to gain a comprehensive understanding of the implications, future directions, and the potential impact of this research project.

Chapter 5: Discussion

5.1 Chapter overview

In this chapter, a comprehensive summary of the collective findings from the distinct studies featured in this thesis is presented. Each study's findings have been thoroughly examined in their respective chapters. The primary objective of this chapter is to consolidate all the findings into a succinct overview and explore their alignment with the existing literature. The conclusion of this chapter encompasses implications for both clinical practice and suggestions for future research endeavours.

5.2 Summary of aims

This thesis aimed to establish the clinical effectiveness of cognitive rehabilitation for people with MS and to understand which groups of people with MS were most likely to benefit from this intervention. The first study was a systematic review (chapter 2) which aimed to determine whether cognitive rehabilitation led to significant improvements in cognition, mood, and functional ability. Once we had established there was strong evidence to support the clinical effectiveness of cognitive rehabilitation, although it is important to consider the quality of evidence when drawing these conclusions, we moved on to the second study which was a secondary data analysis (chapter 3). This study aimed to understand which groups of people with MS benefit most from cognitive rehabilitation. This was important because even though cognitive rehabilitation was effective for people with MS, the degree to which people benefit varied considerably. The final study was a feasibility RCT (chapter 4) which aimed to understand the feasibility and acceptability of an online group-based cognitive rehabilitation. The feasibility RCT also aimed to test the efficacy of the algorithm developed in chapter 3 that may predict who benefits most from cognitive rehabilitation.

5.3 Key findings

The systematic review identified 29 new RCTs which when added to the 15 RCTs from the last Cochrane update, totalled 44 RCTs comprising 2714 participants. These studies were either memory rehabilitation studies or cognitive rehabilitation trials with a specific memory component that included a memory intervention. These trials were mostly of relatively moderate quality, with many still not adhering to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[468] Descriptions of the randomisation protocol, blinding, and content of treatment and control groups were poor in approximately 50% of studies. Studies generally had

modest sample sizes and used impairment-level outcome assessments to determine the effectiveness of the intervention.

Twenty-nine individual studies reported positive results on memory outcomes from their memory rehabilitation groups.[247,248,260,321,322,324–326,329,331,334,337,340–345,347–351,353–355,359,363,365] Between group differences favouring the intervention group were found in the following outcomes: objective measures of verbal memory, both immediate (up to one month post-intervention) and intermediate follow-ups (one to six months post-intervention); objective measures of visual memory at immediate follow-up; objective reports of working memory at immediate follow-up; information processing at immediate and intermediate follow-ups; mood measures of depressive symptoms at immediate follow-up; quality of life measures at immediate, intermediate and longer-term follow-ups. Little to no between group differences were found in activities of daily living measures or measures of anxiety.

The results of this review suggest there is evidence to support the effectiveness of memory rehabilitation on subjective memory measures at immediate follow-up, and this result is sustained at intermediate and longer-term follow-ups of up to one year.

Following on from the systematic review, I investigated the participant characteristics that predicted neuropsychological improvement in people with MS six months after 10 weeks of group-based cognitive rehabilitation. Almost 80% of the intervention group improved in at least one of the six neuropsychological test domains measured by both subjective measures of cognition and objective neuropsychological tests. Four categories of predictors of improvement in neuropsychological test performance were examined at the univariate level and, subsequently, in the context of a hierarchical logistical regression model.

Of all of the variables examined, the most frequently occurring significant predictors of neuropsychological improvement were (i) age, from the sociodemographic category; (ii) type of MS and relapses experienced in the six months prior to receiving the cognitive rehabilitation, from the clinical category; (iii) baseline everyday memory scores and psychological wellbeing scores, from the self-report cognitive symptoms category; and (iv) baselines scores on the Doors and People Test, PASAT scores, and Selective Reminding Test scores, from the neuropsychological test category. These

findings were used to develop an algorithm that could predict whether people with MS were more or less likely to improve in cognition and psychological wellbeing following cognitive rehabilitation.

This algorithm was then tested in the feasibility RCT which was conducted to investigate the feasibility and acceptability of delivering group-based cognitive rehabilitation online. Overall, delivering this intervention remotely was found to be feasible and acceptable to people with MS, with suggested improvements/changes required before proceeding to a definitive trial. While the study demonstrated promising outcomes, some participants offered suggestions for improvement, such as updating the workbook, incorporating workplace-specific strategies, and integrating psychoeducation more throughout the programme.

5.4 Discussion of findings

5.4.1 Systematic review

The results of this review suggest there is evidence to support the effectiveness of memory rehabilitation on subjective memory measures at immediate follow-up, and this result is sustained at intermediate and longer-term follow-ups of up to one year. This is a significant change compared to the previous version of this review,[254] which found no evidence to support that memory rehabilitation had a positive effect on subjective memory measures.

Between group differences were found for quality-of-life outcomes in favour of the intervention group compared to the control group at each follow-up point, suggesting that memory rehabilitation can lead to positive change in the overall quality of life of people with MS. It should be noted that this positive finding has not been observed in previous cognitive rehabilitation reviews for people with MS,[240] or reviews investigating the effects of cognitive rehabilitation in other cohorts such as post-stroke patients.[243] This could be due to more recent trials having a broader focus on 'impact' of cognitive problems on MS, and therefore, likely to affect quality of life, while older trials mainly focused solely on memory impairments. It could also be that memory problems are more detrimental to the quality of life of people with MS compared to people with other neurological conditions and therefore, the tools to cope and self-manage their problems (that they are taught during memory and attention rehabilitation) lead to a greater improvement in their quality of life compared to other patient groups. This could also be due to

methodological quality with more recent trials potentially adhering to higher standards and employing more robust measures, thereby producing more reliable results. Furthermore, the specific content and delivery methods of the cognitive rehabilitation interventions may have evolved, incorporating more holistic approaches that address a wider range of cognitive and emotional challenges faced by people with MS. Additionally, advancements in the understanding of MS and its impact on cognitive function could have led to more targeted and effective intervention strategies in recent studies. Lastly, differences in the demographics and baseline characteristics of study populations might also account for variations in outcomes, as certain subgroups of people with MS may respond differently to cognitive rehabilitation based on factors such as age, disease duration, and comorbid conditions.

Improvements in outcomes were only maintained at follow-up for subjective memory measures and quality of life, which suggests that regular booster sessions of cognitive rehabilitation may be necessary to maintain the improvements made. Age of diagnosis could have a notable impact on subsequent disease progression as people with MS diagnosed earlier, may experience greater negative impact of their work and education which in turn, could significantly impact their quality of life. Felix et al.[541] investigated the longitudinal impact and effects of booster sessions in cognitive training for 50 healthy older adults and found that participants showed much improved performance compared to the control group following the booster sessions.[542] However, the effectiveness of booster session may depend on a variety of factors such as the cognitive domains being targeted, the severity of cognitive problems, and the stage of disease progression so this would need to be investigated in a definitive trial with people with MS before conclusions can be drawn. While there is minimal research on the effectiveness of booster sessions of cognitive rehabilitation for people with MS, studies have investigated the effect of booster sessions of cognitive behavioural therapy (CBT) for mood disorders. A review by Gearing et al.[543] found that studies in which booster sessions were included had larger effect sizes than those without booster sessions. This suggests that booster sessions may lead to more effective interventions and therefore, there is a need to explore this in cognitive rehabilitation for MS.

The size of the literature-base examined in this review allowed us to address the research questions in as much depth as possible. The variety of outcomes in the trials enabled domain-specific memory to be investigated such as visual, verbal and working, thus this review not only showed the positive effects for general memory but also identified which domains were being improved by the rehabilitation intervention programmes and which of these improvements were maintained. This review fully investigated all types of studies, participants, interventions, and outcome measures as stated in the methods. The positive results in trials using computerised interventions have important implications for clinical practice in a post-pandemic world as more and more health services are being offered virtually. This is especially important for people with MS who often struggle with mobility issues, meaning that travelling to a hospital or other clinical setting may be challenging. Furthermore, delivering cognitive rehabilitation virtually would allow for more people to access this intervention, even if their local health services did not offer it. In previous qualitative studies, people with MS felt positively about completing cognitive screening assessments online as travelling the hospital requires time, effort, and planning.[544]

However, computerised interventions may not be as effective as they first appear. The CogEx trial is a large multicentre international clinical trial which aims to understand whether computerised cognitive rehabilitation, or aerobic exercise, or both, can improve cognition in people with progressive MS.[545] The findings from this trial have shown that people with MS did not differ between groups in SDMT scores at 12 weeks post-randomisation which was this trial's primary outcome. Furthermore, at 12 weeks post-randomisation, people with MS in the cognitive rehabilitation plus exercise and the cognitive rehabilitation plus sham exercise, had worse scores on the MSIS-Psy compared to people with MS in the sham cognitive rehabilitation plus sham exercise group. Although previous evidence has suggested that RehaCom, a popular computerised cognitive rehabilitation programme, is effective for improving cognitive performance,[546,547] these studies often have small sample sizes and typically recruit people with relapsing remitting MS. Messinis et al.[523] investigated the effectiveness of RehaCom for people with secondary progressive MS and found significant differences between SDMT scores and other cognitive measures. However, it is important to note that this study had a sample size of 36, compared to the 311 in

the CogEx trial. Furthermore, in the CogEx trial the control group was not inactive while in Messinis et al.'s[523] study, the control group received their usual care only.

The contrasting findings between studies and the complexity of factors such as sample size, MS type, and control group activities underscore the need for further research in this area. Larger, well-controlled trials like CogEx, are essential to draw more robust conclusions about this effectiveness of interventions for cognitive improvement in people with both relapsing remitting and progressive MS. This would allow us to understand whether computerised interventions are not effective within MS, or for people with specific MS-types (e.g., progressive MS).

In the context of our small feasibility study, these contrasting findings highlight several key considerations. The larger sample size and rigorous control conditions of the CogEx trial provide a more robust assessment of the intervention's effectiveness. Our study's smaller scale and different design may have led to different outcomes due to these limitations. However, the most crucial difference is the the CogEx interventions was a computerised intervention that participants completed by themselves whereas the intervention in our feasibility study was delivered by an assistant psychologist in a group remote setting. The differences in findings underscore the need for further research with larger, well-controlled trials to clarify the effectiveness of different cognitive rehabilitation interventions across different types of MS. Understanding whether the lack of effectiveness in computerised interventions is specific to certain MS types, such as progressive MS, or a general issue, is crucial for developing targeted and effective cognitive rehabilitation strategies.

5.4.2 Secondary data analysis

This study demonstrated that the statistical models predicted whether a participant improved or did not improve in neuropsychological function following cognitive rehabilitation in up to 86% of participants. Results suggest that younger participants with medium to high education (e.g., high school to degree level), diagnosed with RRMS and PPMS who have not experienced any recent relapses, with mild to moderate cognitive difficulties as assessed by the BRBN were most likely to benefit from cognitive rehabilitation.

Participants with RRMS (n=159) were more likely to report improvement of their psychological wellbeing, processing speed and sustained attention over time when compared to those with SPMS (n=64). Our findings suggest that people with MS who have had recent releases were less likely to show improvement in cognitive performance following cognitive rehabilitation. Cognitive rehabilitation may be more effective when applied during remission phases, allowing individuals to capitalise on the periods of relative stability. While this has not been expressly investigated in the existing literature, this theory may be supported by research that suggests that early cognitive intervention is important for reducing cognitive decline for people with MS.[548,549]

Participants with PPMS (n=22) were less likely to report improvement in their psychological wellbeing but were more likely to report improvement in processing speed and sustained attention when compared to those with SPMS. These observed enhancements in processing speed and sustained attention may suggest that cognitive rehabilitation interventions can target specific cognitive functions effectively even in the absence of significant improvements in overall well-being.

In outcome studies of patients with acquired brain injuries (without interventions specifically aimed at treating cognitive deficits), injury severity has been predictive of functioning.[550,551] In terms of cognition, relapses might have caused further damage to the areas of the brain responsible for cognitive processes tested. There is evidence that cognition is notably more impaired during and immediately after an active relapse in people with MS compared to stable patients,[552] so it is possible the cognitive deficits of patients immediately following a relapse may be too severe to improve. A recent review posited that cognition declines acutely during a relapse and that cognitive impairment in people with MS may result from incomplete recovery of these relapses.[553] However, there is a lot we still do not understand about the neurophysiology driving cognitive relapse and recovery; thus, these results need to be interpreted with caution.

Younger participants were more likely to improve compared to older participants. This could be due to the nature of the cognitive rehabilitation programme, as a significant part of this programme is teaching and encouraging participants to use technology as external memory aids, such as smartphones and online shared calendars

which may have come more naturally to those of a younger age. While in recent years the number of older adults who are tech users has grown,[554] there are still notable differences in usage between younger and older adults. Therefore, this may have contributed to the improvement in subjective measures of memory.

Digital exclusion, the gap between those who have easy access to technology and those who do not, could have played a significant role in this discrepancy. Older adults are often less familiar and comfortable with digital tools, which can limit their ability to benefit from technology-based interventions. This digital divide might explain why younger participants, who are generally more tech-savvy, showed greater improvement. Similar findings have been shown in people with schizophrenia. Wykes et al.[555] investigated the effects of cognitive rehabilitation across age span and found that younger participants performed better on cognitive tests following cognitive remediation.

While the older participants did have less years in education on average, the groups were otherwise matched on length and severity of illness. Kontis et al.[556] investigated the effects of age and its relationship with cognitive reserve and found that the effects of cognitive rehabilitation may be limited in older participants in the schizophrenia population. This could be explained by research evidence that suggests age may play a significant role in predicting cognitive resilience or improvement linked to cognitive reserve.[557] Higher levels of cognitive reserve in people with MS can protect against disease-related cognitive decline and younger adults tend to have higher cognitive reserves compared to older adults.[85]

Age at diagnosis may also predict cognitive improvement with recent evidence suggesting cognitive impairment is more severe for people with MS who are diagnosed earlier.[558,559] As a progressive disease, MS symptoms experienced gradually accumulate and worsen over time. Disease duration has been found to have a negative impact on both processing speed and working memory.[560]

People with MS living with others were more likely to experience improvement in their memory than those living alone. This could be due to the partner or family providing emotional support to the participants during the intervention period as well as helping with some of the technical aspects of using external memory aids. Recent research suggests that people with MS who are married have a better quality of life

and higher emotional well-being compared to people with MS who live alone.[561] More generally, longitudinal studies have shown that married people with chronic disease have less depression and higher life satisfaction, psychological wellbeing, and quality of life,[562] as well as significantly lower rate of functional decline.[563] In MS there are no studies specifically investigating the role that partners/carers play during cognitive rehabilitation interventions.

Baseline neuropsychological tests, such as lower verbal recall and recognition test scores, were a significant factor in predicting improvement. This finding is in line with the effects of cognitive rehabilitation in other clinical populations. For example, DeTore et al.[564] evaluated whether severity of cognitive impairment was a predictor of response to cognitive rehabilitation in people with severe mental illness and found that people with greater levels of cognitive impairment benefited significantly more than those with less severe cognitive impairment. Similarly, Fiszdon et al.[565] found that performance in cognitive rehabilitation for people with schizophrenia was predicted by poorer baseline cognitive test scores, although the sample size for this study was quite small. Although no participants were performing at ceiling in our study and therefore, all participants had room for improvement, it is plausible that those who scored lower simply had more room for improvement. However, in our study, we found that if people with MS had severe cognitive impairment, then they did not benefit as much as those who had mild or moderate cognitive impairment. We posited that this could be because those with severe cognitive impairment had deficits that were too complex to be significantly improved by cognitive rehabilitation and instead, needed an individualised, more intensive intervention. Post hoc analysis provided some support for this explanation because when the mean gain improvement scores in those that scored below the mean on the EMQ-p at baseline were examined, greater improvements were seen compared to those that score above the mean. Lindenmayer et al.[566] found that psychiatric patients with lower baseline cognitive functioning improved less than those with higher levels of neurocognitive functioning, which supports the findings of our feasibility RCT. However, it is important to note that the patients included in this study had notably lower levels of baseline cognitive functioning compared with the previous studies.

One of the strengths of this study, owing to the large sample size of CRAMMS, is that several predictor and outcome variables were able to be considered. However, the

main limitation of this post hoc analysis is that the findings were based on retrospective data. Therefore, findings from this study should be confirmed using a prospective research design, which was undertaken as part of this thesis.

5.4.3 Feasibility RCT

Analysis of the feasibility RCT revealed some large effect sizes and significant differences between the groups at 3-months post-randomisation. These same large effect sizes were apparent at 6-months post-randomisation, but no further significant differences were found. This may be attributed to the heterogeneity of the sample, a common challenge in clinical research RCTs. It is important to note that this study was not powered to identify significant effects. With this in mind, the subgroup analysis, which divided the cognitive rehabilitation group into those predicted to benefit the most and the least, exposed more apparent signals of efficacy for the SRT, EMQ-p and the EQ-5D VAS score. We also found large effect sizes for these outcomes. In contrast, the CRAMMS trial did not find significant differences on objective measures of cognition.

Differences in cognitive problem severity between the CRAMMS trial (with moderate to severe impairments) and our feasibility trial (with mild to moderate impairments) likely influenced intervention outcomes. The group-based cognitive rehabilitation programme was designed for targeting mild to moderate impairments, and therefore, may have been better suited for demonstrating significant improvements in cognition in our feasibility study sample compared to the CRAMMS trial. Factors such as treatment responsiveness, intervention adaptation, sample characteristics, and outcome measures likely contributed to these differences. The CRAMMS trial had a larger sample size, which can sometimes lead to smaller effect sizes being observed due to a more heterogeneous population. In contrast, our feasibility study, while smaller, may have included a more homogenous sample or those more responsive to the intervention, which could magnify the observed effects.

This study provides positive early signals suggesting it may be possible to predict which individuals with MS are more likely to experience improvements in their cognitive symptoms through a group-based cognitive rehabilitation plan. Larger RCTs are necessary to validate the algorithm's clinical application potential. Despite this limitation, these findings hold promise for future clinical impact.

The feedback interviews yielded valuable insights into patient experiences during the cognitive rehabilitation program. Participants reported enhanced confidence in managing cognitive difficulties, heightened awareness of these difficulties, increased use of compensatory strategies, better understanding of how MS affects cognition, and acceptance of cognitive challenges. These findings closely mirrored those of the CRAMMS trial, upon which this study's framework was based. Notably, differences emerged in relation to the online delivery format of the intervention.

Participants in our study attributed the improvement in their cognitive difficulties to various factors, consistent with existing literature on MS. One key factor was the increased use of strategies, encompassing both internal and external aids. Participants found these strategies effective and applicable to their daily lives. They expressed positive sentiments about the group format, highlighting the opportunity to connect with others who have MS, which made them feel less isolated. Some participants even likened the group experience to conversing with friends. These findings align with social support theory, emphasising the role of social relationships in promoting well-being.[567] The positive rapport with the intervention provider also played a significant role, indicating the importance of a positive therapeutic alliance in enhancing emotional and psychological well-being.[568]

Participants found value in the psychoeducation provided during the intervention, as it enhanced their understanding of how MS affects their cognition and cognitive processes. This understanding, in turn, motivated them to utilise the strategies, as they comprehended why and how these strategies were beneficial. The intervention provider received praise for their skills in facilitating the group, their extensive knowledge about MS, and their approachability. This aligns with the self-determination theory, a psychological framework exploring human motivation.[569,570] According to this theory, three fundamental psychological needs—autonomy, competence, and relatedness—drive intrinsic motivation and well-being. Participants' autonomy was enhanced as they learned about managing their cognitive condition, while their perceived competence and relatedness fostered a sense of comfort and encouragement to engage in the intervention.

Some participants offered suggestions for improvement. They noted that the workbook appeared somewhat outdated, including external aids that are no longer

commonly used and overlooking newer technologies like smart home devices. Participants in our feasibility study also expressed a desire for psychoeducation during the feedback interviews to be more integrated throughout the program, rather than concentrated at the beginning. Additionally, they wished to see strategies designed specifically for workplace use. These suggestions are different from those given by participants in the CRAMMS study, although the suggestion for inclusion of psychoeducation is similar to the suggestion made by CRAMMS participants to include mindfulness to help with focus. These insights provide valuable input for refining and enhancing future iterations of the intervention.

5.4.4 Overall implications for research and clinical practice

I believe the work I have conducted as part of this PhD and discussed in this thesis, has the potential to impact the lives of people with MS.

Providing conclusive evidence that cognitive rehabilitation is effective for people with MS, both in the long-term and the short-term, has led to the inclusion of cognitive rehabilitation in the NICE guidelines for management of MS. Furthermore, two years after publication, our Cochrane review is still the most comprehensive review of cognitive rehabilitation for people with MS in the literature and sits in the top 5% of all research outputs measured by altimetric. However, the landscape of clinical research is changing, and there has been a notable shift in recent years, particularly with the rise of personalised medicine.

Personalised medicine refers to a medical model whereby tailor-made prevention and treatment strategies are created for a defined group of individuals, or a single individual.[571] These strategies take a “one size fits all” approach to diagnostics and drug therapy and turn it into an individualised, targeted approach. Vicente et al.[572] argues that it will transform healthcare by 2030. In MS, the heterogeneity of clinical expression and the response to treatments, including cognitive rehabilitation, pose major challenges to improving patient care.[573,574] Providing personalised care for people with MS can include improving diagnostic tools, better understanding the impact of factors on disease progression, and understanding the potential benefits of various therapeutic interventions.[575,576] This involves the development of predictive models in which the impact of both the disease and possible treatments on people with MS can be understood, such as the one I developed as part of this PhD.

The algorithm I developed as part of this PhD that can predict which people with MS are most likely to benefit from cognitive rehabilitation and could positively impact MS clinical practice, although further testing is required before firm conclusions can be drawn (e.g., a definitive trial). This algorithm will allow clinicians to understand whether their patients are most likely to benefit from cognitive rehabilitation or not, allowing them to target this intervention to those most likely to benefit, whilst offering other treatment types to those less likely to benefit. Similar algorithms are already in use, for example PREDICT which is the most well-known example and is used in breast cancer to understand future cancer risk.[577] However, currently no such prediction tools exist for MS clinical practice which means that the algorithm developed in this PhD is the first.

Currently, cognitive rehabilitation is not routinely provided on the NHS. However, we hope that this evidence provides a strong case for the NHS commissioners to approve funding of cognitive rehabilitation for MS, as this targeted approach will significantly improve the optimisation of neuropsychological resources. This will allow people with MS to have access to a treatment that was previously unavailable to them and furthermore, they will have the added benefit of knowing that they are likely to benefit from this treatment. Although, we found preliminary signals of efficacy for this algorithm during this PhD, further research will need to be conducted with larger groups of people with MS, before drawing strong conclusions. However, these findings are incredibly promising.

These findings indicate that we may be able to move away from asking the question "which treatment is most effective for improving cognitive in people with MS?" and moving into asking the question "which groups of people with MS are the different treatments for improving cognition most effective for?". Thus, is it important that the studies conducted in this PhD around understanding who benefits most from cognitive rehabilitation for MS be replicated for different types of cognitive rehabilitation. By doing this, we will be able to understand whether there is one group of people with MS who benefit most from cognitive rehabilitation and therefore, one group in which this intervention should be targeted to. Alternatively, it is possible that other groups of people with MS in fact benefit most from other types of cognitive rehabilitation, indicating that for example, while group-based cognitive rehabilitation should be targeted to those outlined in chapter 3, individual or computerised cognitive

rehabilitation should be targeted to other groups i.e., older people with MS or people with MS who have more severe cognitive problems. It is important to ensure that we do not exclude people with MS from receiving treatment for their cognitive problems but instead, ensure we conduct research to develop new interventions specifically designed for those who do not benefit from existing treatments. If the algorithm was applied, people with MS that the algorithm does not predict will benefit most from group-based cognitive rehabilitation may be excluded such as older people, those with lower education, those who have had recent relapses and those with severe cognitive impairment. It may be that this population would benefit from an individual type of cognitive rehabilitation that can be personalised towards the needs of this population and is designed to support those with severe cognitive impairment, further research is needed to explore interventions that would most benefit this population.

These findings have significant implications, especially in a post-pandemic context where virtual health services are increasingly prevalent. Remote interventions showcased positive results, offering accessible options for individuals with mobility issues like those with MS. This virtual approach could expand access to cognitive rehabilitation for a wider population.

5.4.5 Future research

While this thesis has made significant strides in unravelling the intricacies of cognitive rehabilitation for MS, it also opens avenues for future research to further enhance our understanding and refine interventions. Firstly, there is a need for longitudinal studies that track the long-term effects of cognitive rehabilitation on a larger and more diverse cohort of individuals with MS. Understanding the sustained impact of such interventions over extended periods will contribute valuable insights into the durability of cognitive improvements. A further robust, large-scale, multi-centre RCT, using ecologically valid outcome assessments (including health economic outcomes) assessed at longer-term time points is needed to be certain about the effectiveness of the predictive algorithm and to conclusively establish the effectiveness of online group-based cognitive rehabilitation for people with MS.

Moreover, investigating the optimal frequency and duration of booster sessions is imperative to design more effective and sustainable rehabilitation programs. The thesis highlighted the potential for regression in the absence of regular boosters,

prompting the question of how to tailor these sessions to individual needs and characteristics.

Additionally, future research should explore the intersectionality of factors influencing cognitive rehabilitation outcomes. While the thesis identifies predictors such as age, MS subtype, and education levels, further investigation into the interaction between these variables and the impact of comorbidities or socioeconomic factors could yield a more comprehensive understanding of individual responses to rehabilitation. Further research is also needed to explore the effects of cognitive rehabilitation intervention in more diverse populations.

Lastly, continuing to delve into the qualitative aspects of the rehabilitation experience can provide deeper insights into the subjective perceptions and psychosocial dimensions of cognitive improvement. This qualitative exploration can complement quantitative findings, offering a more holistic understanding of the lived experiences of individuals undergoing cognitive rehabilitation for MS.

In essence, future research should aim to build upon the foundation laid by this thesis, addressing the gaps identified and embracing a multidimensional approach to advance the field of cognitive rehabilitation for individuals with MS.

5.4.6 Final conclusions

The overall aims of this thesis were to establish the clinical effectiveness of cognitive rehabilitation for people with MS and to understand which groups of people with MS were most likely to benefit from this intervention.

This thesis highlights evidence supporting the effectiveness of memory rehabilitation, particularly on subjective memory and quality of life measures as improvements made in these domains were sustained in the long-term. This positive outcome is distinct from other cognitive rehabilitation reviews in MS and other cohorts, possibly due to a broader focus on the impact of cognitive issues on MS, including quality of life. Regular booster sessions may be necessary to maintain improvements in subjective memory and quality of life, as without them, participants tend to regress.

Furthermore, this thesis determined that younger participants with medium to high education (e.g., high school to degree level), diagnosed with RRMS and PPMS who have not experienced any recent relapses, with mild to moderate cognitive difficulties were most likely to benefit from group-based cognitive rehabilitation. Understanding

who will benefit most from group-based cognitive rehabilitation will allow clinicians to target this intervention towards these groups of people with MS and offer alternative therapies to those less likely to benefit from this intervention.

In navigating the intricate landscape of cognitive rehabilitation for MS, this thesis sheds light not only on the effectiveness of memory rehabilitation but also on the nuanced factors determining who benefits most. The targeted application of group-based cognitive rehabilitation to specific cohorts provides a valuable framework for clinicians, enhancing the precision and efficacy of interventions while facilitating alternative therapeutic approaches for individuals less likely to benefit. This thesis highlights the profound impact that tailored interventions could have on the lives of those with MS. As I delve deeper into exploring personalised rehabilitation, I am prompted to ponder broader questions: What does it truly mean to individualise care amidst the diverse experiences of those with MS? What narratives may these identified predictors conceal, and how can we go beyond statistics to understand the uniqueness of each person with MS's journey? Overall, this thesis not only advances our understanding of cognitive rehabilitation in MS but also offers practical insights that can guide personalised treatment strategies, ultimately improving the lives of those affected by this complex neurological condition.

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Appendices

Appendix A: Systematic review search terms

{attention*} OR {cognition} OR {cognition disorder*} OR {cognitive} OR {concentration} OR {distract*} OR {alert*} AND {training} OR {retraining} OR {therap*} OR {rehabilitation} OR {treatment*} OR {therapeutic*} OR {computer assisted therap*} OR {computer*} OR {neuropsychological test*} OR {neurorehabilitation} OR {neuropsychological rehabilitation} OR {rehabilitation} OR {cognition} OR {neurological system and disorders} OR {memory} OR {cognitive retraining}

Appendix B: Data extraction template used in systematic review.

Memory rehabilitation for people with multiple sclerosis

Using this form, or an adaptation of it, will help you to meet MECIR standards for collecting and reporting information about studies for your review, and analysing their results (see MECIR standards C43 to C55; R41 to R45).

Notes on using data extraction form:

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Report ID	
Report ID of other reports of this study including errata or retractions	
Notes	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study authors contact details	
Publication type *(e.g. full report, abstract, letter)*	Full paper
Country	
Notes:	

Study eligibility

	Eligibility criteria	Eligibility criteria met?	

Study Characteristics	*(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised controlled trial	☐	☐	☐	
	Quasi-randomised controlled trial	☐	☐	☐	
Participants	Adults with MS	☐	☐	☐	
Types of intervention	Memory rehabilitation	☐	☐	☐	
Types of comparison	Intervention vs placebo or usual care	☐	☐	☐	
Types of outcome measures *(please tick all that apply)*	Subjective memory Objective memory Mood Quality of life Activities of daily living (ADL)	☐ ☐ ☐ ☐ ☐			
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*		
Design *(e.g. parallel, crossover, non-RCT)*		

Randomisation *(e.g. block-stratification, quasi-randomisation, etc)*			
Unit of allocation *(by individuals, cluster/ groups or body parts)*			
Blinding *(e.g. double-blind, observer blind, etc)*			
Start date			
End date			
Duration of participation *(from recruitment to last follow-up)*			
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear		
Notes:			

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source *(pg & ¶/fig/table/other)*
Population description *(from which study participants are drawn)*		
Diagnostic criteria (Poser criteria, McDonald criteria, etc)	McDonald criteria ☐ Paty & Poser criteria ☐ Schumacher criteria ☐ Not specified ☐	
Type(s) of MS included *(include number of participants in each group where appropriate)*	Primary progressive MS ☐ N: Secondary progressive MS ☐ N: Relapsing-remitting MS ☐ N:	
Setting *(including location and social context)*	Clinical ☐ Community ☐ Multicentre ☐	
Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants *(e.g. phone, mail, clinic patients)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Total no. randomised		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		

Withdrawals and exclusions *(if not provided below by outcome)*			
Age (Mean, SD)			
Sex (%)	Male:	Female:	
Race/ethnicity			
Severity of illness			
Co-morbidities			
Education *(mean, SD in years)*			
Other relevant sociodemographics			
Subgroups measured			
Subgroups reported			
Notes:			

Intervention groups

Memory intervention

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Rational for intervention *(include key references)*		
Description *(include sufficient detail for replication)*		
Duration of treatment period *(total intervention time e.g. 10 weeks)*		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. individual, group based, computerised)*		
Comparisons *(e.g. two groups, three groups, etc)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic information *(i.e. intervention cost, changes in other costs as result of intervention)*		
Integrity of delivery		
Compliance		
Notes:		

Control group

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period *(total intervention time e.g. 10 weeks)*		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. individual, group based, computerised)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic information *(i.e. intervention cost, changes in other costs as result of intervention)*		
Resource requirements *(e.g. staff numbers, cold chain, equipment)*		
Integrity of delivery		
Compliance		

Notes:

Outcomes

[insert outcome measure]

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Outcome name		
Time points measured *(e.g. baseline, post intervention, 6 month follow up, etc)*		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/ reporting		
Outcome measure(s)		
Scales: upper and lower limits *(indicate whether high or low score is good)*		
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear	
Imputation of missing data *(e.g. assumptions made for ITT analysis)*		
Significant improvements		
Non-significant improvements		
Subgroup analysis		

Assumed risk estimate *(e.g. baseline or population risk noted in Background)*		
Power *(e.g. power & sample size calculation, level of power achieved)*		
Notes:		

Risk of Bias assessment

(See Handbook Chapter 8.)

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(pg & ¶/fig/table/other)*
Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

Data and analysis

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

[insert outcome measure]

	Description as stated in report/paper						Location in text or source *(pg & ¶/fig/table/other)*
Comparison							
Outcome							
Subgroup							
Time point *(specify from start or end of intervention)*	Within group comparison of pre and post scores ☐ Between group comparison of post intervention scores ☐						
Other:							
Results	Intervention			Comparison			
	Mean	SD *(or other variance, specify)*	No. participants	Mean	SD *(or other variance, specify)*	No. participants	
Results at follow up	Intervention			Comparison			
Any other results reported *(e.g. mean difference, CI, P value)*							
No. missing participants							
Reasons missing							
No. participants moved from other group							
Reasons moved							
Unit of analysis *(individuals, cluster/ groups or body parts)*							

Statistical methods used and appropriateness of these *(e.g. adjustment for correlation)*			
Reanalysis required? *(specify)*	☐ Yes ☐ No ☐ Unclear		
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear		
Reanalysed results			
Notes:			

Appendix C: Summary of findings systematic review

Table 19 Summary of findings systematic review.

Memory rehabilitation for people with multiple sclerosis						
Patient or population: people with multiple sclerosis **Settings:** clinic and home-based **Intervention:** memory rehabilitation **Comparison:** active control or no treatment						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Memory rehabilitation**				
Subjective memory - immediate EMQ, MSNQ, CFQ, MFQ[a] Follow-up: within one month	-	The mean subjective memory measures - immediate in the intervention groups was **0.32 standard deviations higher** (0.05 to 0.58 higher)	-	568 (10 studies)	⊕⊕⊕⊖ **moderate**[b]	SMD 0.32 (0.05 to 0.58)
Subjective memory measures - intermediate	-	The mean subjective memory measures - immediate in the intervention groups was	-	1045 (11 studies)	⊕⊕⊕⊕ **high**	Immediate follow-up:

EMQ, MSNQ, CFQ, MFQ[a] Follow-up: 1 to 6 months		**0.23 standard deviations higher** (0.11 to 0.35 higher)				SMD 0.32 (0.05 to 0.58) Longer-term follow-up: SMD 0.16 (0.02 to 0.30)
Subjective memory - longer-term EMQ, MSNQ, CFQ, MFQ[a] Follow-up: 6 months+	-	The mean subjective memory measures - long term in the intervention groups was **0.16 standard deviations higher** (0.02 to 0.30 higher)	-	775 (5 studies)	⨁⨁⨁⨁ **high**	SMD 0.16 (0.02 to 0.30)
Verbal memory - immediate CVLT, AVLT, HVLT, VLT, SRT, MUSIC[a] Follow-up: within one month	-	The mean objective verbal memory measures - immediate in the intervention groups was **0.4 standard deviations higher** (0.22 to 0.58 higher)	-	922 (19 studies)	⨁⨁⨁◯ **low**[c,d]	SMD 0.40 (0.22 to 0.58)

Verbal memory measures - intermediate CVLT, AVLT, HVLT, VLT, SRT, MUSIC[a] Follow-up: 1 to 6 months	-	The mean objective verbal memory measures - intermediate in the intervention groups was **0.25 standard deviations higher** (0.11 to 0.4 higher)	-	753 (6 studies)	⨁⨁⊖⊖ **low**[b,c]	Immediate follow-up: SMD 0.40 (0.22 to 0.58) Longer-term follow-up: SMD 0.13 (-0.03 to 0.29)
Verbal memory - longer-term CVLT, AVLT, HVLT, VLT, SRT, MUSIC[a] Follow-up: 6 months+	-	The mean objective verbal memory measures - longer-term in the intervention groups was **0.13 standard deviations higher** (0.03 lower to 0.29 higher)	-	619 (4 studies)	⨁⨁⨁⊖ **moderate**[d]	SMD 0.13 (-0.03 to 0.29)
Visual memory - immediate BVMT-R, SPART, CMT, ROCF	-	The mean objective visual memory measures - immediate in the intervention groups was **0.42 standard deviations**	-	799 (16 studies)	⨁⨁⨁⊖ **moderate**[f]	SMD 0.42 (0.25 to 0.60)

Follow-up: within one month		**higher** (0.25 to 0.6 higher)				
Visual memory measures - intermediate BVMT-R, SPART, CMT, ROCF Follow-up: 1 to 6 months	-	The mean objective visual memory measures - intermediate in the intervention groups was **0.2 standard deviations higher** (0.11 lower to 0.5 higher)	-	751 (6 studies)	⨁⨁⨁⨀ **moderate**[e]	Immediate follow-up: SMD 0.42 (0.25 to 0.60) Longer-term follow-up: SMD 0.12 (-0.13 to 0.37)
Visual memory - longer-term BVMT-R, SPART, CMT, ROCF Follow-up: 6 months+	-	The mean objective visual memory measures - longer-term in the intervention groups was **0.12 standard deviations higher** (0.13 lower to 0.37 higher)	-	619 (4 studies)	⨁⨁⨁⨁ **high**	SMD 0.12 (-0.13 to 0.37)

Working memory - immediate PASAT, WAIS Follow-up: within one month	-	The mean objective working memory measures - immediate in the intervention groups was **0.45 standard deviations higher** (0.18 to 0.72 higher)	-	655 (12 studies)	⨁⨁⊖⊖ **low**[h,p]	SMD 0.45 (0.18 to 0.72)
Working memory measures - intermediate PASAT, WAIS Follow-up: 1 to 6 months	-	The mean objective working memory measures - intermediate in the intervention groups was **0.16 standard deviations higher** (0.09 lower to 0.40 higher)	-	821 (8 studies)	⨁⨁⨁⊖ **moderate**[f]	Immediate follow-up: SMD 0.45 (0.18 to 0.72) Longer-term follow-up: SMD 0.04 (-0.11 to 0.2)
Working memory - longer-term PASAT, WAIS Follow-up: 6 months+	-	The mean objective working memory measures - longer-term in the intervention groups was **0.04 standard deviations**	-	665 (5 studies)	⨁⨁⨁⨁ **high**	SMD 0.04 (-0.11 to 0.2)

		higher (0.11 lower to 0.2 higher)				
Information processing - immediate SDMT Follow-up: within one month	-	The mean information processing measures - immediate in the intervention groups was **0.51 standard deviations higher** (0.19 to 0.82 higher)	-	808 (15 studies)	⨁⨁⊖⊖ **low**[j,p]	SMD 0.51 (0.19 to 0.82)
Information processing - intermediate SDMT Follow-up: 1 to 6 months	-	The mean information processing measures - intermediate in the intervention groups was **0.27 standard deviations higher** (0.00 to 0.54 higher)	-	933 (8 studies)	⨁⨁⊖⊖ **low**[g,h]	Immediate follow-up: SMD 0.51 (0.19 to 0.82) Longer-term follow-up: SMD 0.21 (-0.03 to 0.45)

Information processing - longer-term SDMT Follow-up: 6 months+	-	The mean information processing measures - longer-term in the intervention groups was **0.21 standard deviations higher** (0.03 lower to 0.45 higher)	-	723 (5 studies)	⨁⨁⨁⨀ **moderate**[l]	SMD 0.21 (-0.03 to 0.45)
Depression (mood) - immediate GHQ, BDI, BDI-FS, Chicago Multiscale Depression Inventory, HADS, EAQ, CES-D, MADRS[a] Follow-up: within one month	-	The mean depression measures (mood) - immediate in the intervention groups was **0.34 standard deviations higher** (0.15 to 0.53 higher)	-	853 (16 studies)	⨁⨁⨁⨀ **moderate**[m]	SMD 0.34 (0.15 to 0.53)
Depression (mood) - intermediate GHQ, BDI, BDI-FS, Chicago Multiscale Depression Inventory, HADS, EAQ, CES-D, MADRS[a] Follow-up: 1 to 6 months	-	The mean depression measures (mood) - intermediate in the intervention groups was **0.20 standard deviations higher** (0.06 lower to 0.45 higher)	-	1003 (10 studies)	⨁⨁⨁⨀ **moderate**[m]	SMD 0.20 (-0.06 to 0.45)

Depression (mood) - longer-term GHQ, BDI, BDI-FS, Chicago Multiscale Depression Inventory, HADS, EAQ, CES-D, MADRS[a] Follow-up: 1 to 6 months	-	The mean depression measures (mood) - longer-term in the intervention groups was **0.15 standard deviations higher** (0.04 lower to 0.34 higher)	-	891 (7 studies)	⨁⨁⨁⨁ **high**	SMD 0.15 (-0.04 to 0.34)
Anxiety (mood) - immediate GHQ, EAQ, STAI, HADS Follow-up: within one month	-	The mean anxiety measures (mood) - immediate in the intervention groups was **0.29 standard deviations higher** (0.01 lower to 0.59 higher)	-	178 (4 studies)	⨁⨁⨁⨁ **high**	SMD 0.29 (-0.01 to 0.59)
Anxiety (mood) - intermediate GHQ, EAQ, STAI, HADS Follow-up: 1 to 6 months	-	The mean anxiety measures (mood) - intermediate in the intervention groups was **0.16 standard deviations higher** (0.15 lower to 0.46 higher)	-	502 (4 studies)	⨁⨁⨁⨁ **high**	SMD 0.16 (-0.15 to 0.46)
Anxiety (mood) - longer-term GHQ, EAQ, STAI, HADS	-	The mean anxiety measures (mood) - longer-term in the intervention groups was **0.27 standard deviations**	-	502 (4 studies)	⨁⨁⨁⨁ **high**	SMD 0.27 (-0.12 to 0.65)

Follow-up: 6 months+		**higher** (0.12 lower to 0.65 higher)				
Quality of life - immediate MSIS, MSQOL, SF-36, SF-12, SWLS, EQ-5D-5L[a] Follow-up: within one month	-	The mean quality of life measures - immediate in the intervention groups was **0.42 standard deviations higher** (0.15 to 0.68 higher)	-	371 (8 studies)	⨁⨁⨁⨁ **high**	SMD 0.42 (0.15 to 0.68)
Quality of life - intermediate MSIS, MSQOL, SF-36, SF-12, SWLS, EQ-5D-5L[a] Follow-up: 1 to 6 months	-	The mean quality of life measures - intermediate in the intervention groups was **0.30 standard deviations higher** (0.02 to 0.58 higher)	-	683 (6 studies)	⨁⨁⨁⨁ **high**	Immediate follow-up: SMD 0.42 (0.15 to 0.68) Longer-term follow-up: SMD 0.17 (0.02 to 0.32)
Quality of life - longer-term	-	The mean quality of life measures - longer-term in the intervention groups was	-	687 (5 studies)	⨁⨁⨁⊖ **moderate**[o]	SMD 0.17 (0.02 to 0.32)

MSIS, MSQOL, SF-36, SF-12, SWLS, EQ-5D-5L[a] Follow-up: 6 months+		**0.17 standard deviations higher** (0.02 to 0.32 higher)				
Activities of daily living - immediate EADL[a] Follow-up: within one month	-	The mean activities of daily living measures - immediate in the intervention groups was **0.02 standard deviations higher** (0.26 lower to 0.29 higher)	-	265 (4 studies)	⨁⨁⨁⨁ **high**	SMD 0.02 (-0.26 to 0.29)
Activities of daily living - intermediate EADL[a] Follow-up: 1 to 6 months	-	The mean activities of daily living measures - intermediate in the intervention groups was **0.06 standard deviations lower** (0.36 lower to 0.24 higher)	-	400 (4 studies)	⨁⨁⨁⨁ **high**	Immediate follow-up: SMD 0.02 (-0.26 to 0.29) Longer-term follow-up: SMD -0.11 (-0.49 to 0.27)
Activities of daily living - longer-term EADL[a] Follow-up: 6 months+	-	The mean activities of daily living measures - longer-term in the intervention groups was **0.11 standard deviations lower** (0.49 lower to 0.27 higher)	-	369 (3 studies)	⨁⨁⨁⨁ **high**	SMD -0.11 (-0.49 to 0.27)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; SMD: standardised mean difference
GRADE Working Group grades of evidence **High quality** ⨁⨁⨁⨁**:** further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality** ⨁⨁⨁⊖**:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality** ⨁⨁⊖⊖**:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality** ⨁⊖⊖⊖**:** we are very uncertain about the estimate.

[a]**CMT**: Contextual Memory Text; **EAQ:** Emotional awareness questionnaire; **EMQ:** Everyday Memory Questionnaire; **HADS:** Hospital Anxiety and Depression Scale; **STAI:** State Trait Anxiety Inventory; **MSNQ:** Multiple Sclerosis Neuropsychological Screening Questionnaire; **MFQ:** Memory Functioning Questionnaire; **RBMT:** Rivermead Behavioural Memory Test; **CVLT:** California Verbal Learning Test; **AVLT:** Auditory Verbal Learning Test; **HVLT:** Hopkins Verbal Learning Test; **VLT:** Verbal Learning Test; LNNB: Luria-Nebraska Neuropsychological Battery; **BRBNT:** Brief Repeatable Battery of Neuropsychological Tests; **GHQ:** General Health Questionnaire; **BDI:** Beck Depression Inventory; **BDI-FS:** Beck Depression Inventory-Fast Screen; **EADL:** Extended Activities of Daily Living; **MSIS:** Multiple Sclerosis Impact Scale; **FAMS:** Functional Assessment of Multiple Sclerosis; **MSQOL:** Multiple Sclerosis Quality of Life; **PASAT:** Paced auditory serial addition test; **SF-36:** 36-Item Short Form Health Survey; **SF-12:** 12-Item Short Form Health Survey.

[b] 1 of 10 studies had possible risk of bias related to random sequence generation, and in 2 of the 10 it was unclear. Allocation concealment was possible in 1 study, and unclear in 3 of the 10 studies. Blinding was a potential source of bias in 2 studies, and unclear in 1 of the 10 studies. Incomplete outcome data may have been biased in 1 study, an unclear in 3 of the 10 studies. Selective reporting may have been biased in 1 study.

Downgraded by 1 due to 95% confidence intervals including no effect, and the upper or lower confidence intervals limit crosses an effect size of 0.5 in either direction.

[b]All or nearly all of the studies used a list-learning task as an objective measure of verbal memory, which has poor ecological validity.

[c]2 of the 6 studies showed unclear risk of bias relating to random sequence generation. 1 study had unclear potential risk of allocation concealment bias. 4 studies had potential risk of bias related to blinding. 3 studies had unclear risk of bias due to incomplete outcome data. 1 study had unclear risk of other bias.

[e]2 of 6 studies showed unclear potential risk of bias related to random sequence generation. 1 study showed unclear potential risk of bias related to allocation concealment. 4 of 6 studies showed potential risk of bias related to blinding. 3 of 6 studies showed unclear risk of bias related to incomplete outcome data.

[f]5 of 12 studies showed unclear potential risk of bias related to random sequence generation. 6 of 12 studies showed unclear risk of bias related to allocation concealment. 7 of 12 studies showed possible risk of bias related to blinding procedures. 1 study showed potential risk of bias related to incomplete data, and 3 of 12 studies were unclear risk of bias. 1 study had potential risk of bias related to selective reporting.

[g]3 of 8 studies showed unclear risk of bias related to random sequence generation. 1 study showed potential risk of bias related to allocation concealment, 2 of 8 studies showed unclear risk of bias. 4 of 8 studies showed potential risk of bias related to blinding procedures, 1 study showed unclear risk of bias. 3 of 8 studies showed unclear risk of bias related to incomplete data.

[h]Inconsistency with results, statistical heterogeneity>50%

Incomplete outcome data may have been biased in 1 study, an unclear in 3 of the 10 studies. Selective reporting may have been biased in 1 study.
Downgraded by 1 due to 95% confidence intervals including no effect, and the upper or lower confidence intervals limit crosses an effect size of 0.5 in either direction.

[c]1 study had possible risk of bias related to random sequence generation, and in 5 of 19 studies this was unclear. Allocation concealment was potentially biased in 1 study, and unclear in 6 of 19 studies. Blinding was a potential source of bias in 7 studies. Incomplete outcome data may have biased 2 of 19 studies and was unclear in 6 of 19 studies. Selective reporting may have been bias in 1 study. May have been other sources in of bias in 1 study and unclear in 1 study.
[d]All or nearly all of the studies used a list-learning task as an objective measure of verbal memory, which has poor ecological validity.
[f]5 of 16 studies showed unclear potential risk of bias related to random sequence generation. 6 of 16 studies showed unclear potential risk of bias related to allocation concealment. 7 of 16 studies showed potential risk of bias related to blinding. 1 study showed potential risk of bias related to incomplete outcome data, 4 of the 16 studies showed unclear risk of bias. May have other source of bias in 1 study.

[h]5 of 12 studies showed unclear potential risk of bias related to random sequence generation. 6 of 12 studies showed unclear risk of bias related to allocation concealment. 7 of 12 studies showed possible risk of bias related to blinding procedures. 1 study showed potential risk of bias related to incomplete data, and 3 of 12 studies were unclear risk of bias. 1 study had potential risk of bias related to selective reporting.

[j]5 of 15 studies showed unclear risk of bias related to random sequence generation. 6 of 15 studies showed unclear risk of bias related to allocation concealment. 8 of 15 studies showed potential risk of bias related to blinding procedures. 2 of 15 studies showed potential risk of bias related to blinding procedures, and 3 of 15 were unclear risk of bias. 1 study showed potential risk of bias related to incomplete data. 1 study showed potential risk of bias related to other bias.

[l]2 of 5 studies showed unclear risk of bias related to random sequence generation. 1 study showed potential risk of bias related to allocation concealment, 1 study showed unclear risk of bias. 3 of 5 studies showed potential risk of bias related to blinding procedures, 1 study showed unclear risk of bias. 1 study showed potential risk of bias related to incomplete data, 1 study showed unclear risk of bias. 1 study showed potential risk of bias related to selective reporting.

[m]2 of 16 studies showed potential risk of bias related to random sequence generation, 3 of 16 studies showed unclear risk. 1 study showed potential risk of bias relating to allocation concealment, 6 of 16 studies showed unclear risk of bias. 5 of 16 studies showed potential risk of bias relating to blinding procedures. 3 of 16 studies showed potential risk of bias relating to incomplete data, 3 of 13 studies showed unclear risk of bias. 1 study showed potential risk of bias relating to selective reporting. 1 study showed potential risk of bias relating to other bias.

[o] 1 study showed unclear risk of bias related to random sequence generation, blinding procedures, and incomplete outcome data, as well as high risk of bias relating to allocation concealment. 1 study showed high risk of bias relating to blinding procedures, incomplete data, and selective reporting.

Appendix D: Sensitivity analysis systematic review.

Table 20 Sensitivity analysis systematic review.

Outcome	**No. of studies**	**No. of participants**	**Effect size SMD (95% CI)**	**Heterogeneity (I^2)**	**Test for overall effect**
Subjective memory - immediate	2	E = 127 C = 117	0.03 [-0.24, 0.31]	10%	Z = 0.22 (P = 0.82)
Subjective memory - intermediate	6	E = 396 C = 343	0.25 [0.11, 0.40]	0%	Z = 3.39 (P = 0.0007)
Subjective memory - longer-term	4	E = 325 C = 294	0.19 [0.03, 0.36]	0%	Z = 2.33 (P = 0.03)
Verbal memory - immediate	5	E = 100 C = 96	0.72 [0.24, 1.19]	59%	Z = 2.96 (P = 0.003)
Verbal memory - intermediate	2	E = 254 C = 209	0.22 [0.03, 0.40]	0%	Z = 2.32 (P = 0.02)
Verbal memory - longer-term	N/A				
Visual memory - immediate	5	E = 100 C = 94	0.27 [-0.01, 0.56]	0%	Z = 1.86 (P = 0.06)
Visual memory - intermediate	2	E = 251 C = 209	-0.11 [-0.29, 0.08]	0%	Z = 1.14 (P = 0.25)
Visual memory - longer-term	N/A				
Working memory - immediate	2	E = 49 C = 42	0.46 [-0.68, 1.59]	84%	Z = 0.79 (P = 0.43)
Working memory - intermediate	4	E = 284 C = 236	-0.06 [-0.28, 0.15]	11%	Z = 0.59 (P = 0.56)
Working memory - longer-term	2	E = 229 C = 193	-0.02 [-0.21, 0.17]	0%	Z = 0.18 (P = 0.86)
Information processing - immediate	4	E = 131 C = 120	0.29 [-0.04, 0.62]	40%	Z = 1.72 (P = 0.05)
Information processing - intermediate	4	E = 294 C = 245	0.02 [-0.14, 0.19]	0%	Z = 0.28 (P = 0.78)

Information processing - longer-term	N/A				
Depression - immediate	4	E = 93 C = 87	0.55 [0.03, 1.07]	65%	Z = 2.07 (P = 0.04)
Depression - intermediate	6	E = 392 C = 350	0.29 [-0.10, 0.67]	79%	Z = 1.45 (P = 0.15)
Depression - longer-term	4	E = 328 C = 270	0.14 [-0.20, 0.48]	63%	Z = 0.80 (P = 0.42)
Anxiety - immediate	N/A				
Anxiety - intermediate	3	E = 257 C = 214	0.29 [0.11, 0.48]	0%	Z = 3.11 (P = 0.002)
Anxiety - longer-term	3	E = 255 C = 193	0.27 [-0.12, 0.65]	43%	Z = 1.37 (P = 0.17)
Quality of life - immediate	4	E = 101 C = 96	0.49 [0.06, 0.91]	54%	Z = 2.25 (P = 0.02)
Quality of life - intermediate	5	E = 340 C = 317	0.31 [-0.01, 0.62]	64%	Z = 1.90 (P = 0.06)
Quality of life - longer-term	3	E = 295 C = 259	0.12 [-0.05, 0.30]	5%	Z = 1.37 (P = 0.17)
Activities of daily living - immediate	N/A				
Activities of daily living - intermediate	2	E = 100 C = 86	-0.13 [-0.60, 0.33]	37%	Z = 0.56 (P = 0.57)
Activities of daily living - longer-term	2	E = 100 C = 86	-0.33 [-0.63, -0.03]	0%	Z = 2.18 (P = 0.03)

E: Experimental; **C:** Control; **SMD:** Standardised mean difference.

Xx

Appendix E: Letter of approval Health Research Authority

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Roshan das Nair
Institute of Mental Health
University of Nottingham
Nottingham
NG7 2TU

Email: approvals@hra.nhs.uk

10 May 2022

Dear Professor das Nair

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Determining Who Benefits Most from Cognitive Rehabilitation for Attention and Memory in Multiple Sclerosis: A Randomised Controlled Feasibility Trial**
IRAS project ID:	**293754**
Protocol number:	**21063**
REC reference:	**22/EM/0051**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **293754**. Please quote this on all correspondence.

Yours sincerely,
Michelle Ahmed

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Angela Shone*

Appendix F: Derby REC favourable opinion letter



East Midlands - Derby Research Ethics Committee
Equinox House
City Link
Nottingham
NG2 4LA

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 May 2022

Professor Roshan das Nair
Institute of Mental Health
University of Nottingham
Nottingham
NG7 2TU

Dear Professor das Nair

Study title:	**Determining Who Benefits Most from Cognitive Rehabilitation for Attention and Memory in Multiple Sclerosis: A Randomised Controlled Feasibility Trial**
REC reference:	**22/EM/0051**
Protocol number:	**21063**
IRAS project ID:	**293754**

Thank you for your letter of 21 April 2022, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: Research registration and research project identifiers).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at:
https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 293754	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



Mrs Janet Mallett
Chair

Email:derby.rec@hra.nhs.uk

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: Ms Angela Shone

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of materials calling attention of potential participants to the research [Recruitment Poster]	1.0	30 November 2021
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Letter]	1.0	26 July 2021
GP/consultant information sheets or letters [Letter of Notification to GP/Neurologist]	1.0	30 November 2021
Interview schedules or topic guides for participants [Interview Schedule]	1.0	30 November 2021
IRAS Application Form [IRAS_Form_04022022]		04 February 2022
IRAS Application Form XML file [IRAS_Form_04022022]		04 February 2022
IRAS Checklist XML [Checklist_25042022]		25 April 2022
Letter from funder [Letter from funder]	1.0	19 October 2019
Letter from sponsor [Letter from sponsor]	1.0	09 December 2021
Letters of invitation to participant [Letter of Invitation]	2.0	31 March 2022
Other [Supervisor CV]	1.0	18 February 2022
Other [Ethical Review Further Information_Responses]	2.0	21 April 2022
Participant consent form [Consent Form]	3.0	21 April 2022
Participant consent form [Consent Form Interviews]	3.0	21 April 2022
Participant information sheet (PIS) [Participant Information Sheet]	3.0	21 April 2022
Participant information sheet (PIS) [Relative Participant Information Sheet]	3.0	21 April 2022
Research protocol or project proposal [Research Protocol]	2.0	31 March 2022
Summary CV for Chief Investigator (CI) [CV Chief Investigator]	1.0	30 November 2021
Summary CV for student [CV Student]	1.0	30 November 2021
Summary CV for supervisor (student research) [CV Supervisor]	1.0	30 November 2021
Validated questionnaire [Participant Questionnaires]	2.0	31 March 2022
Validated questionnaire [Relative Questionnaires]	2.0	31 March 2022
Validated questionnaire [Participant Outcome Measures]	1.0	31 March 2022

Appendix G: Participant information sheet



University of Nottingham
UK | CHINA | MALAYSIA

Local Letterhead to be added

Participant Information Sheet
(Final version 3.0: 21 April 2022)

IRAS Project ID: 293754

Title of Study: Who benefits most from cognitive rehabilitation? A feasibility trial.

Name of Chief Investigator: Professor Roshan das Nair
Local Researcher(s): Lauren Taylor

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will be available to answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

Many people with MS have trouble with attention, concentration, and memory. These cognitive difficulties can have detrimental effects on quality of life. It can be frustrating when your cognitive difficulties go unnoticed by those around you or when you are struggling to find the right word during a conversation. It can also be challenging when you are having difficulty focusing on something due to information overload such as when multiple people are talking at once.

Cognitive rehabilitation is a structured approach to improving these problems, but currently we do not know who benefits most from this intervention. The aim of this study is to compare two groups: an online group-based cognitive rehabilitation programme with people with MS (intervention group), and usual clinical care (control group). We have developed a computer programme that may be able to predict which people are most likely to benefit from cognitive rehabilitation, but at this point we do not know how effective it is. If effective, this programme would allow cognitive rehabilitation to be offered on the NHS, as clinicians will be able to see whether an individual is likely to benefit before it is offered.

We will recruit participants with a range of characteristics that we think could make someone more or less likely to benefit from cognitive rehabilitation. We will also evaluate whether the online group-based cognitive rehabilitation is acceptable for people with MS who have cognitive difficulties. We will also test the feasibility and consider if a bigger study could be conducted to assess the effectiveness of this rehabilitation in reducing memory and attention problems as well as improving overall mood and quality of life.

Why have I been invited?

You are being invited to take part because you have MS and have reported experiencing problems with your cognition. We are asking people with MS who are aged between 18 and 70, who have experienced cognitive difficulties to take part in this study. We are inviting 36 participants like you to take part.

Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and a consent form and be asked to confirm you are happy for us to send out the required questionnaires to complete. You will then be asked to give verbal consent for us to arrange an initial assessment. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

Before the trial

A member of the research team will contact you by telephone to go over the information sheet, explain the procedures, and answer any questions that you may have about the study. If you are still interested, the researcher will arrange an appointment for an **initial assessment** and ask that you complete and return the consent form to us via email before this assessment. You will need access to your own laptop or mobile phone to take part in this study. These initial assessments are needed to see whether you would be suitable to take part in the study. This will include questions about you, your cognitive difficulties (e.g., memory, thinking, attention, information processing) and how MS is affecting your daily life. This first appointment will take approximately up to two hours and will take place online using a video conferencing software, used for virtual meetings (MS Teams). Do not worry if you have never used this before as detailed instructions will be provided. Your medical records will be accessed to confirm your MS diagnosis, including the type of MS and date of diagnosis. Your medical notes will only be accessed if they are needed to confirm your diagnosis.

If it is determined that **you are not suitable** to take part in the study, we will let you know via letter or email, and we will also provide a brief report of your assessment results if you would like one.

If it is determined that **you are suitable** to part in the study, we will let you know via email or phone and a second visit will be arranged at a time convenient for you.

Before the second visit you will be given questionnaires to assess your memory problems, level of fatigue, general health and the impact MS has on your daily life to complete at home. They will take approximately 30 minutes to complete and will be emailed or posted to you depending on your preferences. You will need to complete these online or post them back to us before your second visit. We will also send a copy for a relative/friend to complete on your behalf. During this assessment, you will be given some tasks to complete with the researcher. These are designed to assess the current level of your cognitive functioning and you will be asked some questions which aim to assess your quality of life.

These assessments are important as they allow us to understand the current level of your cognitive difficulties so that we can see whether these improve later in the study. This second visit is called a **baseline visit** and will take approximately one and a half hours.

There may be a short waiting period while we recruit other participants, but the researcher will remain in contact with you during this time. When we have enough participants, we will then randomly allocate you to the intervention group to receive the cognitive rehabilitation or the control group to receive your usual care only (purely by chance); this process is called **randomisation**. Neither you nor the researcher will be able to choose what group you are allocated to.

Due to the Covid-19 pandemic, all assessment visits and rehabilitation sessions will be conducted online via video conferencing (MS Teams).

During the trial

Allocated to usual care group?
You will not have to do anything until the 3-month follow-up point.

Allocated to the intervention group?
You will be invited to attend 10 online group-based cognitive rehabilitation sessions lasting 1.5 hours each which will take place over 10 weeks.

All the groups will be asked to repeat the assessments completed at baseline asking you about your memory problems, level of fatigue, general health and the impact MS has on your daily life during follow-up visits at 3 and 6 months after your randomisation. These visits will last approximately one and a half hours each and will be booked in by the research team shortly after randomisation has occurred. A week or so before each appointment we will send you an appointment reminder. This will also include questionnaires to complete before your appointment (the same ones you completed for the baseline assessment). The time required to complete the questionnaires is around 30 minutes.

Group sessions will take place via MS Teams. A link will be sent via email to enable you to access the group, along with clear instructions. The sessions will be recorded to check how the intervention is delivered and to help us better understand the components of the cognitive rehabilitation that people may found to be more beneficial. If you do not want to be recorded, you can indicate this in the initial assessment. This decision will not affect your ability to take part in the study. However, your first name whilst being spoken to is the only personal detail that will be mentioned in the sessions. We may use these videos for training purposes in the future.

The cognitive rehabilitation sessions will include strategies to retrain attention and memory functions (including those to improve memory encoding and retrieval); strategies to teach you internal aids (such as sorting a list into categories or using rhymes to help you remember), use external devices and other ways of coping with memory and attention problems; and will teach the importance of 'errorless learning' (the importance of not making errors while learning new material). The emphasis will be on finding the most appropriate strategies for you to overcome your cognitive difficulties, and to provide you with a range of techniques which you can adapt to suit you and your lifestyle. Homework assignments will be set at the end of each session to help you practise your newly learnt techniques and these will be reviewed at the start of the next session.

After the trial

At the follow-up appointments you will meet a different member of the research team, who will complete the assessments. It is important that this researcher does not know to which group you were randomised, so you will be asked not to discuss your experiences with them.

Some participants will be invited to give feedback interviews to explore their experiences of being in the study. This will give us information about your view of the intervention and current care. The interviews will take place between the 3- and 6-month follow-up visits and will be audio recorded. The interviews will take place over the phone. They will last approximately 30 minutes to one hour. We may contact you to take part in these interviews, unless you have indicated that you prefer that we do not. Interview recordings will be sent to an external company for transcription (meaning they will type out the interview word for word). The company will have a duty of confidentiality to you as a research participant. An appropriate confidentiality agreement will be in place. We will remove any names of people (including your own name) or services transcription so that you cannot be identified in anything that is said.

Expenses and payments

Participants will not be paid an inconvenience allowance to participate in the study.

What are the possible disadvantages and risks of taking part?

It is not anticipated that your participation in this study will cause you any harm or risk. However, talking about experiences and issues associated with cognitive problems can occasionally be upsetting. If this happens, our researchers are trained to help make you feel as comfortable as possible. You will also have their contact information in case you may become upset after the sessions or interview for reasons associated with your participation. As you will have a friend or relative completing a questionnaire about their view of your cognitive difficulties, it is possible that there may be some differences in the responses given by you and by them about your cognitive difficulties. This may cause some potential distress to you that you will need to be prepared for. It is important to understand that the interview, support sessions and any other aspect of your involvement can stop at any time if you do not wish to continue.

We appreciate that taking part will use your time, and that it may inconvenience you to be available at a specific time during the day to join the intervention sessions, but we will ensure the sessions take place at a time that works best for you.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help people with MS in the future. The information we get from this study may help us decide whether to develop the online group-based cognitive rehabilitation further in the hope of providing a clinical prediction tool that can determine whether a person with MS is likely to benefit from cognitive rehabilitation or not, therefore, allowing this intervention to be offered on the NHS and targeted to those most likely to benefit.

What happens when the research study stops?

Once we collect all the information we need, the research study will stop, and you will not be asked to do anything else for the study. We will then analyse the data obtained from all our participants using appropriate methods to understand the given information in a meaningful way. We will write a summary of our findings in our newsletter and will send you a copy of this to you. We will, therefore, seek your consent to hold your contact details to send a copy of this newsletter.

During and after the study, you will keep receiving your usual care.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting 0800 183 0204 or PALS@nuh.nhs.uk.

In the event that something does go wrong, and you are harmed during the research, and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you and your medical records during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security), and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at:

https://www.nottingham.ac.uk/utilities/privacy.aspx.

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant.

Where possible, information about you which leaves the hospital will have your name and address removed and a unique code will be used so that you cannot be recognised from it.

Your contact information will be kept by the University of Nottingham so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time, your data will be disposed of securely. During this time, all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's, and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information, we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

Although what you say to us is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons e.g., your GP.

What will happen if I don't want to carry on with the study?

Your participation is voluntary, and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw, we will no longer collect any information about you or from you, but we will keep the information about you that we have already obtained as this information may have already been used in some analyses and may still be used in the final study analyses. To safeguard your rights, we will use the minimum personally identifiable information possible.

Involvement of the General Practitioner/Family doctor (GP)

We will inform your GP/Neurologist that you are participating in this study as this is standard practice, unless you specifically request that we not do this. Your involvement in this study will be noted in your MS clinic case notes.

What will happen to the results of the research study?

The information from this study may help us to understand whether a larger version of this study will be feasible which would then enable us to understand who may benefit most from cognitive rehabilitation. This would allow us to offer this treatment to those most likely to benefit, as currently it is not provided on the NHS due to lack of resources. The findings may be published in scientific journals, and presented to scientific audiences, people with MS (e.g., MS Life Conference), policy makers, healthcare networks, relevant organisations, and stakeholders. We will also publish a summary of the results in our newsletter when the study is finished. If you ask the researcher, we would be happy to send you a copy of the results when they are available. The results of this study will also be used by Lauren Taylor as part of her PhD thesis.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the MS Society UK.

Who has reviewed the study?

All research in healthcare is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Health Research Authority [East Midlands – Derby Research Ethics Committee] Research Ethics Committee (Reference number: 22/EM0051) and the University of Nottingham Research Ethics Committee.

Further information and contact details

If you require any additional information or have any concerns, please contact:

Lauren Taylor
PhD Researcher
Mental Health & Clinical Neurosciences Unit
School of Medicine, University of Nottingham
A floor, Institute of Mental Health
Innovation Park, Triumph Road
Nottingham NG7 2TU
Email:
Lauren.Taylor@nottingham.ac.uk

Professor Roshan das Nair
Professor of Clinical Psychology & Neuropsychology
Mental Health & Clinical Neurosciences Unit
School of Medicine, University of Nottingham
B19, Institute of Mental Health
Innovation Park, Triumph Road
Nottingham NG7 2TU
Phone: 0115 8230589
Email: Roshan.dasnair@nottingham.ac.uk

Patient advice and liaison services (PALS): Nottingham University Hospitals NHS Trust:

Phone: 0800 1830204
Address: Derby Road, Nottingham, Nottinghamshire, NG7 2UH (The PALS centre at QMC can be found on B Floor near the Main Entrance)
Email: pals@nuh.nhs.uk

Thank you for taking the time to read this information sheet and to consider this study.

Appendix H: Recruitment poster



Appendix I: Consent form for feasibility RCT.

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CONSENT FORM
(Final version 3.0: date 21/04/2022)

Title of Study: Who benefits most from cognitive rehabilitation? A feasibility trial

IRAS Project ID: 293754

Name of Chief Investigator: Prof Roshan das Nair
Name of Researcher: Lauren Taylor

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 3.0 dated 21/04/2022 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far will not be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. Consent for storage and use in possible future research (Optional)
   I agree that the information gathered about me can be stored by the University of Nottingham, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any data used will be anonymised, and I will not be identified in anyway. **Yes** ☐ **No** ☐
5. I consent to the online cognitive rehabilitation being video and audio recorded. I understand that these recordings may be reviewed by members of the research team and used for training purposes in the future. I understand that no person identifiable data will be used during these sessions apart from first names when being spoken to. **Yes** ☐ **No** ☐
6. (*if no to above*) I consent to the online cognitive rehabilitation being audio recorded. I understand that these recordings may be reviewed by member of the research team and used for training purposes in the future. I understand that no person identifiable data will be used during these sessions apart from first names when being spoken to. **Yes** ☐ **No** ☐
7. I consent for my contact details to be retained for up to 12 months for the purposes of sending me a summary of the results of this study. ☐

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	Yes	No
8. I consent for my GP/Neurologist to be contacted and informed of my participation in this study.	☐	☐
9. I understand that anything I say during the assessments and intervention sessions will remain confidential. However, I also understand that if I disclose something that the researcher feels puts myself or others at risk, this may be reported to the appropriate persons, e.g., my GP.		☐
10. I agree to take part in the above study.		☐

_____ _____ _____

Name of Person taking consent Date Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes (as apporporiate)

Appendix J: Brief Repeatable Battery of Neuropsychological Tests scoring forms.

APPENDIX A

TEST FORMS

SELECTIVE REMINDING TEST

FORM 1

Name:_____ Date:_____

	1	2	3	4	5	6	D
1. direction							
2. memory							
3. owner							
4. mountain							
5. victim							
6. city							
7. victory							
8. dream							
9. hotel							
10. wife							
11. virtue							
12. slave							

	1	2	3	4	5	6	Total
Long Term Storage							
Cons. Long Term Retrieval							
Number of Intrusions							

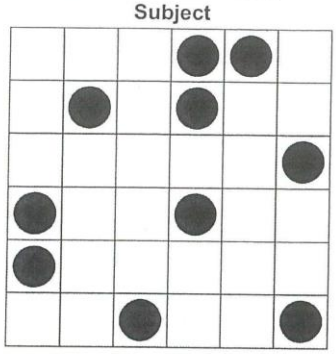
Total Delay ☐

10/36 Spatial Recall Test

Form 1

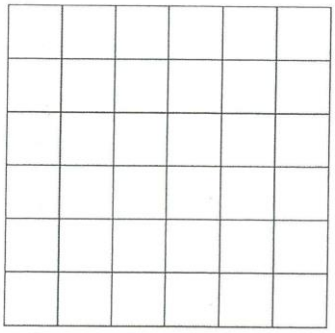
Name:_____ Date:_____

Subject



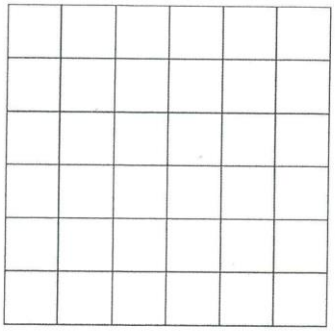
Examiner

Trial 1



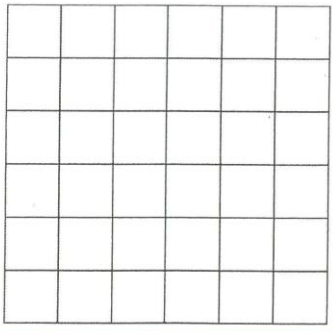
Number Correct ____
Number Intrusions ____

Trial 2



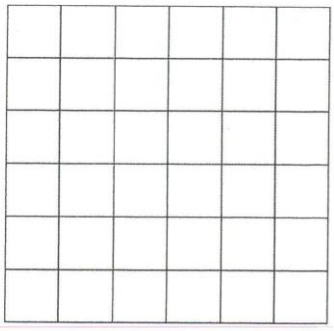
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Number Intrusions ____

Trial 3



Number Correct ____
Number Intrusions ____

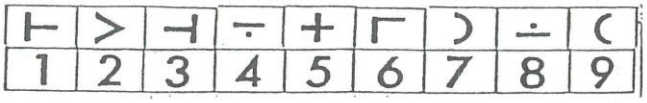
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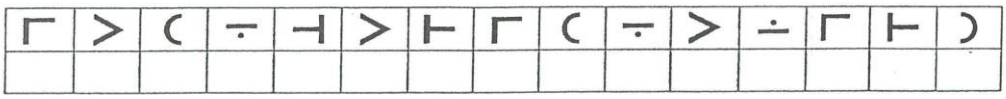
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Number Intrusions ____

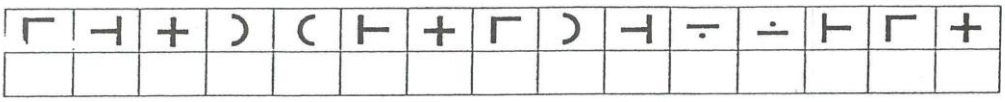
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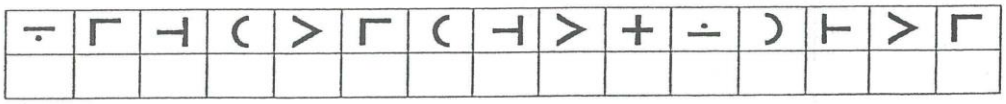
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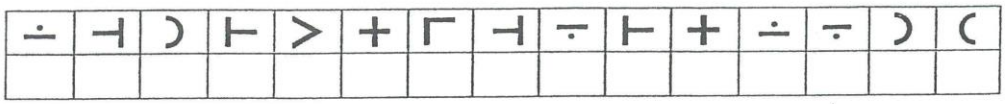


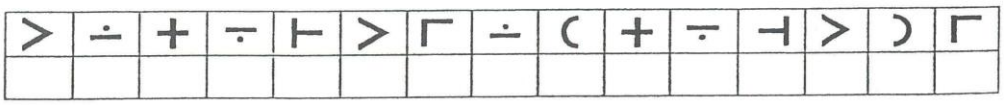


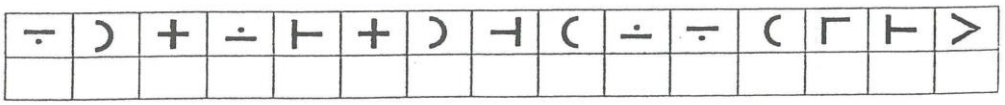


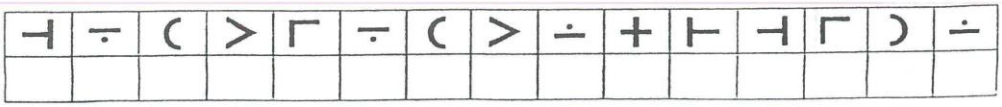












PASAT - Form A

Name_____ Date_____

PRACTICE

9+1	3	5	2	6	4	9	7	1	4
10__	4 __	8 __	7 __	8 __	10__	13__	16__	8 __	5 __

RATE #1
(3")

1+4	8	1	5	1	3	7	2	6	9
5 __	12__	9 __	6 __	6 __	4 __	10__	9 __	8 __	15__
4	7	3	5	3	6	8	2	5	1
13__	11__	10__	8 __	8 __	9 __	14__	10__	7 __	6 __
5	4	6	3	8	1	7	4	9	3
6 __	9 __	10__	9 __	11__	9 __	8 __	11__	13__	12__
7	2	6	9	5	2	4	8	3	1
10__	9 __	8 __	15__	14__	7 __	6 __	12__	11__	4 __
8	5	7	1	8	2	4	9	7	9
9 __	13__	12__	8 __	9 __	10__	6 __	13__	16__	16__
3	1	5	7	4	8	1	3	8	2
12__	4 __	6 __	12__	11__	12__	9 __	4 __	11__	10__

Total Correct (raw) = _____ Percent Correct = _____

PRACTICE

3+8	2	7	9	1	8	5	2	6	4
11__	10__	9 __	16__	10__	9 __	13__	7 __	8 __	10__

RATE #2
(2")

4+3	7	2	5	1	8	6	9	1	7
7 __	10__	9 __	7 __	6 __	9 __	14__	15__	10__	8 __
9	4	6	3	5	8	1	6	2	7
16__	13__	10__	9 __	8 __	13__	9 __	7 __	8 __	9 __
5	9	4	5	2	6	4	8	3	5
12__	14__	13__	9 __	7 __	8 __	10__	12__	11__	8 __
9	7	4	2	8	5	2	1	6	4
14__	16__	11__	6 __	10__	13__	7 __	3 __	7 __	10__
7	3	5	9	6	4	5	3	9	4
11__	10__	8 __	14__	15__	10__	9 __	8 __	12__	13__
1	8	3	1	6	8	5	4	2	6
5 __	9 __	11__	4 __	7 __	14__	13__	9 __	6 __	8 __

Total Correct (raw) = _____ Percent Correct = ___

Appendix K: Questionnaire pack

Final version 1.0 27Mar2023

Welcome!

Thank you for choosing to participate in our study.

You will now be asked to complete a total of seven questionnaires, some are quite short and others are longer. You will find a number at the top of the page next to the questionnaire title which indicates how many questions there are.

Please try to complete all of the questionnaires in one sitting if you can. However, if you find that you're getting quite fatigued then please finish the questionnaire you are on and close down the browser. If you then email me to let me know you've only been able to partially complete the questionnaires, I can then send you a new link which will take you to where you left off and you can complete the rest of the questionnaires on another day when you are feeling better.

If you have any queries, please contact the research team at Lauren.Taylor@nottingham.ac.uk

Multiple Sclerosis Impact Scale (MSIS-29)

The following questions ask for your views about the impact of MS on your day-to-day life during the past two weeks.

For each statement, please check the one box that best describes your situation.

Please answer all questions.

In the past two weeks how much has your MS limited your ability to...

1) Do physically demanding tasks?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks how much has your MS limited your ability to...

2) Grip things tightly (e.g., turning on taps)?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks how much has your MS limited your ability to...

3) Carry things?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

4) Problems with your balance?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

5) Difficulties moving about indoors?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

6) Being clumsy?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

7) Stiffness?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

8) Heavy arms and/or legs?
- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

9) Tremor of your arms or legs?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

10) Spasms in your limbs?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

11) Your body not doing what you want it to do?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

12) Having to depend on others to do things for you?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

13) Limitations in your social and leisure activities at home?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

14) Being stuck at home more than you would like to be?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

15) Difficulties using your hands in everyday tasks?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

16) Having to cut down the amount of time you spend on work or other daily activities?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

17) Problems using transport (e.g., car, bus, train, taxi, etc)?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

18) Taking longer to do things?

- ○ Not at all
- ○ A little
- ○ Moderately
- ○ Extremely

In the past two weeks, how much have you been bothered by...

19) Difficulty doing things spontaneously (e.g., going out on the spur of the moment)?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

20) Needing to go to the toilet urgently?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

21) Feeling unwell?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

22) Problems sleeping?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

23) Feeling mentally fatigued?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

24) Worries related to your MS?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

25) Feeling anxious or tense?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

26) Feeling irritable, impatient, or short-tempered?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

27) Problems concentrating?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

28) Lack of confidence?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

In the past two weeks, how much have you been bothered by...

29) Feeling depressed?

- ◯ Not at all
- ◯ A little
- ◯ Moderately
- ◯ Extremely

Everyday Memory Questionnaire 30-Participant

There are two sections to this questionnaire.

Section 1

Below are listed some examples of things that happen to people in everyday life. Some of them may happen frequently and some may happen very rarely. We would like to know how often on average you think each one has happened to you over the past month. For each item, tell us if you forgot it:

Once or less in the last month/ never
More than once a month but less than once a week
About once a week
More than once a week but less than once a day
Once or more a day

Please click one box for each item.

1)	Forgetting where you have put something. Losing things around the house.	◯ One or less in the last month/never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ One or more a day
2)	Failing to recognise places that you are told you have often been to before.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
3)	Finding a television story difficult to follow.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
4)	Not remembering a change in your daily routine, such as a change in the place where something is kept, or a change in the time something happens. Following your old routine by mistake.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
5)	Having to go back and check whether you have done something that you meant to do.	◯ One or less in the last month/never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ One or more a day
6)	Forgetting when it was that something happened; for example, whether it was yesterday or last week.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
7)	Completely forgetting to take things with you, or leaving things behind and having to go back and fetch them.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day

8)	Forgetting that you were told something yesterday or a few days ago, and maybe having to be reminded about it.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
9)	Starting to read something (a book or an article in a newspaper, or a magazine) without realising you have already read it before.	◯ One or less in the last month/never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ One or more a day
10)	Letting yourself ramble on to speak about unimportant or irrelevant things.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
11)	Failing to recognise, by sight, close relatives or friends that you meet frequently.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
12)	Having difficulty picking up a new skill. For example, finding it hard to learn a new game or to work some new gadget after you have practised once or twice.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
13)	Finding that a word is 'on the tip of your tongue'. You know what it is but you cannot quite find it.	◯ One or less in the last month/never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ One or more a day
14)	Completely forgetting to do things you said you would do, and things you planned to do.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
15)	Forgetting important details of what you did or what happened to you the day before.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
16)	When talking to someone, forgetting what you have just said. Maybe saying 'what was I talking about?'.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
17)	When reading a newspaper or magazine being unable to follow the thread of a story; losing track of what it is all about.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day

18)	Forgetting to tell somebody something important. Perhaps forgetting to pass on a message or remind someone of something.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
19)	Forgetting important details about yourself, e.g., your birth date or where you live.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
20)	Getting details of what someone has told you mixed up and confused.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
21)	Telling someone a story or joke that you have already told them once already.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
22)	Forgetting details of things you do regularly, whether at home or at work. For example, forgetting details of what to do, or forgetting at what time to do it.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
23)	Finding the faces of famous people seen on television or in photographs, look unfamiliar.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
24)	Forgetting where things are normally kept or looking for them in the wrong place.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
25)	Getting lost or turning in the wrong direction on a journey, on a walk or in a building where you have OFTEN been before.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
26)	Getting lost or turning in the wrong direction on a journey, on a walk or in a building where you have ONLY BEEN ONCE OR TWICE before.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day
27)	Doing some routine thing twice by mistake. For example, putting two lots of tea in the teapot, or going to brush/ comb your hair when you have just done so.	◯ Once or less in the past month / Never ◯ More than once a month but less than once a week ◯ About once a week ◯ More than once a week but less than once a day ◯ Once or more a day

28) Repeating to someone what you have just told them or asking them the same question twice.

- ◯ One or less in the last month/never
- ◯ More than once a month but less than once a week
- ◯ About once a week
- ◯ More than once a week but less than once a day
- ◯ One or more a day

EuroQol Five Dimension

Under each heading, please tick the ONE box that best describes your health TODAY.

Please select the ONE box that best describes your health TODAY.

1) MOBILITY

- ◯ I have no problems in walking about
- ◯ I have slight problems in walking about
- ◯ I have moderate problems in walking about
- ◯ I have severe problems in walking about
- ◯ I am unable to walk about

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Please select the ONE box that best describes your health TODAY.

2) SELF-CARE

- ◯ I have no problems washing or dressing myself
- ◯ I have slight problems washing or dressing myself
- ◯ I have moderate problems washing or dressing myself
- ◯ I have severe problems washing or dressing myself
- ◯ I am unable to wash or dress myself

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Please select the ONE box that best describes your health TODAY.

3) USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- ◯ I have no problems doing my usual activities
- ◯ I have slight problems doing my usual activities
- ◯ I have moderate problems doing my usual activities
- ◯ I have severe problems doing my usual activities
- ◯ I am unable to do my usual activities

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Please select the ONE box that best describes your health TODAY.

4) PAIN / DISCOMFORT

- ◯ I have no pain or discomfort
- ◯ I have slight pain or discomfort
- ◯ I have moderate pain or discomfort
- ◯ I have severe pain or discomfort
- ◯ I have extreme pain or discomfort

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Please select the ONE box that best describes your health TODAY.

5) ANXIETY / DEPRESSION

- ◯ I am not anxious or depressed
- ◯ I am slightly anxious or depressed
- ◯ I am moderately anxious or depressed
- ◯ I am severely anxious or depressed
- ◯ I am extremely anxious or depressed

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6) We would like to know how good or bad your health is TODAY.

You will see a scale numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.
Please indicate on the scale how your health is TODAY.

0 - The worst health you can imagine | 50 | 100 - The best health you can imagine

(Place a mark on the scale above)

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Fatigue Severity Scale 5

Below are a series of statements regarding your Fatigue. By Fatigue we mean a sense of tiredness, lack of energy or total body give-out. Please read each statement and choose a number from 1 to 7, where 1 indicates you completely disagree with the statement and 7 indicates you completely agree. Please answer the questions as they apply to the past TWO WEEKS.

Please select the number between 1 and 7 which you feel best fits the following statements.

1)	I am easily fatigued	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7	[Strongly disagree] [Strongly agree]
2)	Fatigue interferes with my physical functioning	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7	[Strongly disagree] [Strongly agree]
3)	Fatigue causes frequent problems for me	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7	[Strongly disagree] [Strongly agree]
4)	Fatigue interferes with me carrying out certain duties and responsibilities	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7	[Strongly disagree] [Strongly agree]
5)	Fatigue interferes with my work, family, or social life	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7	[Strongly disagree] [Strongly agree]

Appendix L: Consent form for feedback interviews

University of Nottingham
UK | CHINA | MALAYSIA

(Form to be printed on local headed paper)

CONSENT FORM FEEDBACK INTERVIEWS
(Final version 3.0: 21/04/2022)

Title of Study: Who benefits most from cognitive rehabilitation? A feasibility trial.

IRAS Project ID: 293754

Name of Chief Investigator: Prof Roshan das Nair

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 3.0 dated 21/04/2022 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far will not be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand that the interview will be recorded and that anonymous direct quotes from the interview may be used in the study reports. ☐
5. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐
6. I understand that anything I say during the feedback interviews will remain confidential. However, I also understand that if I disclose something that the researcher feels puts myself or others at risk, this may be reported to the appropriate persons, e.g., my GP. ☐
7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes (as apporporiate)

Appendix M: Semi-structured interview schedule

Who benefits most from cognitive rehabilitation? A feasibility trial

Participant Semi-structured Interview Guide

Final Version 1.0: date 30/11/2021

[Note: As per the methodology, the semi-structured interview is only a guide, and is necessarily an iterative process (i.e., it gets modified slightly after each interview, based on the information that participants provide).

Overview of cognitive difficulties:

1. Please can you tell me about the cognitive difficulties that you have experienced since your MS diagnosis?
2. Please can you tell me about any advice you received for managing your cognitive difficulties before the trial? (if any)
3. Have you received any treatment to manage your cognitive difficulties before you were recruited for the trial?
4. Please can you tell me about any changes to your cognitive problems that you've experienced in the last six months? (*if any*)

Online intervention:

5. How did you find the online format of the cognitive rehabilitation?
    a. Was the software easy to use?
    b. Were the instructions you were given useful?
    c. Did you feel you were given enough support throughout?
    d. Were you able to engage in discussions with other groups members during the rehabilitation sessions?
6. Do you think the online format of the rehabilitation impacted its effectiveness in any way, either positively or negatively?
7. Can you tell me about anything that would have improved your experience of being involved in the trial?
8. Would you recommend online group-based cognitive rehabilitation to someone else with MS?
9. Can you tell me about how the cognitive rehabilitation programme has impacted the way you manage your cognitive difficulties and your everyday life?
10. Can you tell me about the most important thing you feel you gained from the programme?
11. Is there anything you experienced during the programme that you perhaps did not expect?
12. Do you feel more confident in managing your cognitive difficulties now?
13. How did you find the psychologist that delivered your cognitive rehabilitation programme?

How variables affected their participation:

14. Did the severity of your MS affect your participation?
15. Did your cognitive problems affect your participation?
16. Has your lifestyle such as employment, family, etc affected your participation?

Closing:

17. Is there anything else that you would like to tell me about?

Appendix N: Summary of cognitive rehabilitation session example

Group 1: Cognition study sessions

Week one summary

This week's session was focused on introducing the programme to you all but more importantly, it was focused on introducing you all to each other.

We began by outlining how all the sessions are going to be structured:

- We will begin with a recap of the last session.
- We will then discuss the take home activity/start with some initial discussion topics.
- We will then move into the main areas to be focused on that week.
- We will have a 10/15-minute break in between
- We will finish with questions and an outline of that week's take home activity.

We then discussed the work booklet and how to use it. We noted down the dates of all upcoming sessions, these can be found on page 3 of the work booklet.

Following this we did introductions whereby everyone in the group, where everyone shared a little bit about themselves such as age, location, their MS journey, cognitive difficulties experienced and what they want to get out of the programme. I think that a key theme from these introductions was that most people could relate to the cognitive difficulties mentioned and there was a real sense of "I'm not alone, other people experience this too".

Things people wanted to get out of the sessions:

- Tips to help manage cognitive difficulties better on a day-to-day basis
- Help remembering where things are
- Looking to do as much as possible to maintain existing cognition
- Help remembering the names of people
- Help remembering conversations
- Help managing MS related stress
- Be a part of research into topics close to you

I then reiterated an important point made which was that one of the most valuable things about the sessions is being able to speak with people who are experiencing the same things you are, to share tips and strategies but also to share your stories and build these bonds and connections which are deeply meaningful.

We then discussed the aims of the programme which are listed on page 4 but in summary they include developing your own personal "toolbox" of strategies to help manage your cognitive difficulties as well as allow you to reflect on and share your experiences of cognitive difficulties. We then went over the structure of the next 9 weeks; this can be found on page 5. We then discussed the group rules, ensuring that we all agreed which are listed on page 8 but include being respectful when other people are speaking, respecting all opinions, and trying to attend as many sessions as possible.

Discussion topics

Sometimes I forget certain things, such as…

- Plots of books or films, a few people mentioned not being able to read anymore due to not being able to remember what they have previously read and no longer being able to watch a show tv each week due to forgetting what they've already watched so they now prefer to binge watch and even then, it can be tricky to remember the entire plot. Audiobooks were also mentioned as an alternative to reading due to struggling to concentrate on the page.
- Faces but not names, or names but not faces
- What you have previously mentioned in conversation, not knowing whether the point they were trying to make has been made so you just keep talking. Also mentioned here was often asking friend/family/colleagues is they've made sense or not.
- Second guessing yourself was also mentioned here, which could lead to some feelings of anxiety. Sometimes you know what you want to say but you've lost your train of thought and lost track of where you were in a conversation.

How do you feel when you are having difficulty with attention and memory?

- Invisible symptoms were mentioned during this discussion, people not believing that anything is wrong because they can't see it – this was someone that everyone seemed to relate to. One point mentioned here was that on the outside you may look fine, but in reality it has taken everyone in you to show up that day and not having this be acknowledged can hurt and raise negative feelings especially in relation to work. – a good analogy used here was like a duck or a swan so graceful and elegant on the surface but underneath they're paddling like crazy just to stay afloat.
- Frustration came up a lot here, one topic mentioned was being able to remember things from 10 or 20 years back but not being able to remember something that happened recently.
- Exasperation.

Strate*gies you've already put in place to help with cognitive difficulties.*

- Writing lists, always having pads of paper to hand to make notes on everything
- Using a calendar, both paper and digital
- Making a list of key points immediately following a meeting, also reviewing notes made during a meeting straight away to ensure you don't forget why you wrote something down.
- Dragon Speak which is a Dictaphone app to dictate notes and thoughts rather than writing them down.
- Work specific apps such as HubSpot which copies emails into a system so that can tasks and reminders can be added.
- Working from home to avoid distractions and allow multiple screens, as well as allowing you to have the set up that you want without affecting anyone else.
- Being honest with clients regarding cognitive issues so that expectations can be set from the beginning.
- At the end of the meeting, going over actions for everybody at the end together so that if you have missed something someone else could remember it and this also ensures that the actions are everyone's responsibility and not just you.
- 2 A4 sheets of paper, with AM and PM so that tasks for the day can be broken down clearly.
- Planners.

- Access to work – this can help with accommodations at work and can be especially helpful when you're not sure what sort of things you are entitled to.

Take-home activity

We finished by going over the take home activity which is to complete the table on table 14 of the work booklet. For this, if you could please write down any memory problems that you experience and then rank them 1 to 5 and then listing any strategies you already have in place to tackle them.

Appendix O: Example of framework matrix used in study

Table 21 Framework matrix example

	Management of cognition before trial		**Online format of intervention**		**Perceived cognitive changes**		**Perceived mechanism of change of cognitive function**		**Possible improvements**	
	Cognitive difficulties	Advice received	Effectiveness impacted	Experience	Improved	Everyday life impacted	Increased strategy use	Psychoeducation	Update memory aids	Additional content
01	I - I found at times I'd forget that I had meetings even though I had like my Teams calendar and stuff. So, I – I'd end up being late to some of those meetings.	No, no it's still something that isn't really acknowledged by the team really, it's it it's kind of dismissed.	I think I'm a person that that learns by getting up and about and doing things and moving around. So, I didn't necessarily kind of value that, but I could see that there's a lot of benefit.	I wasn't keen on it being online if I'm honest.	Yeah, I feel like I have got some options to try.	I don't feel entirely hopeless and despondent that that you know what I think the internal dialogue has changed from and I can't do this there's no point in doing this to let's see what tools I've got that I can I can try and see if it makes it makes it makes a difference if that makes sense and I think the other thing was.	Yeah, have you known the there's - there's several tools that that - that I use. I think one of the ones that that really stick out is kind of the 5W's and the H, when you're getting a lot of information.	And you know and I think it [the science behind the strategies] that was that was quite clear by the end of the programme that we gotta talk about it.		I think probably a few more visuals. I think it would have been helpful just to have more focus on kind of work based skills and like they were quite lifestyle tools really for kind of living your life.
02	And also multitasking, which is something that I did used to do a lot of in my work and now I	I don't think so.	I think the only thing that it impacted me negatively and I don't know whether this others have	I didn't have any problem at all with the explanation of what was required and the group		Yes, the visualisation. So that that certainly does help.	I think there are one or two that are stuck in my mind, others that I have to go back to the			

	have to concentrate on the one thing in hand and have a simple set of instructions to follow		experienced this - is it is just so frustrating when my links don't work.	tasks. We were very clearly spoken through them, yes.			workbook and remind myself.			
03	My ability to remember instructions and appointments is very, very unreliable now. You know, you couldn't say I'll see you in the pub Thursday night because unless it's written down, unless I use a prompt or whatever, I wouldn't be there.	No, not really.	I would say it was I could, I could put more energy into it, into the meeting. Which if it had been a face to face, I wouldn't have been able to. Yeah, it was good. That was nice.	I'm much more productive over this – sort of - format than I am travelling to go and see face to face, even when I'm travelling literally 5 miles down the road to a face to face that I'm finding more and more exhausting.	I'd like to think so, yeah. Yeah, I do. I do. I do think.	I've certainly taken some of the techniques away from it that I was surprised were so effective.	The things like grouping the things like making up a little story to remember things, categorising kind of knew about them already. But I hadn't realised how powerful they were and why they worked so well. So yes, I've most definitely taken a lot, but those are my key learning points from it.	The more I understand about an issue and the problem I'm having, once I've recognised it, once someone said, yeah, that's the issue that you've got. The more I understand it, the more it relaxes me, calms me down. I realise it's not that major deal and the more interested I get into it.		
04	I think last year I had a bit of a relapse; I think. I think and one of the things that came out of it is I just don't feel as sharp as	He said, ohh, yeah, there's some studies coming up. And that was kind of it really.	I'm quite biased because I work online anyway, think if it was, say, for me, it was easy because, and I think for	It was very positive and I think because you're all in the same boat everyone was quite open and		Yeah, there was some like you say, like the way she put it was the session is there going to be like a toolkit? So at the end of	There was the grouping together of things so like if you've got like 20, I don't know. Different	I like all of that and I said because my job and stuff I do like the like the theory behind things. So to me that was I like that bit of it. And I	And there was no sort of mention of like and like iPhones or anything like that in there. There was no	

	I did if that makes sense.		some of the other ladies it was easy too, because you just log on like now at like 2 minutes to 10 and you log off, you're done, aren't you?	you could really relate.		it you go away with like little ideas.	names and numbers and bits. Group them together into categories. Yeah, that's definitely helped work as well.	thought that's actually really interesting, and it makes sense that if I'm sort of listening.	mention of like Alexa or the artificial intelligence that you use. There was no mention of just all those kinds of things. You could tell the book was probably like 10 years, so out of date, say.	
05		The support that he gave me was like, ohh, I'm gonna speak to somebody and see what we can do for you.	Fabulous. It was for me to go anyway because I work from home which to me it's just like a godsend.	I know I'm home. I don't need to be commuting. So, it's fine. And it works for me. Um. So, if these things had to happen outside, I don't think I would have been able to participate. So, I think this, this is fab. Yeah. It's really good.	This has helped me improve and I have learned a lot with it.	I'm just quite, quite grateful that I participated in it and it was a really good experience. Yeah. And I'm taking a lot of tips with me from this session, which is really good and I use them and I'll carry on using them. So yeah, it did impact me in in in things that we use and even the day-to-day like I said.	I think the 5 W's and the H - I think that's what made me focus on the emails help me that their technique there. So that helped me there as well and just like focusing in on the little bits that I needed to do now like write the things.	So, I think it's just yeah I felt a bit better I felt more relieved and a bit more confident in myself that that OK. It's not just me and it's I'm all right. Yeah.		

06		No, no, I mean I think I may have read something on the MS Society, but that's it.	Yeah, I'm very comfortable on here. So it worked for me.	Yeah, yeah, yeah. I've got no problem with IT teams. So that that part of it absolutely fine and you know it was nice that we got to sort of know each other a bit and you know yeah that that that part was fine	Absolutely. Yeah, definitely.	So, it sounds silly but it's a bit life change. Names and faces - I, now, this doesn't sound much to you, but to me it is absolutely amazing. I now know the names of and faces of some of my neighbours.	I can now picture and remember names of faces and I know how to keep them in there. But that's, that's absolute vast improvement, you know.	Learning that so much of it was in my control that I'd given up but it was my attention, so I had to do more with this huge learning point. So, you know sort of you know those first few weeks were just learning.	I think we all said the book needs updating because it's not you know it's got things like Dictaphones and Filofax and stuff like that and then sort of her calendar and mobile phone and sort of they're integrated and so you need to yeah it needs updating with to the to the modern world.	we talked very much about learning stuff new and then and then putting it in and then and then remembering to retrieve it. But if it's already in there, you know something I've learnt? Retrieving all that stuff, that's the only thing that I don't think we covered

Appendix P: Recommendations for progression criteria during feasibility RCT.

Feasibility area	Progression to full trial
Recruitment	Amber
Randomisation	Green
Attrition	Green
Measures	Amber
Signal of efficacy	Green
Patient work booklet	Amber