A Randomised Controlled Trial of Efficacy of Cognitive Rehabilitation in Multiple Sclerosis:
A Cognitive, Behavioural and MRI Study.

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A thesis submitted in partial fulfilment of the requirements of the University of Brighton for the degree of Doctor of Medicine

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Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed:

Date:

Contribution to thesis:

The author was involved in the study design and ethics application. The author was solely responsible consenting participants to enter the study and in the acquisition of all subsequent cognitive and behavioural data.

Image acquisition was undertaken with the assistance of trained radiographers. All image analysis was performed by the author under the guidance of the primary supervisor.

Disclosures:

Dr Jamie Campbell has nothing to disclose and no financial or other interests in Hasomed plc who kindly provided the cognitive rehabilitation software for use in this study.

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Abstract

Background

Multiple sclerosis is the most common cause of non-traumatic disability in young adults. In addition to the physical disability associated with the condition there exists significant non-motor symptoms. Cognitive dysfunction in multiple sclerosis is common and presents significant morbidity for patients.

There is mounting evidence for neuroplasticity playing a role in limiting the functional impact of pathology in MS. However, the degree to which neuroplasticity can ameliorate the impact of cognitive dysfunction and the potential that exists for structured cognitive rehabilitation are largely unknown.

Aims

To explore the feasibility and efficacy of computerised, home-based cognitive rehabilitation in patients with multiple sclerosis using neuropsychological assessment and advanced structural and functional magnetic resonance imaging.

Methods

38 patients with MS and evidence of cognitive impairment as defined as scores below the 5th centile for normative data on the Brief International Cognitive Assessment for MS test battery were enrolled in an open-design randomised, controlled, exploratory trial of computerised cognitive rehabilitation. Neuropsychological and MRI data were obtained at baseline (time 1) as well as immediately following a 6-week intervention period (time 2) and after an addition twelve week follow up period (time 3). Changes in cortical activations were explored using a visual n-back fMRI paradigm and microstructural changes were explored using quantitative magnetisation transfer imaging.

Patients were randomly assigned to undergo 45-minutes of computerised cognitive rehabilitation (RehaCom software, n = 19) three times weekly for six weeks or to a control condition (natural history DVDs, n = 19).

Results

The n-back fMRI task was associated with robust cortical activations in known working memory networks. The spatial extent and magnitude of the activations were greater for the 2-back than the 1-back condition.

At time 3 significant increases in activation were seen in both the 1-back and 2-back conditions in the treatment group relative to controls. In the 1-back task, increased activation was seen in the left frontal and right temporo-parietal regions ($p<0.05$ $_{FWEcorr}$). In the more demanding 2-back task, there was increased activation in the bilateral prefrontal cortex and right temporoparietal regions relative to control group at time 2 ($p<0.05$ $_{FWEcorr}$). No significant changes were observed on quantitative magnetisation transfer imaging.

Compared to time 1, a significantly higher proportion of patients in the treatment group showed 10% or greater improvement in the Symbol Digits Modality Test (SDMT) at time 2 ($\chi2 = 0.008$) however no significant difference in cognitive performance was seen between the groups at time 3. Quality of life outcome measures did not significantly differ between the groups.

Conclusion

This study supports the hypothesis that home-based, computerised cognitive rehabilitation may be a feasible and effective approach to improving cognitive performance in patients with MS. The alterations in cortical activation in attention and executive centres are likely to represent more efficient neural processing. The changes at the microstructural level that underpin this adaptation may be beyond the resolution of current imaging techniques.

Improvements in quality of life as a result of cognitive rehabilitation may result from improved work place or social performance, which may occur over a longer timeframe. Quality of life outcome measures may need to be conducted over a longer period of follow up.

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List of Abbreviations

ADC	apparent diffusion coefficient
ARR	annualised relapse rate
BICAMS	brief international cognitive assessment for MS
BOLD	blood oxygen level dependent
BRBNT	brief repeatable battery of neuropsychological tests
BVMT-R	brief visuospatial memory test revised
CI	confidence interval
CIS	clinically isolated syndrome
CNS	central nervous system
CVLT-II	California Verbal Learning Test 2nd edition
DMT	disease modifying therapy
DTI	diffusion tensor imaging
DMN	default mode network
EDSS	expanded disability status scale
EQ-5D	EuroQol Group. Quality of Life Questionnaire.
f	macromolecular bound fraction
FA	fractional anisotropy
FAMS	functional assessment of multiple sclerosis
FLAIR	fluid attenuation inversion recovery
fMRI	functional magnetic resonance imaging
GA	glatiramer acetate
Gd	gadolinium diethylenetriaminepentaacetic acid
HADS	hospital anxiety and depression scale
HR	hazard ratio
IFN	interferon
K_f	forward exchange rate
MD	mean diffusivity
MPRAGE	magnetisation-prepared rapid gradient echo
MRI	magnetic resonance imaging
MRSI	magnetic resonance spectroscopic imaging
mSMT	modified Story Memory Technique
MS	multiple sclerosis

MSNQ	MS neuropsychological screening questionnaire
MTI	magnetization transfer imaging
MTR	magnetisation transfer ratio
NAA	N-acetylaspartic acid
NABT	normal appearing brain tissue
NAWM	normal appearing white matter
PAM-13	patient activation measure – 13 item
PET	position emission tomography
PASAT	paced auditory serial addition test
PVSAT	paced visual serial addition test
PPMS	primary progressive multiple sclerosis
QMT	quantitative magnetisation transfer
QOL	quality of life
R_a	longitudinal relaxation time
RCT	randomised clinical trial
RM-ANOVA	repeated measures analysis of variance
ROI	region(s) of interest
RRMS	relapsing remitting multiple sclerosis
RSN	resting state network
SD	standard deviation
SDMT	symbol digit modalities test
SPMS	secondary progressive multiple sclerosis
T_{2b}	T2 relaxation time of bound pool
USE-MS	unidimensional self-efficacy scale for MS
VBM	voxel-based morphometry
WCST	Wisconsin Card Sorting Test
WM	white matter
WMV	white matter volume

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Introduction

1.1 Background and introduction

1.1.1 Aims

This chapter serves to provide an overview of the current understanding of the pathophysiology of multiple sclerosis (MS) pertinent to this thesis. The clinico-cognitive features of the condition are discussed in detail.

1.1.2 Clinical subtypes of multiple sclerosis

Multiple sclerosis is a common inflammatory condition affecting the central nervous system (CNS). It is characterised by recurrent episodes of inflammation and demyelination which result in cumulative axonal injury, irreversible damage to brain tissue and accumulation of permanent disability [1]. MS is the most common cause of acquired, non-traumatic disability in young adults [2]. Overall the estimated lifetime risk of developing MS in the UK is 5.3 per 1000 in women and 2.3 per 1000 in men [3].

A number of subtypes with distinct clinical courses are recognised (figure 1.1). The most common subtype of MS is relapsing-remitting MS (RRMS) which affects approximately 80% of patients and is twice as common in women as men [1]. RRMS is characterised by recurrent episodes of distinct neurological symptoms (relapses) reflective of foci of inflammation at different sites within the CNS. There may be complete or partial recovery from these relapses. Relapses are followed by periods where the disease appears clinically quiescent (remissions). Eventually about 65-80% of patients with RRMS will enter a phase of progressively accumulating disability, which is largely independent of relapses and is referred to as secondary progressive multiple sclerosis (SPMS) [4].

The term "clinically isolated syndrome" (CIS) refers to the first clinical presentation of CNS inflammation. It is recognised that not all patients with a single episode of inflammation affecting the CNS will go on to develop further

episodes that define MS. If lesions are present at sites remote to the symptomatic lesion on magnetic resonance imaging (MRI), the chance of a second clinical attack increases to 80% at 20 years compared to 21% if no additional lesions are seen [5].

In approximately 15% of cases, the clinical course is progressive from the outset and is referred to as primary progressive MS (PPMS) [6]. There is some debate as to whether PPMS is a distinct disease as there are considerable demographic and pathological differences from RRMS [7-9]. The onset of PPMS is usually around the start of the 5th decade [10] with only a slight excess of women being affected [11]. Progressive relapsing MS is characterised by a progressive decline from the onset of the disease interspersed with discreet periods of clinical worsening from which there may only be partial recovery. Such phenotypes are based solely on a clinical basis. With a greater understanding of the pathophysiology of the condition, phenotyping that includes MRI and biomarkers may provide more precise descriptions and prognostic value [12].

Figure 1.1. Different Clinical Subtypes of Multiple Sclerosis
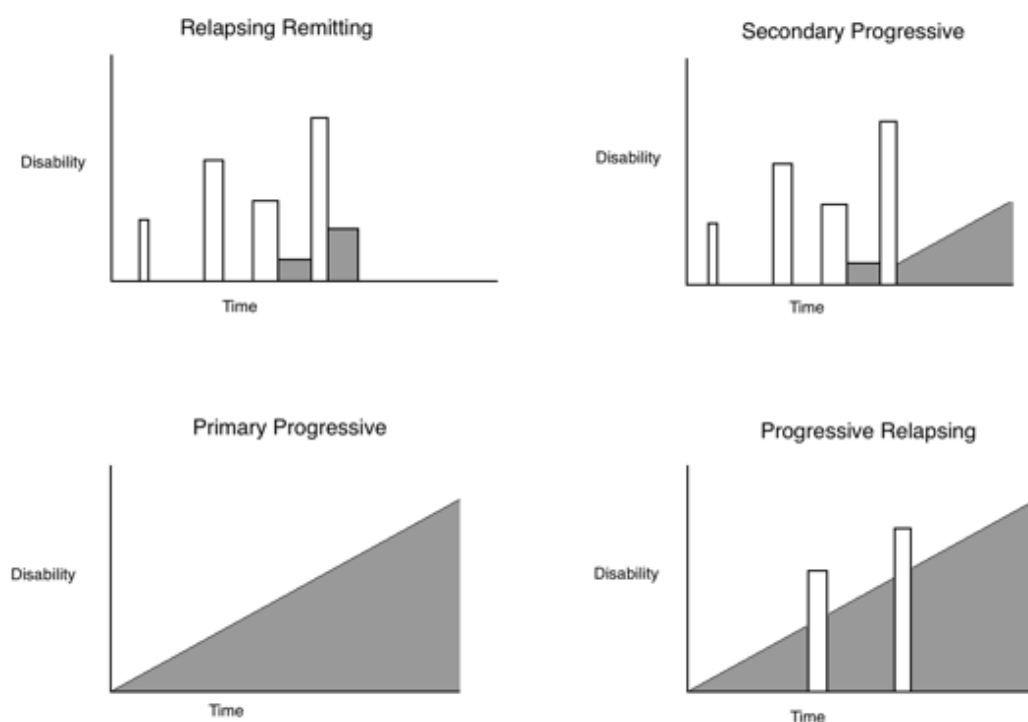
In the early stages of multiple sclerosis the rate of progression is particularly variable ranging from a severe fulminant form from the onset (Marburg's variant)[13] to more "benign" variants. Debate exists regarding the concept of benign MS (BMS) as even though some patients can follow a prolonged course with minimal disability [14], many will eventually accrue significant disability over a longer timeframe [15]. There is evidence that when a patient enters the secondary progressive stage of the illness, progression is more uniform [16]. Up to 50% of patients with MS will require a walking aid after 15 years disease duration [17].

There is an associated increase in mortality with MS and although survival appears to be improving there is still an observed reduction in life expectancy of 5-10 years with a median survival time of 40 years from disease onset [18-20]. Increased mortality often results from complications associated with immobility in more severely disabled patients

There are a number of other conditions that can present in a similar manner to MS and diagnosis relies on exclusion of such mimics, as well as the clinical history, examination and other "paraclinical" tests. Although in many cases MRI is central to the diagnosis [21, 22], occasionally additional tests are undertaken (table 1.1). These include analysis of cerebrospinal fluid (CSF) to examine for intrathecal synthesis of oligoclonal immunoglobulins and visual evoked potentials (VEPs) to detect evidence of previous demyelination affecting the optic nerves.

Table 1.1 The 2010 Revised McDonald criteria

Clinical Presentation	Additional Data Needed for MS Diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

The 2010 revised McDonald criteria for the diagnosis of MS [21].

From: Polman, C.H., et al., *Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.* Ann Neurol, 2011. **69**(2): p. 292-302.

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As well as the physical disability associated with MS, there exists a significant non-motor symptom burden. Fatigue is one of the most common symptoms in MS and for some may be the most disabling symptom[23]. Rates of depression, suicide [24], and cognitive dysfunction [25-27] are higher among patients with MS and may have a significant impact upon quality of life (QOL) and employment [28].

1.1.3 Aetiology

The aetiology of MS remains to be fully elucidated. There exists a wealth of evidence for a multi-factorial basis for the condition with both genetic [29, 30] and environmental factors implicated [29-32]. While generally considered an autoimmune condition, the co-existence of MS and "classical" autoimmune conditions is sufficiently low that the aetiology is considered quite distinct [33].

Place of residence during childhood appears to confer some risk of subsequent adult onset of MS. Migration studies show that the risk of the country of origin is maintained if migration occurs at older ages [34]. Migration at a younger age (<15 years old) may result in an individual acquiring a risk similar to of the region to which they migrate [31]. Furthermore, children of immigrants to the UK (a high risk region) have a risk of developing MS similar to UK born children [34]. This data, illustrating an age depended migratory risk and rapid change in risk over a single generation, would seem to imply environmental risk factors acquired in early childhood or possibly even in-utero are particularly important in the aetiology of MS [35]. Exposure to sunlight [36] and the associated levels of Vitamin D [37, 38], have been identified as a risk factor for the development of MS. The latitudinal variation in MS is illustrated in figure 1.2.

Childhood exposure to Epstein-Barr virus (EBV) [39], smoking [40] and other environmental toxins [41, 42] have all been implicated in the aetiology of MS.

Figure 1.2 Geographical Distribution of Multiple Sclerosis with Migrations
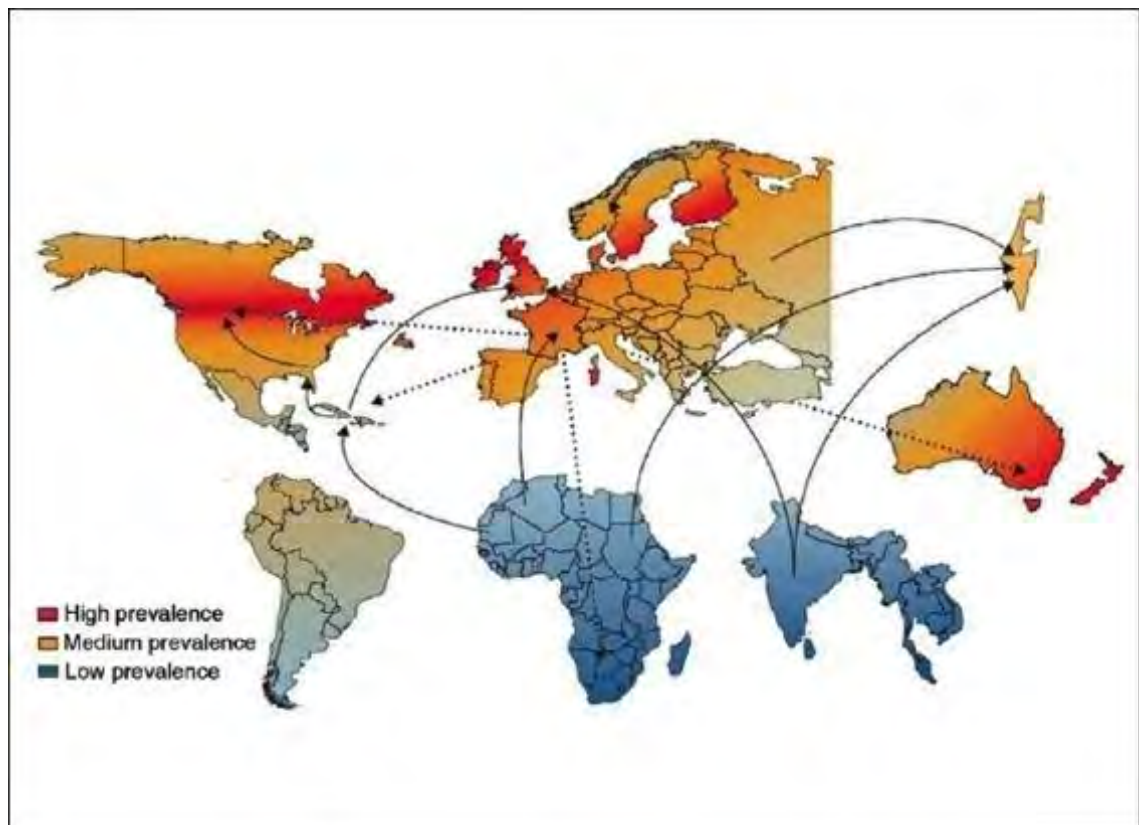
The five continents are depicted to show medium prevalence of multiple sclerosis (orange), areas of exceptionally high frequency (red), and those with low rates (grey-blue). Major routes of migration from the high-risk zone of northern Europe, especially including small but informative studies, are shown as dotted arrows. Studies involving migrants from low-risk to high-risk zones are shown as solid arrows. Compston, A. and A. Coles, *Multiple sclerosis.* Lancet, 2008. 372(9648): p. 1502-17.

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There is a clear genetic component to the risk of developing MS (figure 1.3). Twin studies have revealed a concordance rate of approximately 25% in monozygotic twins while dizygotic twins have an incidence closer to that of non-twin siblings of between 3-5%. This contrasts with a background risk of approximately 0.1% [30].

Figure 1.3 Recurrence Risks for Multiple Sclerosis in Families.
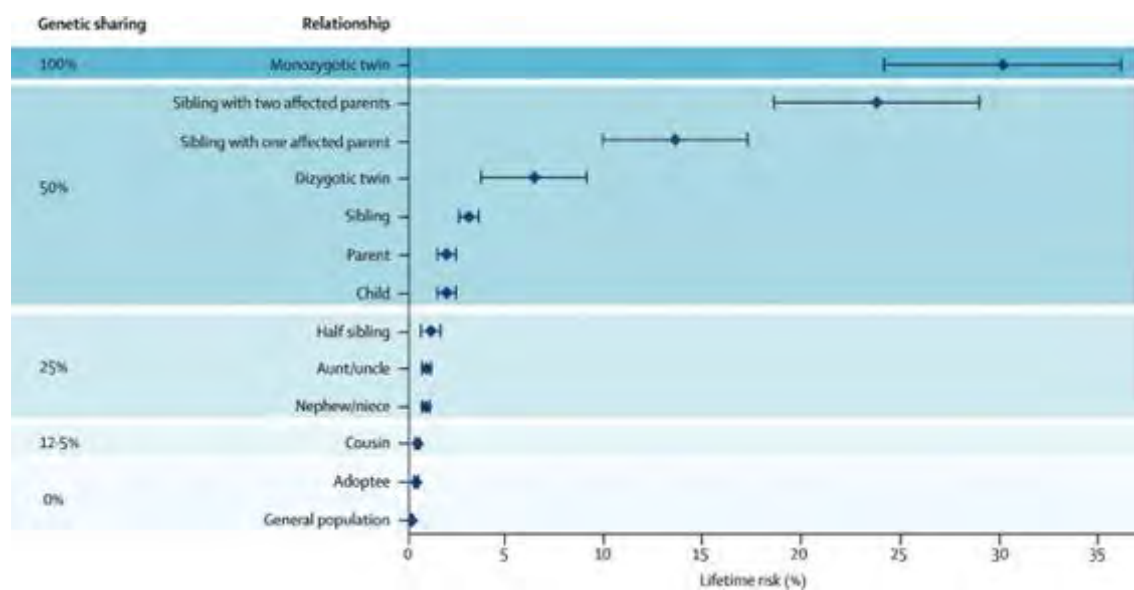
Age-adjusted recurrence risks for different relatives of probands with multiple sclerosis. Pooled data from population-based surveys. Error bars indicate the estimated 95% CIs.

Compston, A. and A. Coles, *Multiple sclerosis.* Lancet, 2008. 372(9648): p. 1502-17.

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1.1.4 Pathology

MS is characterised by focal areas of demyelination (lesions) within the CNS. Inflammation, demyelination, gliosis, remyelination and varying degrees of axonal loss are all known to occur within these lesions [44]. The end stage of this focal inflammatory process is the sclerotic plaque.

Inflammatory lesions can be present throughout the CNS but have a particular predilection for the optic nerves, juxtacortical and periventricular white matter as well as the brainstem, cerebellum and spinal cord [45]. It is unclear why MS preferentially affects these regions although animal studies have hinted at a complex interaction between immune response and vascular anatomy [46].

Remyelination is known to occur to a variable extent even in areas of on-going demyelination [47, 48]. Remyelination results in thinly myelinated axons with short intranodal distances [49]. These regions appear vulnerable to further episodes of inflammatory demyelination and/or axonal injury from the associated repeated cytotoxic insults. Aberrant redistribution of sodium channels may create a state of relative hypoxia whereby the increased energy that is required for signal conduction is met with deficits in adenosine triphosphate production [50].

Classically, MS was thought of as a disease exclusively affecting the white matter within the CNS. However, certain clinical features of MS are difficult to understand with an exclusively white matter basis for the disease and the role for intrinsic grey matter pathology in MS is now well established [51, 52]. Certain aspects of cognitive dysfunction and the increased incidence of epilepsy among patients with MS [53], may all point to the additional cortical-based pathology being clinically relevant.

Pathology has been identified within both the cortical and subcortical cerebral grey matter [54, 55]. In their seminal paper, Brownell and Hughes found that of all the demyelinated lesions detected post-mortem, 5% were within the cortex, a

further 4% in the central grey matter and 17% were at the grey-white matter junction [45]. In-vivo imaging methods of assessing grey matter pathology have evolved significantly in recent years. Magnetic resonance spectroscopic imaging (MRSI) which provides measures of neuronal integrity have revealed widespread abnormalities within the grey matter [56] and many more grey matter lesions have been identified with double inversion recovery sequences than were previously thought to be present [57].

The primary starting point for MS is felt to result from increased migration of auto-reactive T-lymphocytes across the blood-brain barrier (BBB). Although the exact sequence of this cascade is poorly understood, it is clear there is a failure of the normal regulatory mechanisms resulting in an inflammatory cascade with astrocyte proliferation and microglial activation. This localised immune mediated inflammatory response results in focal brain tissue damage further perpetuating BBB disruption [58, 59]. Although classically considered to primarily result from cell-mediated immunity, there is a growing recognition for a role for humoral immunity in the pathogenesis of MS with different immunopatterns being described (figure 1.4) [60].

Figure 1.4 Immunopatterns in MS
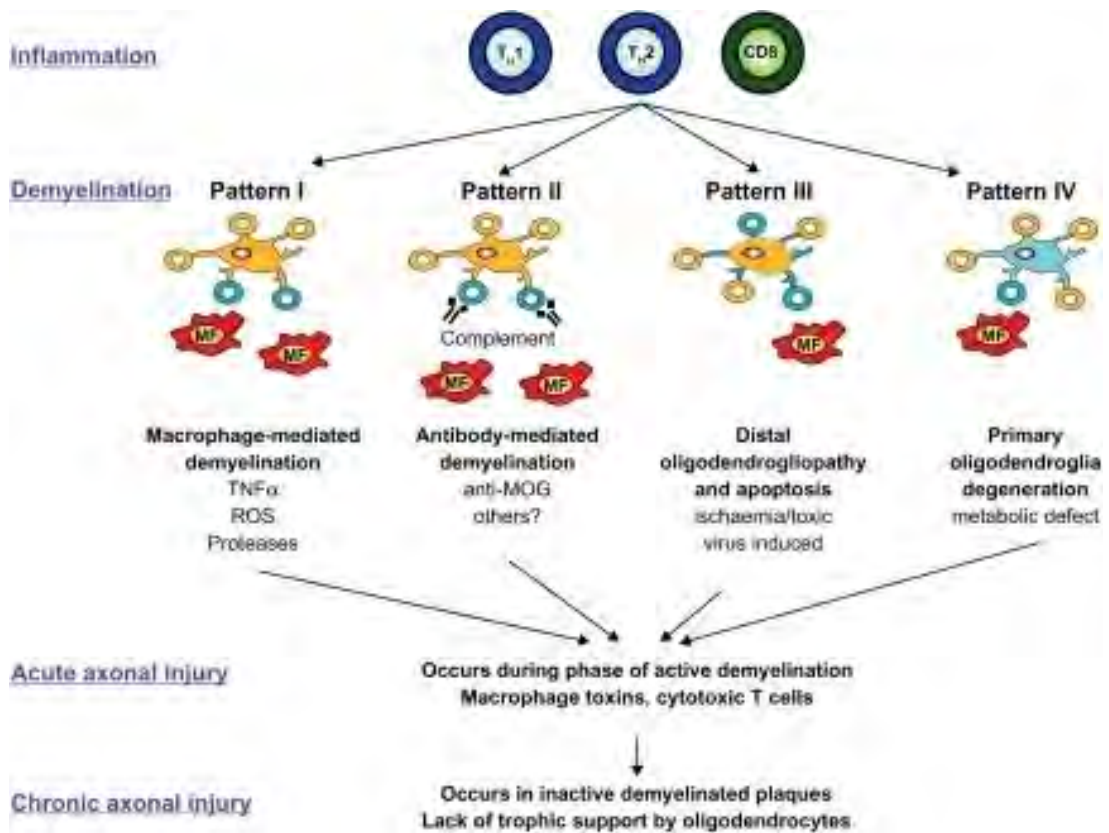
Classification of MS lesion pattern. Pattern I and II lesions are characterised by a combination of cellular (macrophages and activated microglia) and humoral (antibodies and complement) immune components. Pattern III and IV lesions show less inflammation and are characterized by oligodendropathy.

From: Barten, L.J., et al., New approaches in the management of multiple sclerosis. Drug Des Devel Ther, 2010. 4: p. 343-66. Copyright Dove Medical Press Ltd 2010 with permission [61].

There is a clear neurodegenerative aspect to MS that appears to be at least partly independent of inflammatory demyelination with axonal loss and ultimately brain atrophy felt to underpin disability progression [62]. Post-mortem studies have revealed axonal injury to be present in the macroscopically normal appearing white-matter (NAWM) in MS patients [62, 63]. Even in CIS, axonal injury is seen remote to the symptomatic lesions implying axonal injury occurs early and in the absence of overt inflammatory activity [64].

The implications of this evidence are that there may be several processes that give rise to axonal loss in MS. Firstly, axonal injury may occur in the context of acute inflammation as a result of mitochondrial oxidative stress [65], glutamate excitotoxcity [66] or the deleterious effects of local nitric-oxide [67]. It may also be a low grade immunological process persists even in seemingly indolent lesions perpetuating these toxic insults [68]. These factors may result in abnormal reparative processes with inefficient redistribution of axonal sodium channels predisposing axons to subsequent degeneration [69]. This may be compounded by the lack of oligodendrocyte and myelin derived trophic support [70].

Secondly, axons transected during episodes of demyelination may result in Wallerian or retrograde degeneration of axons in the NAWM [71]. Finally however, a diffuse primary axonopathy can not be excluded and may particularly be the case in PPMS where inflammatory lesions are relatively uncommon.

Atrophy in MS is the end result of neurodegeneration and the rate of brain atrophy is increasingly being used as an endpoint in pharmaceutical trials in order to assess for potential neuroprotective properties of the latest generation of disease modifying therapies (DMTs) [72].

1.1.5 MS therapeutics

A number of DMTs are available for RRMS. These treatments act through various mechanisms to modulate the immune response and reduce the clinical relapse rate [73-75]. The effect on disability progression and rate of brain atrophy however appears modest [76-79]. Current DMTs predominantly target the inflammatory phase of the condition and as such, do not appear to be of benefit in progressive forms of MS where neurodegenerative processes may have become established [80]. A number of new immunomodulatory therapies have been developed that have been shown to reduce the relapse rate and may have a greater effect on arresting the process of neurodegeneration and reducing disease progression (see table 1.1). At present however, there is no licensed therapy for progressive MS.

Even these new potent immunomodulatory treatments do not appear to completely arrest processes responsible for cerebral atrophy [81] implying that the processes giving rise to atrophy may be in motion early in the condition or that they are driven by pathological processes not fully addressed by these therapies.

Table 1.2 Efficacy of Current Disease Modifying Treatments

Study Agent	Natalizumab	Fingolimod	Teriflunomide	Laquinimod	BG-12
Relapse rate reduction	68%	54%	31%	23%	53%
Annualized relapse rate	0.23	0.18	0.37	0.28	0.17
Absolute relapse rate reduction	0.50	0.22	0.17	0.09	0.19
Number needed to treat (2-year relapse)	2	5	6	11	5
Relative reduction in new T2 and gadolinium-positive (Gd+) MRI activity	83% in T2 92% in Gd+	74% in T2 82% in Gd+	67% in T2 80% in Gd+	30% in T2 37% in Gd+	85% in T2 90% in Gd+
Relative reduction in Expanded Disability Status Scale progression	42%	30%	30%	36%	38%
Absolute reduction in proportion progressing	0.120	0.064	0.071	0.036	0.110
Number needed to treat (2-year progression)	8	14	14	28	9

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1.2 Cognitive Function in MS

"In most of the patients affected by the multi-locular sclerosis [. . .] there is a marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality". Charcot 1877 [83].

1.2.1 Overview of cognitive dysfunction in MS

MS is often considered a disease primarily characterised by physical disability however it has long been recognised that there exists a significant non-motor symptom burden.

Cognitive dysfunction is particularly poorly understood, under recognised, and currently, presents limited opportunity for intervention or treatment. Cognitive impairment is often considered to constitute part of the neurodegenerative spectrum of MS. Independent of the physical limitations imposed by the disease, cognitive dysfunction negatively impacts upon social functioning [28], including ability to partake in the activities of daily living [84], employment [85, 86], ability to drive [87] and also negatively impacts upon caregivers [88].

Cross sectional studies have revealed cognitive impairment to be present in 40-65% of individuals with clinically definite MS on neuropsychological testing [26]. Cognitive impairment has been identified at all stages and affects all subtypes of MS [89]. MS typically spares semantic memory and it is rare for MS to manifest with language difficulties or deficits in "general intelligence". The most consistently affected cognitive domains include executive functions [90, 91] and working memory [92, 93]. Information processing speed [26, 94] and attention [95, 96] are often particularly affected.

Studies have also shown cognitive deficits to be present in the early stages of MS [97-99], including CIS [100-102]. Those CIS patients with the highest lesion load

at baseline have been shown to have a greater rate of cognitive decline in longitudinal follow up studies. Cognitive impairment at presentation with CIS however may be predictive of subsequent conversion to MS [103].

The precise pathophysiology of cognitive dysfunction in MS is unclear. It is generally felt to result from a "disconnection" syndrome affecting the various cortico-cortical connections through disruption to the subcortical white matter tracts [104]. However, there is an increasing recognition of the important role that grey matter disease may play in the pathophysiology of cognitive impairment [27] and indeed, "cortical" presentations are recognised [105]. Grey matter pathology may also explain some of the subtle personality changes, such as disinhibition that can be observed in MS patients [106].

Position emission tomography (PET) studies have revealed widespread hypometabolism of cortical grey matter in patients with MS and this appears to be more pronounced in patients with cognitive dysfunction compared to those without evidence of cognitive impairment [107]. Lesions have also been identified within the subcortical grey matter and lesions particularly within the thalamus may be associated with a variety of cognitive deficits. [55, 107]

1.2.2 Risk factors for cognitive dysfunction

The rate of cognitive decline appears far from uniform [108, 109]. Several potential reasons exist that may explain some of this apparent variability in cognitive performance over time. Differing disease subtypes, differing methods of cognitive assessment, as well as the influence of DMTs, cognitive reserve, pre-morbid educational attainment and genetic factors may all act as possible modifying variables [27].

1.2.2.1 Relationship to physical disability

Physical disability in MS is most commonly quantified using the Kurtzke Expanded Disability Status Scale (EDSS) [110]. The correlation between the severity of physical disability as typically measured on the EDSS and degree of cognitive impairment is variable [111-114].

It should be noted that measures of motor disability do not necessarily reflect on-going cerebral pathology. It is thought that, particularly in the progressive forms of the disease, there is a particular predilection for accumulation of spinal cord pathology that may explain some of the divergence in motor disability from cognitive decline [115].

In CIS, cognitive impairment has shown to be only weakly related to extent of physical symptoms [99, 101] suggesting cognition may be a marker for an on-going and diffuse disease process independent of clinically apparent relapses. Early axonal loss for example is known to occur remote to macroscopic lesions early in the course of MS [116, 117] and identification of cognitive dysfunction may provide a surrogate assessment for diffuse pathology. In future this may have important implications for deciding when to instigate disease modifying therapies. Cognitive status at presentation with CIS may predict subsequent conversion to clinically definite MS (CDMS) [103].

1.2.2.2 Association with MS subtype

There is considerable clinical heterogeneity among patients with MS, in particular between the relapsing remitting stages and the progressive forms. In the absence of relapses, patients with RRMS exhibit relative stability in measures of physical disability (as measured by EDSS) compared to the progressive forms.

There is some data comparing cognition in the various subtypes of MS [118-120]. Several of these studies found that SPMS patients had a greater degree of slowing on tests of information processing speed than RRMS [118, 119] even for similar levels of disability [115]. Using the Brief Repeatable Battery of Neuropsychological Tests (BRBNT) for MS [121], Huijbregts et al found that with exception of verbal fluency, patients with RRMS performed better than either SPMS or PPMS in all other cognitive tasks [119]. SPMS patients in general performed worse than PPMS with respect to higher order working memory tasks.

In trying to ascertain the rate of decline of cognition, many studies try to draw conclusions from examining heterogeneous groups of patients at different time points in their disease course. These studies are limited by the cross sectional nature of the data. Longitudinal studies have the potential to provide a better estimate of cognitive decline over time but are also not without their limitations. In particular, attrition bias, the potential effect of various DMTs over time and a lack of a control group to account for practice effects of the various neuropsychological tests used to measure cognitive function can all have a confounding influence [122].

One of the longer studies by Amato et al which included a longitudinal control group, showed an increase in the incidence of cognitive dysfunction (as defined through an extensive cognitive battery) in the MS group from 26% to 56% over a 10-year period [123]. Furthermore, it was found that over time, progressively more diffuse cognitive domains become affected. At baseline, the RRMS group

had significantly lower scores on assessments of concentration, verbal memory and abstract reasoning compared to controls. At 4.5-year follow up, additional deficits were identified in verbal fluency and verbal comprehension in addition to the aforementioned deficits. Finally, at 10-year follow up short-term verbal memory and short-term spatial memory deficits also emerged in the MS group compared to the control group.

Kujala and colleagues showed that when patients are divided into mild cognitive impairment (MCI) versus normal cognitive function, a modest proportion (35%) of those with normal cognitive function showed only mild deterioration at 3 years. In contrast, 77% of those patients with MCI at baseline showed a ***significant decline*** in cognitive function with worsening of scores in previously identified affected domains but with additional dysfunction emerging across new domains [124].

It has been postulated that up to a certain point, a variety of adaptive mechanisms may be employed. The point at which these mechanisms become overwhelmed may herald decline in cognition experienced by some individuals [104]. The efficiency and extent of these adaptive mechanisms may account for some of the inter-patient variability seen in cognitive performance.

1.2.2.3 Cognitive reserve

The potential for "cognitive reserve" to influence the rate of decline in cognitive function has been noted in a number of neurodegenerative conditions in particular, Alzheimer's disease [125]. Similarly, cognitive reserve may be of protective benefit against cognitive decline in MS [126, 127].

It has been proposed that cognitive reserve is related to greater "maximal lifetime brain growth" and is determined by factors such as genetics as well as "enriching lifetime experiences", such as education and employment [128]. Vocabulary knowledge is commonly used as a measure of "lifetime intellectual enrichment" as determined by factors such as educational attainment and occupation [129].

Sumowski et al, utilised the Wechsler Vocabulary test as an assessment of lifetime educational enrichment and found that cognitive function as measured on the BRBNT declined most precipitously among patients with MS with low educational enrichment while patients with moderate levels of educational enrichment declined less rapidly over 4.5 year follow up (figure 1.4). Patients with high levels of lifetime educational enrichment remained largely stable on assessments of cognitive function [130]. A similar pattern was seen on assessments of cognitive efficiency as measured on tests of information processing speed such as the Symbol Digit Modalities Test (SDMT). Benedict et al found that individuals with 14 or more years of formal education had maintained scores on SDMT at 5 years follow up [131].

Quite how increased education exhibits a moderating effect on cognitive decline is unclear. It may somehow slow the rate of brain atrophy or alternatively result in enhanced connectivity of neural networks [132].

Figure 1.5 Intellectual Enrichment and Cognitive Decline
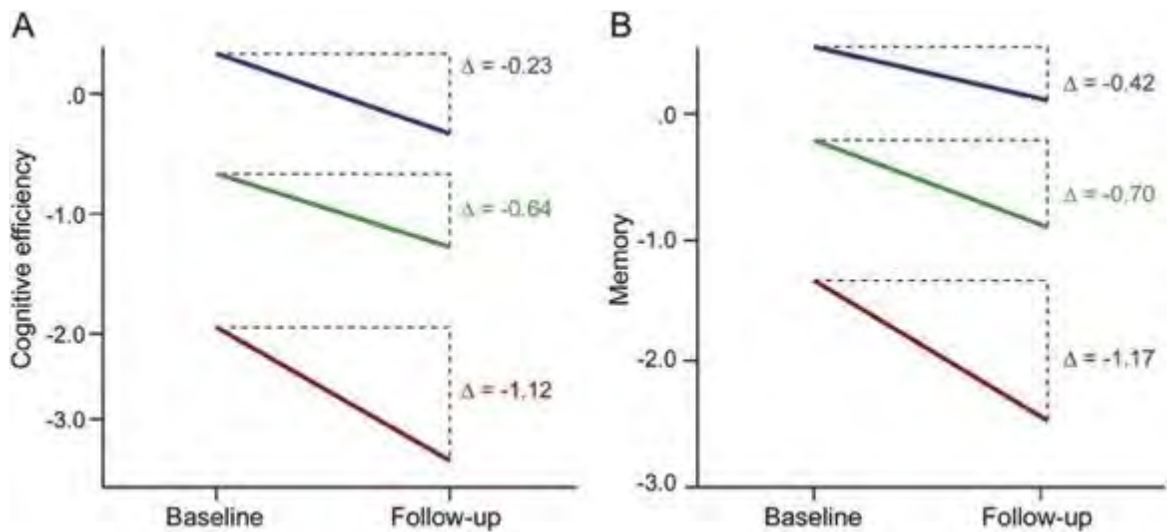
Decline in cognitive efficiency (A) and memory (B) from baseline to follow-up for patients with multiple sclerosis who had low (red), moderate (green), and high (blue) lifetime intellectual enrichment. Cognitive efficiency and memory are represented as norm-referenced z scores.

From Sumowski et al. *Brain reserve and cognitive reserve protect against cognitive decline over 4.5 years in MS.* Neurology, 2014. 82(20): p. 1776-83.
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1.2.2.4 Influence of disease modifying therapy

Data relating to the effect of conventional first line DMTs on cognitive function is relatively sparse and often conflicting [133-135]. The early pivotal trials did not generally include cognitive function as a primary outcome measure and extrapolating long-term measures of disability progression from relatively short randomised controlled trials is difficult. Attempts have been made to perform subgroup analyses of this early data as well as other studies looking at the potential benefit of DMTs on cognition.

The COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study was performed to evaluate the progression of cognitive decline in patients with early RRMS receiving treatment with either interferon beta-1a (IFNb-1a) 22, or 44 mcg administered subcutaneously three times weekly [135]. Three-year follow up data on 318 patients taking INF β-1a (44 μg: n =153; 22μg: n =165) showed that the proportion of patients who were cognitively impaired (as measured on BRBNT) had increased slightly from the baseline value of 23.5% to 24.8% in the IFNb-1a 22mcg treatment group, but had remained stable at 15.2% in the IFNb-1a 44 mcg treatment group. A protective effect on cognitive function was therefore seen with higher dose INF β-1a (HR 0.68, 95% confidence interval [CI]: 0.48-0.97). This corresponds to a 32% risk reduction in cognitive impairment for treatment with 44 μg INF β-1a versus 22μg INF β-1a. However, higher levels of baseline cognitive impairment among the 22μg INF β-1a group must be borne in mind (23.5% vs 15.2% p= 0.058).

The BENEFIT trial in which patients with CIS and at least two clinically silent brain MRI lesions were randomised to alternate day interferon beta-1b (IFNB-1b) 250 mcg subcutaneously (n = 292) or placebo (n = 176), revealed that IFN-1b delayed the time to diagnosis of CDMS (p < 0.0001) and McDonald MS (p < 0.00001). Three and five year follow-up data on patients in the original cohort (including patients who subsequently converted to CDMS and were subsequently commenced on IFNB-1b) showed that improvement in the PASAT was more pronounced in the early treatment as compared with the delayed

treatment group; the difference increased during the course of the study until year 5 (year 3, p=0·064; year 5, p=0·005) [136].

Tertiary endpoints derived from the initial AFFIRM trial [137] suggests that natalizumab may reduce the progression of cognitive deficits compared with placebo in patients with RRMS [138]. Using the PASAT the authors report natalizumab reduced the risk of confirmed progression of cognitive deficits by 43% compared to placebo (HR 0.57 [95% CI 0.37, 0.89], P=0.013). No significant difference was seen between treatment and control groups in SENTINEL with respect to cognitive function [139].

1.3 Neuropsychological assessment

1.3.1 Aims

Formal neuropsychological testing may be perceived as complex and time consuming and, as such, does not form a routine part of clinical assessment in the outpatient setting [140]. Formal neuropsychological testing, however, does provide a much more detailed understanding of the cognitive profile of patients with MS and how such impairments might negatively impact on daily life [141]

To understand the various assessments used and how they pertain to the pathology in MS, one must have a basic understanding of the structure and function of the relevant memory systems [142].

1.3.2 Working memory

Working memory, commonly referred to as "short-term" memory comprises the systems that subserve the holding and simultaneous processing of transitory information [143]. Depending on the task, it may involve visual or verbal information. Working memory is central to undertaking complex cognitive tasks such as learning and reasoning. It is dependent upon a degree of executive functioning in setting the goal directed behaviour for a given task in the face of external distraction. Efficient working memory is also highly dependent on attention and speed of information processing [144]. Considering the complexity of working memory, it may be one of the earliest cognitive domains to be affected in MS [92, 93].

Working memory systems involve diffuse networks and is often considered in terms of the "multi-component model" proposed by Baddeley and Hitch [143]. In this model, the initial storage and manipulation of sound-related information takes place in the "phonologic loop" while the "visuo-spatial sketchpad" is the equivalent system for storage and manipulation of non-verbal information [145]. The "central executive" is then responsible for organising transitory material into more structured "blocks" to attenuate task difficulty [146].

Functional MRI (fMRI) and position emission tomography (PET) studies have better defined these anatomical areas involved in working memory [147-150]. Such work has revealed a consistent fronto-parietal network central to working memory [151-153]. The "central executive" of this model of working memory is thought to be within the left prefrontal cortex (BA 46) and anterior cingulate cortex [154, 155].

Tests of working memory rely on a participant repeating or recalling progressively longer sequences of auditory or visually acquired information and can be assessed in a number of ways [156, 157]. Typical bedside clinical tests include the serial subtraction test. More formal neuropsychological tests include the frequently utilised PASAT or n-back tests.

The n-back test examines patients' ability to identify if a currently presented visual or auditory stimulus matches previously presented information. This can relate to information presented immediately before (n=1) or further back in the sequence increasing "n" (see figure 1.6). The task becomes more difficult with increasing "n" and therefore becomes a more complex task involving working memory and is highly dependent on information processing speed [158]. N=0 tasks tests the simple ability to recognise a specific visual stimulus and thus may be a more "pure" measure of attention, relatively independent of working memory.

The PASAT is primarily a test of working memory although performance is also highly dependent on speed of information processing. In the PASAT, patients are presented a continuous stream of numbers every few seconds aurally and are asked to add the new number to the preceding number. The PASAT is a relatively sensitive measure for cognitive dysfunction in MS with a sensitivity and specificity of 74% and 65% respectively [159].

Figure 1.6 Diagrammatic Representation of N-Back Test
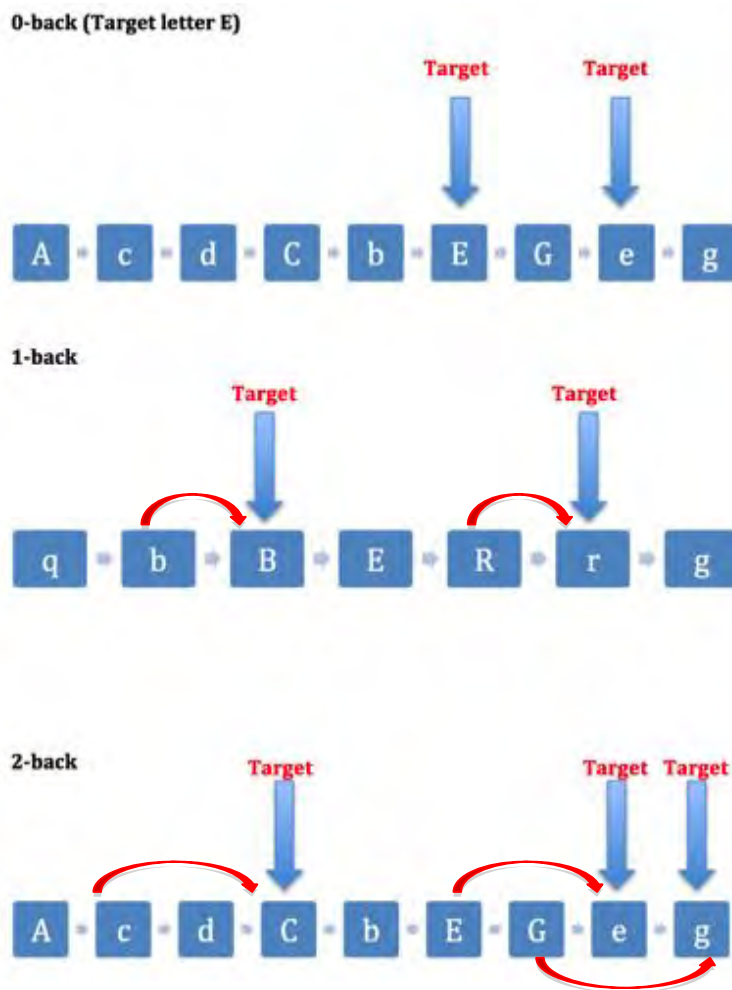
N-back test with three conditions.

A constant stream of letters is visually presented. The n=0 ("0-back") task tests the ability to simply recognise a specific visual stimulus highlighted in advance of the task. Increasing "n" places greater demands on working memory. In the "1-back" the respondent is asked to indicate if the letter presented matches that presented immediately before, while the "2-back" requires a response if the letter presented matches that which came two letters before in the sequence.

1.3.3 Speed of information processing

Speed of information processing is felt to be the central deficit in MS and underlies impairments in diffuse cognitive domains [160]. Information processing speed is central to efficient working memory [161, 162] and executive function [163]. Deficits observed in both semantic and phonemic also are most likely reflective of this deficit in speed of processing [164-166]. Similarly, while language is generally considered to be unaffected in MS, some studies have identified impairments in sentence comprehension difficulties, which the authors acknowledge are primarily related to slowed verbal processing speeds [167].

Impairment of information processing speed is one of the most consistently identified deficits on cognitive testing in multiple sclerosis [95, 160, 162, 168-171]. The SDMT may be among the most sensitive tests of slowed information processing speed and is often utilised to identify cognitive impairment in MS [172, 173]. As an individual assessment tool for cognition in MS, the SDMT may have a greater validity and reliability than the PASAT and may also be less susceptible to ceiling and learning effects [174].

Speed of information processing has been shown to decline more rapidly than other measures with disease duration [175, 176] and the presence of such deficits may be predictive of cognitive decline over the longer term [177]. Despite evidence of slowing of reaction times on a number of studies, given sufficient time, patients with MS are otherwise accurate on various measures [178].

1.3.4 Executive function

Executive function refers to the planning and execution of goal directed, multi-step behaviour while being able to adapt to a changing environment [179]. It therefore relies upon the ability to plan and anticipate the potential consequences of one's actions while being able to "inhibit" actions or behaviours that may be contrary to the primary goal. It requires an individual to exhibit a degree of mental flexibility in taking measures to alter one's behaviour or

actions in the face of changing circumstances. An inability to alter one's behaviour in this manner may result in stimulus bound or perseverative behaviours which may be evident on formal testing or as a tendency to repeat a verbal or motor action despite cessation of a stimulus.

Executive dysfunction that interferes with the ability to plan and organise the routine tasks of daily living has clear implications for social functioning, employment and quality of life. A wide variety of dysexectuive symptoms have been identified in patients with MS [90, 91, 180, 181]. In a community-based sample, Drew et al identified some degree of executive dysfunction in 17% of patients with MS of variable disease duration [180].

Formal tests of executive function have been devised including trail making tasks, the Tower of London task and replicating the complex Rey-Osterrieth figure. The Wisconsin card-sorting task is another test of executive function and in which patients with MS often exhibit deficits in set shifting [182].

The anatomy of dysexecutive syndromes is more complex than previously thought. Initially attributed to "frontal lobe" pathology, fMRI studies have revealed involvement of more extensive fronto-parietal networks [183, 184], the limbic system [185], as well as basal ganglia circuitry [186, 187]. It has been shown that the lateral prefrontal cortex is also critical in the executive control of working memory and has a role in response inhibition [146, 188-190].

1.3.5 Attention

Attention is the preferential allocation of neural resources to a particular task at a given time and is crucial to the optimum functioning of multiple memory systems [191]. Measures of sustained attention are frequently identified as being impaired in MS [192]. Performance at tests of simple attention such as repeating digits is generally unaffected in patients with MS [193].

The functional anatomy of attentional networks is complex. Several key attention networks are thought to involve bilateral temporo-parietal regions. A

right hemisphere dominant "ventral attentional network" consisting of the temporo-parietal junction, ventral prefrontal cortex and anterior insula is thought to be responsible for directing attention to salient events [153, 194, 195] while a "dorsal attention network" is thought to exist consisting of the superior parietal lobule and the dorsal frontal cortex and is responsible for linking stimuli and responses [196].

1.3.6 **Long-term memory**

Long-term (remote) memory is the ability to recall information encountered at a remote time point and includes declarative and procedural memory. Declarative memory can be further subdivided into semantic and episodic memory. Semantic memory relates to our *factual knowledge* of the world including word meaning and is unrelated to our sense of "self". Episodic memory by contrast is self-referential.

Memory consolidation is dependent upon both encoding and storage. Efficient long-term memory relies upon adequate working and executive memory systems to consolidate new information as well as adequate retrieval strategies. Problems with "learning" [111] and "long term" memory impairment is frequently reported in the MS literature but caution should be exercised in interpreting such data as clear deficits are known to exist in both the systems subserving working memory and executive function which may negatively impact on learning strategies.

Although impaired retrieval strategies had long been postulated to be responsible for long-term memory deficits in MS [197, 198], more recently it has been proposed that the initial encoding of information may be the major deficit in what otherwise appears to be a remote memory problem [199, 200]. De Luca et al illustrated that in MS patients, more trials were required to acquire new information, however once this new information was acquired, they performed similarly to controls on tests of remote recall (see figure 1.7) [201]. This led the authors to conclude that memory impairment among MS subjects is as a consequence of inadequate acquisition of new information rather than impaired retrieval.

Figure 1.7 Trials Required for Acquisition of New Information
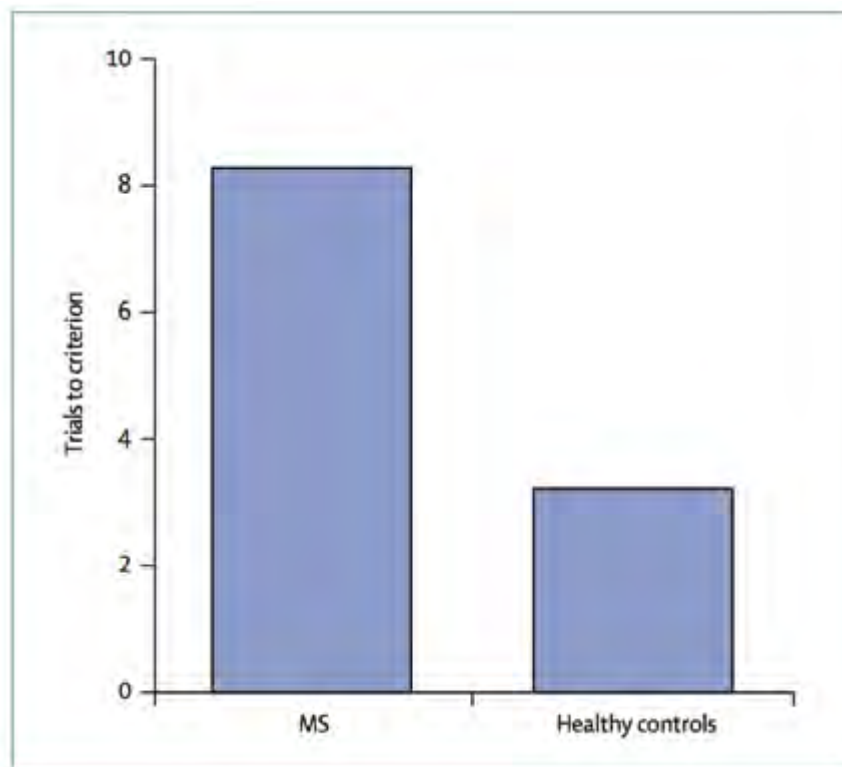
Comparison between the number of trials needed for patients with MS and healthy controls to successfully recall ten words in two consecutive trials. Mean number of trials to reach criterion (correct recall of 10 words on two consecutive trials).

From: DeLuca, J., S. Barbieri-Berger, and S.K. Johnson, *The nature of memory impairments in multiple sclerosis: acquisition versus retrieval.* J Clin Exp Neuropsychol, 1994. **16**(2): p. 183-9.

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1.3.7 Neuropsychological tests

It can be seen from a discussion of the complex structural and functional anatomy of the various memory systems, that it is often difficult to test a particular cognitive domain in isolation (table 1.3).

Table 1.3 Common Neuropsychological Tests in Multiple Sclerosis

Cognitive test	*Domain*
Symbol Digit Modalities Test	Processing speed, concentration (& visual working memory)
California Verbal Learning Test-II	New learning & verbal memory
Brief Visuospatial Memory Test (Revised)	New learning & visual memory
Paced Auditory Serial Addition Test (PASAT)	Working memory & information processing speed, concentration & interference suppression
Wisconsin Card Sorting Test	Executive function
Controlled Oral Word Association Test	Language, verbal fluency & executive function

Various "batteries" of tests have been devised which employ a number of neuropsychological tests to encompass a greater range of cognitive domains (table 1.4). Among these the Brief Repeatable Battery of Neuropsychological Tests (BRBNT) is one of the most widely utilised and comprehensive tests in the research setting with a reported 94% specificity and a 71% sensitivity for detecting cognitive dysfunction in MS [172]. One potential shortcoming of the BRBNT in MS is the lack of assessment of higher executive function.

The Minimal Assessment of Cognitive Function in MS (MACFIMS) is often considered the "gold-standard" assessment for cognitive impairment in MS [202]. MACFIMS incorporates the California Verbal Learning Test 2nd edition, (CVLT-II) as well as replacing the original spatial recall test with the Brief Visuospatial Memory Test Revised (BVMT-R) to provide better assessment of spatial processing.

More recently a consensus panel of experts in the field of cognition in MS proposed the Brief International Cognitive Assessment for MS (BICAMS) which is a brief (15-minute), practical but sensitive means of identifying cognitive impairment in MS [203]. It comprised the SDMT, BVMT-R and CVLT-II. As there is little evidence that delayed recall adds discriminatory value or increases validity in MS, only the initial three learning trials of the BVMT-R, and the five learning trials of the CVLT-II are recommended.

Table 1.4 Test Batteries Utilised in Assessment of Cognitive Function in MS

Cognitive Battery	Components	Domain Assessed
Rao's Brief Repeatable Battery of Neuropsychological Tests (BRBNT) *Time to administer: Approx. 30 minutes*	Buschke selective reminding test 10/36 spatial recall test Controlled Oral Word Association Test (COWAT) Paced Auditory Serial Addition Test (PASAT) Symbol Digit Modalities Test	Verbal learning & memory Visual learning & memory Verbal fluency & word retrieval Working memory & attention Information processing speed & working memory
Minimal Assessment of Cognitive Function in MS (MACFIMS) *Time to administer: Approx. 90 minutes*	California Verbal Learning Test – second edition (CVLT-II) Symbol Digit Modalities Test Brief Visuospatial Memory Test - Revised (BVMT-R) Paced Auditory Serial Addition Test (PASAT) Controlled Oral Word Association Test (COWAT) Delis-Kaplan Executive Function System	Verbal learning & memory Information processing speed & working memory Visual learning & memory Working memory & attention Verbal fluency & word retrieval Executive function & problem solving
Brief International Cognitive Assessment for MS (BICAMS) *Time to administer: Approx. 15 minutes*	California Verbal Learning Test – second edition (CVLT-II) Symbol Digit Modalities Test Brief Visuospatial Memory Test - Revised (BVMTR)	Verbal learning & memory Information processing speed & working memory Visual learning & memory

1.3.8 Confounding factors in neuropsychology

Assessment of cognition in MS is fraught with potential difficulties. The physical impairments that an individual may possess can negatively impact upon a number of important measures of cognition [204]. For example visual impairment, either from previous optic neuritis, or fixation difficulties from prior brainstem inflammatory lesions can result in difficulty participating in a wide variety of cognitive assessments. As well as the physical limitations imposed by the condition, the neuropsychological co-morbidities may potentially impact upon self-reports of cognitive dysfunction [205] as well as formal assessments of cognition [206]. Many of the medications that are used to ameliorate the symptoms of MS have a potent CNS mode of action and may have sedative side effects. Few studies have systematically examined the effect of such medications on measures of fatigue, depression or cognitive impairment [207].

Depression and anxiety may be early features of MS [208, 209]. The pathophysiology of depression in MS is unclear but numerous factors have been associated with its development [210]. Depression may independently impact upon measures of cognition [211-213]. Few attempts have been made to quantify the degree to which anxiety impacts on cognitive functioning and have found only a weak association between the presence of anxiety and the degree of cognitive dysfunction [214].

Fatigue is among the most pervasive of symptoms in MS affecting up to 90% of patients [215, 216]. The construct of fatigue is poorly defined, in part due its inherent subjectivity and lack of tools to identify and quantify this measure. However close correlation between patients self-reporting of fatigue and measures of depression may imply a common structural or biochemical mechanism [217]. While patients may self-report that fatigue adversely impacts on cognition [218, 219], studies investigating the relationship between fatigue and cognition in MS are sparse and often have failed to find a significant

relationship on formal testing [220, 221]. It has been found that self-reported measures of fatigue do not correlate cognitive performance [222].

Furthermore, Bol et al showed that while anxiety, depression and mental fatigue all significantly contributed to the self-reporting of cognitive complaints, both physical and mental fatigue did not significantly contribute to cognitive performance on formal examination [223]. Fatigue may however explain some of the "within session" decrements seen on a variety of cognitive tests [224].

While it is clear that cognitive impairment may exist independently of mood disturbance, anxiety and fatigue, studies examining cognition in MS must be mindful of the potential confounding effects of these variables and be designed appropriately. Commonly used measures of depression and fatigue are the Beck Depression Inventory Scale or the Hospital Anxiety Depression Score and the Fatigue Severity Scale respectively [225, 226].

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1.4 Summary

Multiple sclerosis is a complex condition, the aetiology and pathogenesis of which remain poorly understood. It may be the case that a variety of environmental factors precipitate the condition in genetically susceptible individuals.

Despite advances in the understanding of the pathology underlying MS, the relationship between inflammation and neurodegeneration remains complex and incompletely understood. The two processes may be partly independent. Repeated episodes of inflammation or a perpetuation of other as yet, poorly understood mechanisms result in progressive accrual of axonal injury and eventual atrophy over time. It is these latter factors that are felt to underpin the neurodegenerative aspects of MS. Only through understanding the basic pathology can in-vivo measures of MS activity be developed and utilised effectively. Both the microscopic and macroscopic distribution of pathology is relevant to the subsequent development of progressive disability in MS.

Cognitive dysfunction is prevalent in MS and associated with significant morbidity for patients. It has been shown that cognitive dysfunction can affect all subtypes of MS including CIS. Indeed, cognitive impairment in CIS may be predictive for subsequent conversion to MS. Cognitive dysfunction and decline do not clearly mirror accumulation of physical disability and may provide an alternative means of assessing for disease activity and a surrogate marker of accumulating pathology. Early identification of cognitive dysfunction may therefore become important when considering the efficacy of the next generation of DMTs or other interventions.

Largely felt to represent a "disconnection syndrome" it is unclear to what extent cognitive impairment reflects underlying neurodegeneration or how much is potentially recoverable through various mechanisms of repair. How best to manage cognitive impairment is therefore, at present, far from clear. The effect

of pharmacological therapies remains uncertain. It is clear however, that adequate identification and management of cognitive impairment in MS remains a significant unmet need for patients and their relatives.

2

MRI and Cognition in MS

2.1 MRI Introduction

2.1.1 Introduction

Magnetic resonance imaging (MRI) is a versatile imaging modality with a variety of sequences that seek to utilise the paramagnetic features of different tissues to highlight aberrations, identify different pathological processes and map the spatio-temporal evolution of MS[21].

2.1.2 Aims

This chapter will focus on the MRI sequences commonly used in both the clinical and research settings with a view to better identifying the pathological processes relevant to cognitive dysfunction in MS. Particular focus will be given to techniques relevant to this thesis. Detailed description of the physics of MRI is beyond the scope of this thesis but can be found elsewhere [227].

2.1.3 Conventional MRI

"Conventional" MRI techniques primarily refer to T2-weighted, fluid-attenuated inversion recovery (FLAIR) and pre and post-contrast T1-weighted sequences. Such sequences are commonly utilised in the diagnosis of MS. Such lesions have been shown to have a role in prognosticating CIS) [5]. Whilst the diagnostic criteria have evolved over time [21, 22], diagnosis is still fundamentally based on the demonstration of lesions of a particular morphology and distribution while satisfying the criteria of dissemination in time (see figure 2.1).

The presence of post-contrast Gadolinium diethylenetriaminepentaacetic acid (Gd) T1-weighted enhancement indicates recent BBB breakdown as seen in acute inflammatory demyelinating lesions. The role of post-contrast T1-weighted imaging has evolved to include providing evidence for dissemination in time as evidenced by the presence of simultaneous enhancing and non-enhanced lesions [21]. The identification of post-contrast T1 Gd-enhancing lesions is important for monitoring for on-going disease activity and identification of such lesions is now integral to the criteria for commencement of various second line DMTs.

Figure 2.1 Conventional MRI Showing Typical Appearance associated with MS
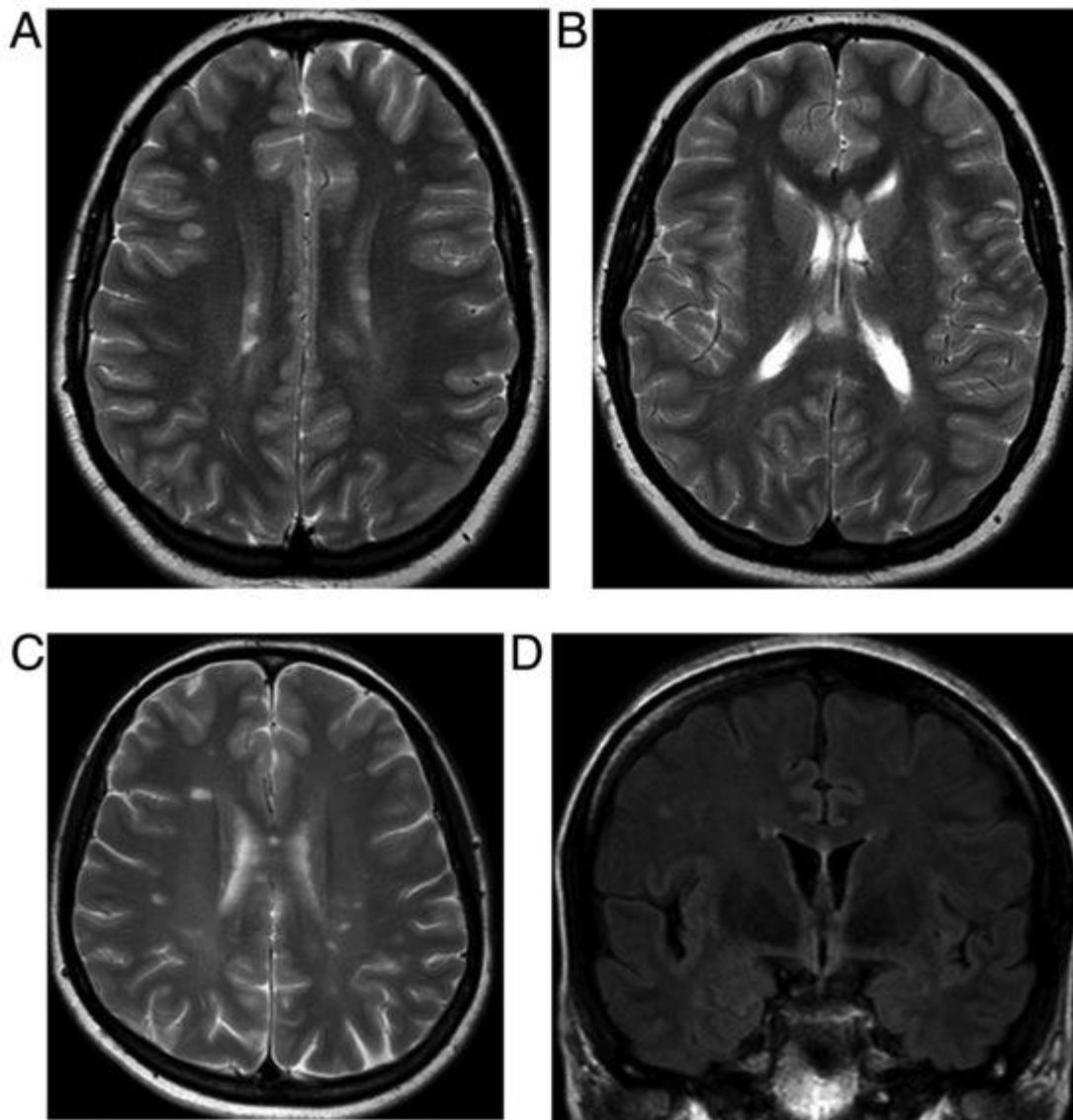
Figure 2.1. MRI showing two patients with MS (A,B) and (C,D). T2-weighted axial MRI's (A-C) and FLAIR coronal MRI (D) showing typical hyperintense appearance of MS plaques: multiple, small, well-defined ovoid lesions predominantly present in the periventricular and subcortical white matter involving the corpus callosum. The long axis of the lesions is usually perpendicular to the long axis of the ventricles.

From. Renowden S. Practical Neurology 2014;14:231–241. [228]

While MRI scanning has added immeasurably to our understanding of MS, it has also brought with it ever more complex questions. It is clear from serial MRI even in the clinically asymptomatic and apparently "stable" patient with MS, there is often an accumulating radiological disease burden[229]. Conversely, there is often poor correlation between conventional measures of disability and the accrual of lesions as seen on current standard diagnostic MRI sequences. There are many potential reasons for this so called, "clinico-radiological paradox", in particular the relative insensitivity of conventional MRI sequences for detecting the entire heterogeneous spectrum of MS pathology as well as the limitations of current measures to assess severity of physical disability [230].

Standard T2-weighted MRI appears to underestimate pathology even within the white matter (with significant pathology existing at the microscopic level beyond the resolution of conventional MRI [63]) and is particularly insensitive to grey matter (GM) lesions due to their relaxation characteristics [230].

It has also been widely acknowledged that the most common measure of MS disability, the EDSS, is heavily weighted towards motor impairment and likely disproportionately influenced by spinal cord pathology which may confound attempts to correlate brain lesions with disability [231]. A better correlation between physical disability and conventional MRI parameters may be achieved using alternative clinical measures of disability such as the MS Functional Composite [232] but there remains significant pathology that is known to exist beyond the resolution of standard imaging techniques.

2.1.4 T2-weighted MRI and cognitive dysfunction

The pathology represented by T2-weighted hyperintense lesions ranges from oedema and inflammation to demyelination, axonal loss and even subsequent remyelination or gliosis as each of these processes results in increased water content of the tissue and therefore may appear hyperintense on T2-weighted sequences [44].

Studies examining the link between brain lesion load on T2-weighted sequences and the degree of cognitive impairment have provided often conflicting results [233-239]. Many of these early studies however were cross sectional in nature and examined patients with moderate to severe cognitive difficulties. A longitudinal study by Penny et al did show that baseline T2 lesion load was predictive of progression of cognitive dysfunction over the subsequent 5 years in [240]. However in one 14-year longitudinal study, the correlation was only modest leading the authors to conclude that other processes distinct from lesion formation are implicated in the development cognitive decline[241].

Widespread T2-hyperintense lesions effecting the subcortical U-fibres has been associated with executive dysfunction [242]. It has also been shown that a high frontal lesion load is associated with difficulties with executive tasks and with tasks of conceptual reasoning [90, 91]. A high lesion burden within the fronto-parietal white matter is associated with deficits on tasks of sustained complex attention [243].

2.1.5 T1-weighted MRI

T1 hypointense lesions ("T1 black holes") are seen particularly in patients with advanced MS. Such lesions are thought to represent more severe tissue damage including significant axonal loss [244, 245]. The degree of hypointensity has been correlated with the severity of tissue injury [246-248].

T1 black holes in MS correlate better with disability than other conventional MRI measures and their presence has potential implications for cognitive dysfunction in patients [249-252]. Such lesions may therefore be representative of neurodegeneration in MS and be seen to correlate with atrophy [253].

However, despite the fact that T1 black holes are often associated with severe tissue damage, some T1-hypointense lesions appearing in conjunction with areas of Gd-enhancement on post-contrast T1-weighted images, may subsequently assume normal intensity indicating reparative processes [254]. A longitudinal study by Van Waesberghe, persistent black holes (indicating irreversible axonal loss) represented only 36% of total T1 black-hole lesion load at any given point.

2.1.6 Atrophy and cognitive dysfunction

It has been illustrated that diffuse pathology exists beyond the resolution of conventional imaging and occurs early in MS and that there appears to be a significant, possibly even distinct, pathological processes present in both the grey and white matter. Atrophy appears to be at least partly independent of inflammatory demyelination [255-257] and is likely to represent the end result of cumulative and diverse pathological processes. Demyelination, axonal transection and reduced synapse density have all been shown to be present, particularly later in the course of MS [116, 258]. It is this net neuronal and structural loss that is felt to underpin progression in the condition [259].

Longitudinal studies have revealed the rate of annual brain volume loss to be 0.2-0.5% in healthy adults [260, 261]. In untreated patients with MS the rate of atrophy may be up to 1.5% per year [262] and may accelerate in SPMS as compared to RRMS [263, 264]. Atrophy is usually assessed on T1-weighted sequences. Three-dimensional magnetisation-prepared rapid gradient echo (MPRAGE) provides a means of rapidly acquiring high spatial resolution, whole brain, T1-weighted images [265]. Some difficulties exist in obtaining accurate measures of atrophy. Grey matter is difficult to study due to regional variations and undulating gyral patterns as well as prolonged T1 relaxation times while white matter (WM) may exhibit a greater degree of reactive gliosis which may result in "pseudo-normalisation" of the white matter volume (WMV) and thus may confound measures of atrophy [266, 267].

Images may by analysed by voxel-based morphometry (VBM), a process in which a brain image is registered to a template, thereby removing much of the differences in brain anatomy between subjects and thus have the images from different subjects existing in the same stereotactic space. Images are subsequently "segmented" and "smoothed" such that every voxel represents an average of itself and neighbouring voxels allowing for a voxel-wise comparison of grey matter volumes between subjects [268, 269]. Relatively few studies have examined the relative contribution of white and grey matter atrophy to

whole brain atrophy but grey matter atrophy may have closer correlations to physical disability than white matter atrophy [270-273].

Figure 2.2 T1-Weighted Images Showing Increasing Degrees of Cortical Atrophy in Four MS Patients
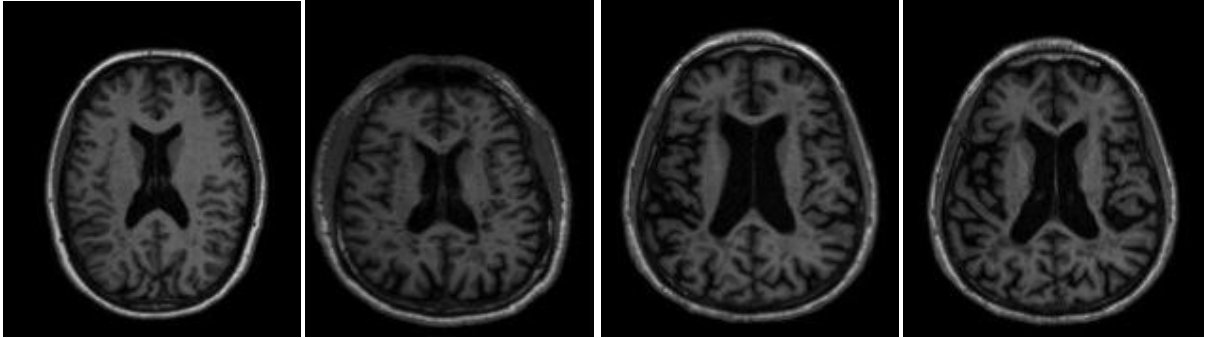
Brain atrophy is clearly associated with measures of physical disability in MS [274-277]. Atrophy is known to be present early in the course of MS [272, 278-281] and to be progressive even in the absence of obvious clinical deterioration [282, 283]. Measures of brain atrophy have been correlated with cognitive dysfunction in MS and assessments of the extent and rate of brain atrophy are potentially predictors of cognitive dysfunction [284-288]. Amato et al found that in patients with MS who experience cognitive decline, the rate of neocortical volume loss was significantly greater than in cognitively stable MS patients over a 2.5-year period [289].

Certain imaging surrogates have been proposed as a means to assess for more widespread atrophy. These include assessment of "central atrophy" through measuring ventricular volumes [290, 291] as well as measurements of the bicaudate ratio indicative of frontal subcortical atrophy [292]. Generalised ventriculomegaly has been associated with cognitive impairment [293] while third ventricular width has been shown to be increased in patients with MS exhibiting cognitive difficulties [55, 284]. It may be that atrophy of the structures in close relation to the third ventricle (thalamus and limbic structures) are of particular importance in the development of cognitive impairment [294]. Compared with total lesion load, third ventricular enlargement has been found to have a greater predictive value than total lesion load in predicting cognitive status [295].

Regional atrophy has been associated with specific cognitive deficits. Benedict et al found that atrophy of the bilateral superior frontal cortex was associated with impairments in verbal and spatial learning, attention and conceptual reasoning [296]. Selective atrophy of the left fronto-parieto-temporal area may go some way to explaining the particular deficits in working memory tasks [287, 297]. Frontal atrophy has also associated with a variety of dysexecutive measures [298].

Hippocampal atrophy has been linked with deficits in memory encoding [299] as well as verbal and episodic memory [300]. Atrophy of other deep grey matter

structures may be associated with deficits in information processing, free recall and new learning [294, 301-304].

2.2 Quantitative MRI and cognitive dysfunction

While conventional MRI, including T2-weighted imaging and FLAIR appear to be sensitive to inflammatory demyelination [305], it is has long been apparent that it is relatively insensitive to neuronal cell loss and axonal degeneration which are felt to play a major role in the progression of disability in MS and may account for much of the cognitive impairment seen in MS [306-311]. Such sequences are therefore suboptimal for assessing the full extent of heterogeneous MS pathology and unsurprisingly are known to only modestly correlate with measures of physical disability and cognitive dysfunction.

In the radiological respect, "normal appearing" with reference to normal appearing white matter (NAWM) has, by convention, been used to refer to areas of brain devoid of T2-weighted MRI abnormality [230]. However, it has long been recognised that even in areas of NABT as seen on conventional MRI there can exist significant pathology at the microscopic level [63, 312].

Quantitative MRI sequences are more sensitive to microscopic pathology in the NABT and indicate significant extra-lesional disease processes in MS [313, 314]. Modern quantitative MRI techniques including magnetisation transfer imaging (MTI) and diffusion tensor imaging (DTI), have provided additional means of identifying abnormalities in NABT [315-318] which may provide better correlation with disability and cognitive dysfunction [319-322].

2.2.1 Magnetisation transfer imaging

Within the brain there exist interactions between hydrogen protons in free water and those attached to macromolecules in myelin (such as proteins and lipids) that constitutes most of the macromolecular structure in the brain [323, 324]. MTI relies on the transfer of magnetisation between the free water protons ("liquid pool") and those protons bound to macromolecules ("macromolecular pool"). The liquid pool is the main contributor to MRI signal due to its relatively long T2 relaxation time (>10ms) during which time a spatial encoding gradient can be applied and images obtained. The macromolecular pool by contrast is not well visualised on conventional MRI due to its short relaxation times (<1ms).

The macromolecular pool, however has a much greater range of resonant frequencies than the free pool. MTI uses an off-resonance radio pulse to saturate these less mobile protons (see figure 2.4). This magnetisation is subsequently transferred to more mobile protons in surrounding water via dipole-dipole interactions thus reducing the observed signal intensity. The degree of signal reduction depends on the relative density of largely immobile macromolecules in a particular brain region [325]. This allows these structures, whose relaxation times are otherwise too short, to be visualised. MTI is useful in MR angiography (resulting in background suppression of static tissue) and in contrast-enhanced brain MRI, to grant increased contrast of enhancing MS lesions [326, 327] as well as to probe the integrity of NABT.

A simple approach to quantify the magnetisation transfer (MT) effect is the so-called magnetization transfer ratio (MTR). The MTR can be calculated as the percentage difference between two images acquired with and without off-resonance saturation. Lower MTR values correspond to a reduced capacity of the larger macromolecules to exchange magnetisation with the surrounding protons in tissue water thus giving an indirect measure of the integrity of these structures. MTI therefore enables detection of diffuse pathology in the otherwise NABT [328-330]. This allows for in-vivo measures of greater

pathology than conventional MRI. MTR can either be utilised in certain regions of interest [331, 332] or in whole-brain histogram analysis [333, 334].

Figure 2.3 Macromolecular Proton Saturation
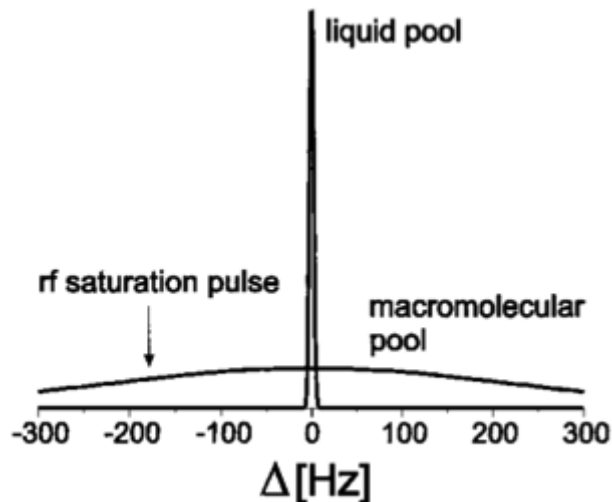
Protons within macromolecules have a short T2 and thus exhibit a broad resonance line. Using an off-resonance radiofrequency pulse (frequency well away from central narrow resonance line of water), the macromolecular pool can be preferentially excited and saturated.

From Henkelman et al. Magnetization transfer in MRI. Review Article. NMR Biomed. 2001. 14:57-64. [325]. Copyright 2001 with permission John Wiley & Sons Ltd.

MTI has been utilised in the study of MS. Decreased MTR has been consistently identified in NAWM of patients with MS but is most pronounced in the vicinity of lesions [316]. This has been substantiated from post mortem studies in which reduced MTR correlated with both reduced axonal density [335] as well as myelin content [336]. Whole brain MTI measures in MS using histogram analysis have revealed that MS patients typically exhibit lower average MTR, lower histogram peak height and peak position than healthy subjects[324]. Such abnormalities have been shown to exist at the earliest stages of MS including CIS [337, 338] and may be of predictive value in assessing the risk of

subsequent conversion to CDMS [339, 340]. In future, MTR may have a greater role as an imaging outcome measure in pharmaceutical trials [341].

Serial MTI studies have been undertaken to chart the temporal course of lesions in MS [342-346]. It has been shown that a reduction in MTR (indicative of myelin break down) can be identified up to four months prior to the appearance of a new T2-weighted lesion [342, 343, 347]. Van Waesberghe et al showed that MTR metrics were low in acute MS lesions as defined as areas of T1-weighted post-contrast Gadolinium enhancement. The areas that subsequently returned to isointense signal on T1-weighted sequences had a significant MTR increase towards normal over time indicating resolution of inflammation and likely remyelination. This was in contrast to lesions that remained hypointense over the same period following resolution of enhancement (indicative of more severe tissue injury) [254]. Such metrics may be a marker for assessing remyelinating properties of future DMTs.

MTR may also vary between MS phenotypes with lower MTR helping to distinguish progressive forms of MS from RRMS [331, 348]. Overall metrics have been shown to be lowest in PPMS followed by SPMS with RRMS having the least reduction in global MTR [107]. Progressive reductions in MTR appear to be more pronounced in SPMS than RRMS over a similar period [349].

Reduced MTR measures in NABT have been associated with cognitive dysfunction in a number of studies [350-353]. MTR reduction appears to correlate with cognitive dysfunction in MS patients even with clinically mild disease [352]. Early reductions in NAWM MTR, indicative of diffuse axonal injury, may in fact be predictive of subsequent development of cognitive dysfunction [354] and reduced whole brain MTR metrics may correlate better with cognitive impairment than brain atrophy measures [350, 351].

Quantitative Magnetisation transfer

One limitation of the MTR is that it does not have a direct physical or biological interpretation since it is dependent on the sequence parameters used [355] and combines the entire MT effect into a single parameter, thus potentially reflecting several discrete pathological processes [356]. The MTR is dependent on the density of macromolecules as well as the T1. Within demyelinating lesions, the T1 can be seen to increase thus resulting in an apparently normal MTR despite reduced macromolecular density.

Quantitative magnetisation transfer (QMT) is an analytical description of the two-pool model in which the MRI signal is expressed by a function of a set of parameters instead of a single MTR value [357]. Such analytical models of the MT phenomenon typically describe the signal attenuation as a function of the relaxation rates of the free and macromolecular pools (T_{2a} and T_{2b} respectively) as well as the macromolecular bound fraction *(f)*. Other parameters that can be derived include the forward exchange rate (K_f), which reflects the efficiency of transfer between the two pools and R_a, the longitudinal relaxation time.

A reduction in *f* has been shown in ex-vivo human studies to indicate reduced myelin content and has been shown to discriminate between myelinated and demyelinated lesions [358]. Such metrics in healthy controls reflect what is known about the normal distribution of tissue myelination [359]. Animal models have also suggested that *f* may provide measures of myelination independent of axonal loss [360, 361]. The interpretation of R_a and K_f are less clear but the R_a has been shown to be sensitive to AD pathology within the hippocampus and thus may reflect some of the metabolic processes linked to neurodegeneration in AD [362].

Relatively few studies have examined QMT parameters in multiple sclerosis [363-368]. It has been shown that *f* is reduced most significantly within lesions but also within NAWM compared to healthy controls [364, 367]. The parameter *f* may therefore be a particularly useful measure of brain myelin content and in monitoring for the remyelination in newer therapies. Narayanan et al showed

that although f was reduced in NAWM of patients with MS compared to controls, it did not appear to correlate with NAA levels using MRSI [364]. This would appear to provide further evidence that reduction in f reflects demyelination as opposed to axonal loss. In benign MS a reduction in f within the corticospinal tract can be observed [368]. In contrast, no reduction in fractional anisotropy on diffusion imaging was seen leading the authors to suggest this was reflective of demyelination without axonal loss. K_f has also been shown in some studies to be reduced in NAWN of patients with MS [363].

2.3 Functional MRI and Neuroplasticity

Functional MRI (fMRI) relies on there being a close association between neuronal activity, oxygen metabolism and blood flow into a given region. Functional MRI utilises blood-oxygen-level-dependent (BOLD) contrast, i.e. the difference in magnetisation between oxygen rich (diamagnetic) and relative oxygen deplete (paramagnetic) tissue to infer neuronal activity in a given region [369]. Functional MRI therefore provides insight into the areas of the brain active during particular tasks and provides a measure, albeit indirectly, of neuronal activity in a given region.

It is apparent that even at rest and in the absence of external stimuli the spontaneous BOLD signal is characterized by low frequency (≤0.1Hz) fluctuations that occur synchronously across multiple regions [370, 371]. Such areas of coherent activity are thought to represent complexes of synaptic connections in spatially diffuse but functionally related neural "resting-state networks" (RSNs).

Several RSNs have been identified including the salience network (devoted to attention of specific external stimuli in the presence of distractor stimuli), executive control network, as well as visual and auditory networks [370-378] (see figure 2.5). The most extensively investigated is the so-called "default mode network" (DMN) [379, 380]. Quite what the resting state activity within the DMN represents is unclear. It has been hypothesised to represent "self-related mental representations" [381] or "introspection" [382, 383]. What is clear is that with goal orientated behaviour, the DMN becomes deactivated while other task-specific networks become active [384-386].

Functional MRI has provided valuable insight into the role of neuroplasticity both in health and in disease states. Brain plasticity is the fundamental basis for learning and adaptive behaviour through life. It may also provide a means by which to limit the deleterious impact of accumulating brain pathology in a number of neurodegenerative conditions. Clearly there is a limit to which the brain can compensate for progressive damage to maintain normal performance

and the point at which that threshold is surpassed may determine when individuals become clinically symptomatic.

Figure 2.4 Identified Resting State Networks

Five RSNs from a single subject illustrating those commonly identified across 10 healthy subjects.
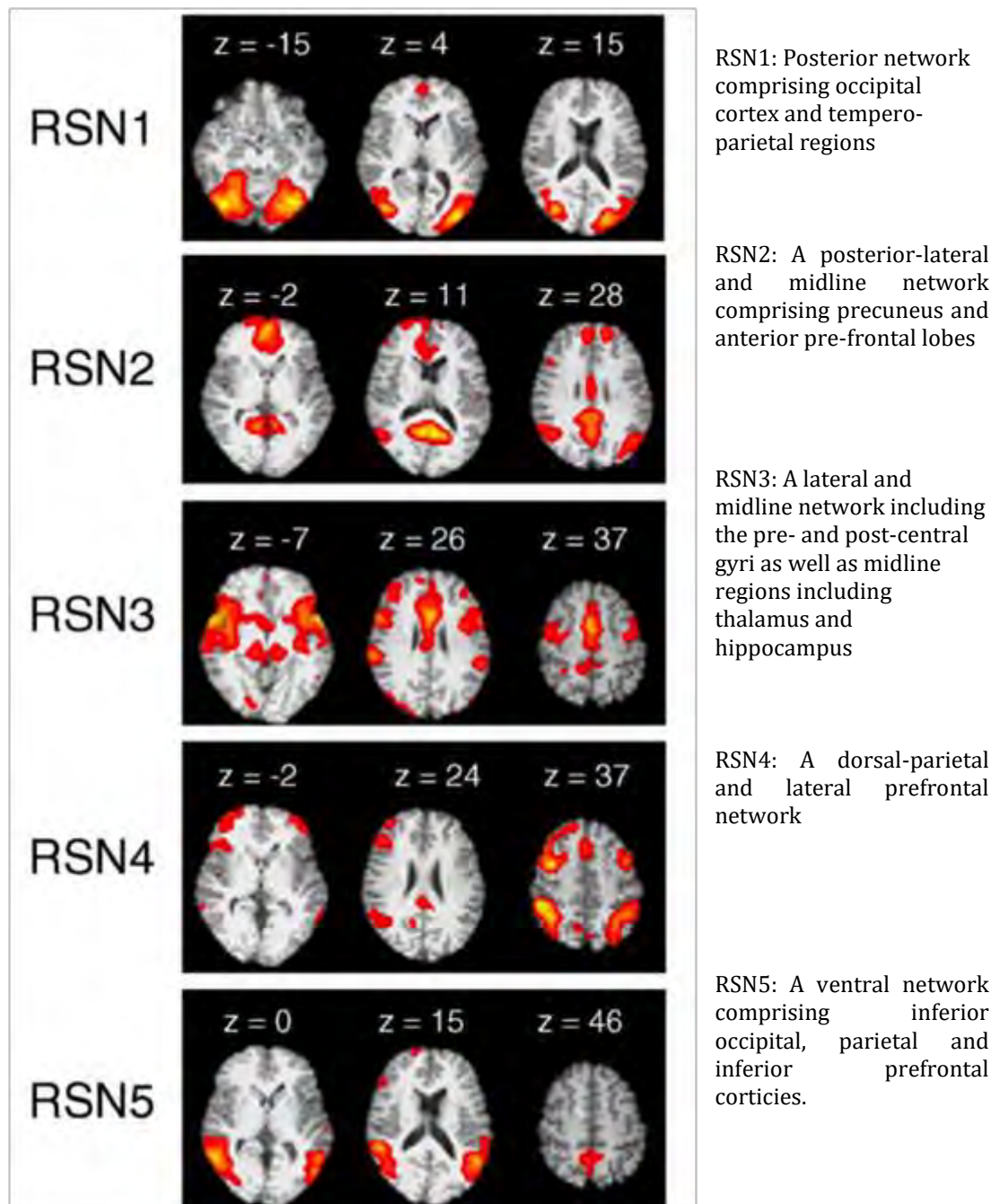
RSN1: Posterior network comprising occipital cortex and tempero-parietal regions

RSN2: A posterior-lateral and midline network comprising precuneus and anterior pre-frontal lobes

RSN3: A lateral and midline network including the pre- and post-central gyri as well as midline regions including thalamus and hippocampus

RSN4: A dorsal-parietal and lateral prefrontal network

RSN5: A ventral network comprising inferior occipital, parietal and inferior prefrontal corticies.

From: De Luca, M., et al., *fMRI resting state networks define distinct modes of long-distance interactions in the human brain.* Neuroimage, 2006. **29**(4): p. 1359-67. [378]

2.3.1 Brain plasticity and learning

At a fundamental level, it might be proposed that brain plasticity results from improved efficiency of previously utilised connections or through the development of novel connections for a given process.

The patterns of activity on fMRI and, in particular, the changes seen over time have provided some insight into the functional basis of a number of cortical functions. It has become well recognised that healthy individuals undertaking a familiar task show *decreased activity* in the task specific area with practice. This is likely to represent improved neural efficiency within a given area while maintaining the same basic functional anatomy [387]. This would appear to result in less "cognitive effort" being required and this mechanism is likely therefore to be important for the development of "automatic" responses to a given task [388]. Conversely, with novel or increasingly complex tasks, even in healthy individuals, increased BOLD activity often in "new" cortical areas is observed and therefore likely represents increased spatial extent of activation for a given task [389].

Ipsilateral supplementary motor cortex activation has been shown to occur with increasingly complex motor tasks [390]. "Expansion" of the primary cortex in this manner to utilise to pre-motor areas might result from utilisation of corticospinal projections that are known to exist in this area and are normally "redundant" for more simple tasks [391, 392]. Similarly, studies of mirror reading have revealed functional brain reorganisation as evidenced by a shift from activation of the dorsal visual stream, the so called "where" pathway (involved in visuospatial processing) to the ventral visual stream or "what" pathway (involved in object recognition) as participants became better practiced at mirror reading [393].

These adaptive fMRI changes may result from a number of mechanisms. There may be a greater degree of bilateral representation of a number of functions than traditionally recognised, the response to cerebral damage may be to promote changes at a cellular level or create new connections in remote

locations. Improved neural efficiency might result from increased synaptic activity whereas novel strategies might be dependent upon the development of new or remote pathways or utilisation of normally redundant pathways in a process of functional cortical reorganisation [389, 394, 395].

Animal studies have revealed evidence for changes at a cellular level with learning and plasticity associated with increased synapse turnover [396], net synaptogenesis [397] as well as changes in dendritic length [398]. Similar findings have been observed following brain injury in animal models including at sites remote from the brain injury [399]. Other animal studies however, have revealed evidence for normally inactive intracortical pathways that can become activated much more rapidly than one would expect if synaptogenesis were the sole mechanism of neural plasticity [400]. There is some evidence for inhibitory interneurons existing between opposite motor cortices which as a result of injury to one hemisphere, might result in disinhibition and activation of the contralateral cortex [401]. This "unmasking" of parallel pathways may explain the relatively rapid changes seen in fMRI in certain circumstances [402, 403].

Some studies have examined both functional and structural changes seen with learning in healthy adults [404-406]. This data would appear to suggest that, at least in part, neural plasticity results from structural brain changes. Studies showing increasing grey matter volumes with learning would appear to challenge the traditional understanding that, aside from neurodegenerative conditions and normal age associated atrophy, the fundamental brain structure is static [407]. It is often assumed to be the case that in neurodegenerative conditions, the observed grey matter loss is reflective of neuronal loss. Therefore, quite why such a short period of training should result in grey matter increase is unclear. Several potential mechanisms have been proposed including synaptogenesis, remodelling of the intracortical axonal architecture, increased size of the relevant glial cells or activated neurons, or localised hyperplasia of glial cells in response to repeated activation [396-398].

2.3.2   Brain plasticity in disease states

One might surmise that in the presence of pathology, the processes that underpin plasticity in normal learning are employed in a compensatory fashion to include both extension of the areas normally dedicated to a particular function as well as recruitment of other pathways not normally utilised in a particular function in other to minimise the functional impact of pathology [408]. There is increasingly congruent evidence for both of these mechanisms to have a role in brain plasticity in disease states.

Current models of brain plasticity in disease states have come from a number of sources and there is evidence of the brain making a functional recovery from both static and dynamic brain injury. In patients making a recovering from stroke, PET studies and fMRI studies have shown increased activation in the primary motor cortex contralateral to the ischaemic hemisphere [409-411]. This implies increased recruitment of the unaffected hemisphere possibly through neural disinhibition and unmasking lateral connections not normally used for a given task [412].

Interestingly, the degree of cortical reorganisation (inferred from the extent of increased activation), appears to be related to the time elapsed since a particular insult which might be expected if neuroplasticity is felt to result from changes at a cellular level. Serial PET studies in stroke patients have revealed progressively decreasing activity of ischaemic hemisphere and increasing activity in the contralateral hemisphere with increasing time elapsed from the stroke [413]. Similarly, fMRI studies of patients with brain neoplasia involving eloquent areas of motor cortex have revealed increased activity of the contra-lesional motor cortex again indicative of cortical reorganisation [414-416]. This may in part explain why individuals with low-grade gliomas and thus a slow rate of growth can remain relatively asymptomatic for long periods, as there is sufficient time for adaptive responses to occur. This is often in contrast to higher-grade tumours or metastases of a similar size.

2.3.3 Brain plasticity in MS

Recovery in the context of an MS relapse may result from a number of mechanisms such as resolution of the acute inflammation, remyelination [417, 418] or redistribution of ion channels to allow more efficient signal conduction within axons [419]. However in-vivo [420, 421] as well as ex-vivo studies [116, 258] have revealed significant axonal damage early in the course of MS that may be irreversible [422]. Therefore, even in the presence of partial remyelination, one may infer that more complex compensatory or repair mechanisms must exist to minimise the functional impact of accumulating pathology. This may be particularly important in progressive forms of MS where the inflammatory component is less apparent. The variable efficiency of such mechanisms may in part explain some of the clinico-cognitive heterogeneity seen in MS and a better understanding of such mechanisms may prove to be vital in developing more efficacious pharmacological and rehabilitative interventions.

Functional MRI changes suggestive of cortical reorganisation and plasticity are well recognised in MS [423-426]. Patients with CIS and early MS who are given a simple motor task show increased activation of the primary motor areas bilaterally, extension of activation to include the supplemental motor areas as well as remote areas not normally activated for a given task [427-429]. Following an episode of optic neuritis, it has also been shown that more widespread activation occurs following a visual stimulus into the affected eye as opposed to the unaffected eye. Areas remote to the primary visual cortex become activated including thalamus, and posterior-lateral parietal cortices [430].

The degree of reorganisation may be related to the extent and severity of disease burden. Increasing T2 lesion volume [425], average reduced lesion MTR and increased mean diffusivity (MD) on DTI have been seen to be associated with increased extent of shift of activation [426]. Altered functional connectivity therefore seems likely to be a surrogate marker for diminished structural integrity in a particular brain region.

Several studies have also shown the degree of cortical reorganisation in MS to evolve over time [424, 428, 431]. In one longitudinal study, Pantano et al found that the activation in the ipsilateral motor cortex correlated to the age and extent of T1 lesion load suggesting that those individuals with increasing disease activity required increased compensatory mechanisms in an attempt to maintain motor function [424]. This body of evidence may indicate that a degree of cortical reorganisation occurs early in the course of MS but later becomes more extensive in response to increasing pathology in an attempt to limit the functional impact of an accumulating disease burden [432].

2.3.4 Neuroplasticity and cognition in MS

It has been established that the pathophysiology of cognitive dysfunction in MS is complex and its structural and biochemical basis remains to be fully elucidated. Functional MRI however, does provide valuable insight into pathophysiology of cognitive dysfunction as well as mechanisms of repair. It follows that if functional reorganisation for motor tasks occurs in response to pathology, cognitive functions may exhibit a similar pattern of reorganisation in an attempt to ameliorate the impact of accumulating pathology.

Indeed, similar patterns of increased BOLD activation are seen with respect to cognitive impairment [433-435]. In addition to the normal neural networks associated with working memory, generally more extensive networks are utilised in patients with MS with a particular tendency for bilateral activation in such patients.

In order to examine working memory circuitry in MS it is important to have an fMRI paradigm that involves activation of functionally relevant regions that subserve information processing, simple attention (vigilance) as well as sustained attention. Using the n-back test as a test of working memory, Wishart et al examined a similar task in both MS patients with evidence of cognitive impairment as well as healthy controls [436]. Overall, similar frontal and parietal areas were seen to be active during the task in both groups and a greater spatial extent of activation was observed in response to increasing

complexity of the task in both groups (figure 2.5). Patients with MS however, were seen to have relatively less activation in these regions than healthy controls while exhibiting activation in some areas outside of conventional working memory circuitry (bilateral frontal, cingulate and parietal regions).

Figure 2.5 Activation Maps for MS patients during n-back Task
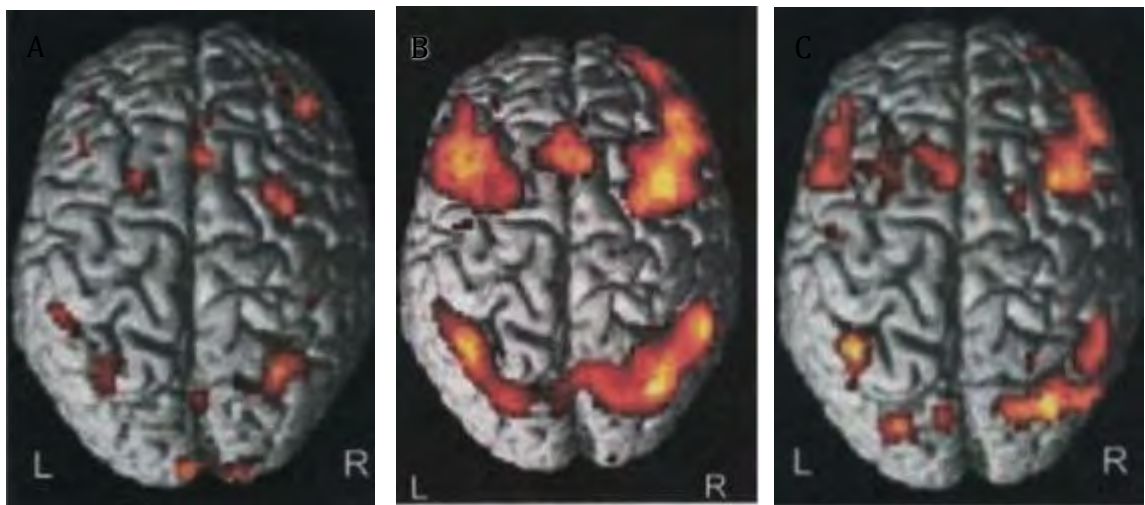
Activation map for patients with MS showing bilateral frontal activation during n-back task. Increasing voxels are seen to be activated with increasing task complexity.

A: 1-back > 0-back, B: 2-back >0-back, C: 2back > 1-back. (*p* = <0.01, k =3).

From Wishart, H.A., et al., *Brain activation patterns associated with working memory in relapsing-remitting MS.* Neurology, 2004. **62**(2): p. 234-8. [436]. Copyright 2004 with permission.

Using a similar n-back paradigm, Sweet et al studied 15 patients with MS with minimal cognitive impairment and it was observed that these patients had greater cortical activation of left frontal regions compared to age and sex matched controls. The central executive of working memory is thought to lie within the left prefrontal cortex (Brodmann area 46) [154, 155] and it may be the case that MS patients require greater utilisation of such executive processes to perform complex tasks [157].

Similarly several studies have observed that patients with CIS performing effortful cognitive tasks testing working memory (PASAT) had increased activation of the lateral prefrontal cortex relative to controls [434]. Audoin et al also showed that CIS patients with normal scores on PASAT exhibited larger activations in bilateral Brodmann area 45 (BA45) and right BA44 leading the authors to suggest that cortical reorganisation was occurring early in the course

of MS and may be successful in maintaining normal cognitive function in some individuals [437]. Staffen et al found that patients with RRMS with normal performance on the PASAT had increased activation of bilateral frontal and parietal regions [433].

Using the PASAT to test working memory, Chiaravalloti et al, also found that in addition to activating these areas, MS patients with cognitive impairment had increased activations of the right frontal and right parietal lobe during the task in contrast to the normal pattern of activation in healthy controls. The authors postulate that the involvement of the right hemisphere is due to cortical reorganisation or the "unmasking" of parallel networks.

With respect to attention, (known to be one the most frequently identified deficits in patients with MS), one fMRI study compared the patterns of activation in mildly cognitively impaired versus severely cognitively impaired individuals. It was found that those with mild impairment exhibited additional activations in frontal and parietal cortices as compared to healthy controls [438]. The effect was seen to decrease with increasing task complexity. Interestingly, in the patients with the most severe cognitive impairment, activation did not differ from controls leading the authors to suggest that alterations in activation are effective up to a point and that adaptive mechanisms in those most symptomatic patients had been exhausted. Alternatively however, patients may have had difficulty comprehending and performing the task due to the degree of cognitive impairment.

Activity within default mode network also appears to differ between MS patients with cognitive deficits and healthy controls with reduced resting activity within the anterior cingulate cortex correlated with reduced cognitive performance [439]. This brain region is thought to have a role in attention disorders [440].

The role of the cerebellum in cognition remains incompletely understood [441] but further evidence for its role in cognition is to be found from lesional studies as well as fMRI in tests of working memory [442]. There is evidence that the

right and left cerebellum may be involved in language processing and visuospatial processes respectively [443].

In summary, the most consistent features of fMRI studies in MS patients including those with cognitive dysfunction are of increased BOLD activation in regions beyond that normally activated in healthy individuals and a tendency for bilateral cortical activation for a given task. This body of evidence points to cortical reorganisation playing an important role in neuroplasticity in an attempt to ameliorate the effects of accumulating pathology.

2.4 Summary

Only with an understanding of the pathology of MS can MRI be optimally utilised to provide diagnostic information as well as to add to the body of understanding of pathogenesis of MS. Conventional MRI abnormalities, including hyperintensities on T2-weighted and FLAIR sequences are known to only modestly correlate with measures of disability and appear suboptimal for assessing the full extent of heterogeneous MS pathology. Assessment of the extent and rate of brain atrophy have however, emerged as potentially useful markers of cognitive dysfunction in MS. The rate of brain atrophy has become an important outcome measure in clinical trials assessing the efficacy of many newer generation disease-modifying therapies.

Quantitative MRI techniques have provided valuable insight into the pathological substrate of cognitive impairment in MS through in vivo identification of MS pathology beyond the resolution of conventional MRI sequences. Such techniques have gone some way to reconcile what is known about MS at a histological level with the clinico-cognitive features of the condition.

In recent years considerable advances have been made in understanding the basic mechanisms of plasticity both in physiological and disease states. A greater understanding of the brain's functional neuroanatomy and the areas responsible for various cognitive functions has provided insight into the pathophysiology of cognitive impairment in MS.

While remyelination and the resolution of acute inflammation may have some role in the recovery from an acute inflammatory demyelinating episode, clinical recovery has also been shown to occur as a result of brain plasticity through complex mechanisms of functional reorganisation by utilising relatively unaffected brain regions. In general it has been shown that patients with MS tend to recruit more extensive neural networks than healthy controls for a given task. With increasing burden of disease and reduction in brain tissue of normal integrity, these compensatory mechanisms may be overwhelmed and

brain plasticity may fail to ameliorate the decline both in physical and cognitive function.

A better understanding of the mechanisms that underpin plasticity and the extent to which recovery can occur for a given burden of disease also need to be elucidated. Promoting neural plasticity through both pharmacological and non-pharmacological means may provide an alternative therapeutic target for cognitive impairment in MS.

3

Cognitive Rehabilitation in MS

3.1 Introduction

There exists mounting evidence for neuroplasticity as a mechanism to compensate for accumulating pathology in MS and minimise both the physical and cognitive impact of the condition. Attention has turned to developing interventions targeting these particular mechanisms of repair to promote cognitive rehabilitation.

Structured cognitive rehabilitation may have a role in addressing some of the specific cognitive deficits identified in MS. The optimum means of promoting brain plasticity through these methods however remains unclear.

3.1.1 Background and Aims

Early studies of cognitive rehabilitation had inconsistent results often having utilised unclear definitions of cognitive impairment and non-standardised interventions. Non-specific interventions across multiple domains may have confounded outcome measures. In light of these study limitations and lack of definitive evidence for efficacy, previous Cochrane reviews have concluded there is only a low level of evidence for benefit of cognitive rehabilitation in MS [444, 445].

The need to individualise treatments according a patients needs and abilities, mindful of the physical limitations that MS can present, has led to difficulty in establishing a standardised approach to cognitive rehabilitation. A precise definition of cognitive impairment, the intervention offered and identification of appropriate outcome measures may be crucial.

With increased understanding of neuroplasticity derived from fMRI, more recent studies have utilised more robust study designs and utilised MRI to explore these factors in detail. This section will seek to review what evidence currently exists for cognitive rehabilitation strategies in MS.

3.1.2 Approaches

It is recognised that MS can result in a diverse range of cognitive deficits. It is unclear if certain domains are more amenable to intervention than others. The specificity of any intervention may therefore be an important consideration when evaluating it's efficacy. Some non-specific interventions such as memory aids, calendars and diaries have not been shown to be effective [446].

Several studies have found that patients with MS remember more information if it is self-generated rather than acquired through didactic learning [447, 448]. The "Story Memory Technique" promotes learning through the utilisation of context and imagery to facilitate acquisition of new information [449, 450].

Based on their earlier work and the emerging understanding that the primary memory deficit in MS may be partly related to the acquisition of new information, Chiaravalloti et al conducted a double-blind, placebo controlled randomised clinical trial (RCT) using the Modified Story Memory Technique (mSMT) [451]. 86 patients were randomly assigned to 10-sessions of this behavioural intervention or non-interventional meetings with a therapist of similar duration and frequency. 62% of patients in the treatment group showed improvement in the CVLT "slope" (defined as greater than 10% improvement from pre-test to post-test) compared to only 37% of the control group ($\chi^2 = 5.64$, p =0.009). General contentment scores as measured by the Functional Assessment of Multiple Sclerosis (FAMS) were also seen to increase in the treatment group compared to controls (figure 3.1).

This work and the knowledge of the cognitive domains affected in MS have led to specific interventions being developed to promote cognitive rehabilitation. Most studies have focused on measures of attention, verbal and/or visuo-spatial learning or executive skills.

Figure 3.1 Effects of Training with Modified-Story Memory Technique.
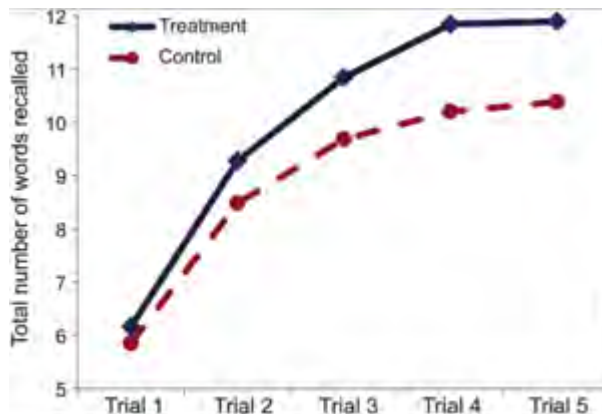
a: b:
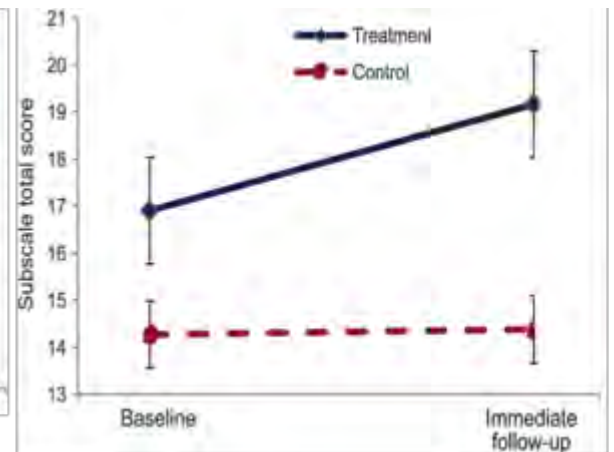
A: California Verbal Learning Test (CVLT) learning slope across the 5 learning trials of the CVLT immediately post-treatment, by treatment group (p < 0.05).

B: Baseline and immediate follow-up Functional Assessment of Multiple Sclerosis general contentment scores for the treatment and control groups (p < 0.05).

From Chiaravalloti, N.D., et al., *An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial.* Neurology. 81(24): p. 2066-72.

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3.1.3 Computer-assisted cognitive rehabilitation

Computer-assisted cognitive rehabilitation has been utilised in an increasing number of studies to provide a structured and standardised approach to rehabilitation (see table 3.2) [452-457]. This approach also particularly lends itself to home-based rehabilitation [458-461] although it is not without its limitations as the physical restrictions imposed by MS may make certain aspects of interfacing with a computer difficult [457].

One of the earliest studies to explore the potential of computerised rehabilitation was conducted by Plohmann and colleagues [452]. This quasi-experimental single-group design study targeted attention deficits in 22 patients with MS with a total of 12 computerised training sessions in the outpatient setting. Training was seen to result in improvements across a number of measures of attention examining alertness, divided attention, selective attention and sustained attention but was limited by lack of a control group.

RehaCom is one particular type of software designed and utilised for treatment of cognitive impairment in a number of disease states such as stroke, brain injury and psychiatric disorders [462, 463]. It has been used in a limited number of trials of cognitive rehabilitation in MS as a more standardised intervention [454-456]. The package can include a specially designed keyboard with minimal inputs and large buttons to minimise motor and coordination impairments. Training can target particular domains and also allows for individually tailored therapy. The difficulty level of the computerised tasks adapts to an individual's performance only increasing in difficulty in response to improving performance.

Solari and colleagues conducted a randomised controlled, double-blind trial utilising Rehacom as a means to target attention deficits in 82 patients with MS of various subtypes (RRMS n=39, progressive MS n=38) [464]. Patients were treated in the outpatient setting with twice weekly 45-minute sessions for 8

weeks targeting memory and attention. The study included an active control group that undertook training in visuo-motor and co-ordination as a sham intervention. Improvement (defined as 20% improvement in two subtests of BRBNT) was seen in 45% interventional group and 43% of control group. The authors concluded that the trial did not support the efficacy of training specifically targeted at memory and attention. This study however, included self-reported memory deficits as an inclusion criteria and required confirmation of only a score of below the 80th centile in at least two tests of BRBNT. This may have led to a heterogeneous group of patients and the inclusion of individuals without significant cognitive impairment. The authors suggest that the repeated stimulation associated with the sham intervention (a visuo-construction task) may have improved attention and thus influenced some measures of BRBNT. According to the authors, there was also an unexpectedly high refusal rate in this study which they suggest may have been due to work commitments and thus being unable to attend the frequent outpatient appointments required for the training.

Mattioli and colleagues conducted a randomised controlled study on a group of 20 patients with RRMS and low levels of disability (EDSS $\leq$ 4.0) [455]. Patients were identified as having cognitive impairment based upon impaired performance in both the PASAT (z = -1.5) and the Wisconsin Card Sorting Test (WCST) (T =35 in either total errors, number of perseverative errors or number of perseverative responses). Using RehaCom software, 10 patients undertook the modules "plan a day" (targeting executive function) and "divided attention". The 10 controls did not receive training.

The BRBNT was administered at baseline and after three months of training. After undergoing one hour training sessions, three times weekly for three months, it was found that compared to controls, the treatment group showed statistically significant improvements in both the PASAT 2" (p = 0.023) and WCST (p =0.037). The treatment group also exhibited significantly reduced depression scores on the Montgomery-Asberg Depression Rating Scale (p = 0.01). Such improvements were confirmed when adjustments were made for

EDSS, age and baseline performance. Improvements were not seen in tests of domains other than those targeted in the intervention.

Mantynen et al conducted a randomised controlled trial in 102 patients with RRMS and isolated attentional deficits [465]. Inclusion criteria included total score on SDMT of ≤50 (as measure of attentional deficit) but without evidence of overall cognitive impairment (<1.5 SD on overall BRBNT). Participants were randomised to either a computer-assisted program of cognitive rehabilitation or a control group that did not receive any training. The BRBNT was performed at baseline, after 3 months and after 6 months. The interventional group underwent training using ForamenRehab cognitive software comprising attention and working memory modules as well as psychoeducation and teaching of compensatory strategies. The schedule consisted 60-minute sessions once weekly for 13 weeks. Primary outcomes measures were the SDMT and the Perceived Deficits Questionnaire to assess patient's perceptions of their cognitive impairment.

There were no significant differences in performance on SDMT at follow up. After intervention and at six-month follow-up, the treatment group did however report significantly fewer cognitive deficits than the control group in the Perceived Deficits Questionnaire (PDQ; mean baseline 36.0±11.9 vs 38.2±12.6, after intervention 28.7±12.0 vs 37.3±13.0, p<0.001) (figure 3.2). The authors raise the question of what should be considered the ultimate aim of cognitive rehabilitation and perhaps the goal of cognitive rehabilitation ought to be to minimise the psychological and social impact of cognitive impairment. The authors suggest that improving a patient's awareness of their cognitive symptoms may help them devise compensatory strategies independent of a specific intervention and suggest that subjective improvement in cognitive symptoms may be an important outcome measure [466, 467].

Amato and colleagues used a home-based computerised program for specific retraining of attentional deficits in RRMS [461]. Patients were identified as having cognitive impairment if they scored <1.5 SD on at least two tests of

attention. 88 of the 102 patients initially recruited completed the study. Participants were randomised to specific (n=55) versus "non-specific" (n=33) attentional training. Specific training consisted of an "Attention Processing Training" program targeting focused, sustained, selective, alternating and divided attention. The non-specific training consisted of exercises such as text and newspaper article reading and comprehension. At three-months follow-up, significant improvement was seen relative to baseline in the PASAT and SDMT in both groups but was more pronounced in the specific treatment group. There was however no statistically significant difference between groups. The authors suggest focused awareness of cognitive issues may lead to improvements in cognitive performance across both groups independent of the specific intervention offered.

Figure 3.2 Subjective Change Cognitive Deficits Following Rehabilitation
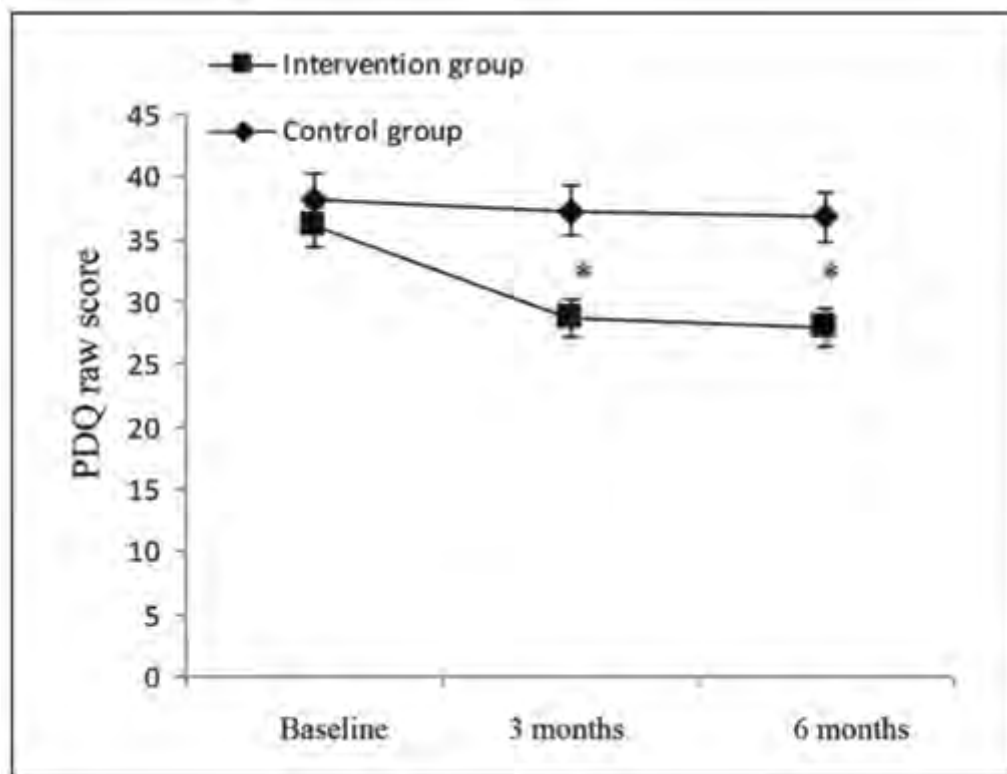
Change in perceived cognitive deficits (mean and SD) following cognitive rehabilitation. Following intervention, the treatment group reported significantly fewer cognitive deficits than the control group (p = <0.001).

Mäntynen, A et al. Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: a randomised, controlled, multi-centre trial. Multiple Sclerosis Journal, 2014. (20) p.99-107.
Copyright 2014 with permission from Sage [465].

Table 3.1 Selected Studies of Computer Assisted Cognitive Rehabilitation

Study	Design	Type of Computer training	Duration & Frequency	Sample	Outcomes
Solari et al., [464] 2004 (Italy)	Randomised controlled trial	Rehacom	Two 45minute sessions per week for 8 weeks	Treatment group = 40 Control group = 37	No statistically significant differences between treatment & control group
Tesar et al., [453] 2005 (Austria)	Randomised controlled trial	Rehacom	Twelve 1hour sessions over 4 weeks	Treatment group = 10 Control group = 9	Treatment group showed significant improvement in executive function & spatio-construction abilities
Hildebrandt et al., [458] 2007 (Germany)	Randomised controlled trial	VILAT-G 1.0	30 minute sessions, 5 days per week for 6 weeks	Treatment group = 17 Control group = 25	Treatment group showed improvement in verbal learning & working memory
Vogt et al., [459] 2009 (Switzerland)	Quasi-experimental 3 group design	BrainStim	(i) Four 45-minute sessions per week for 4 weeks or: (ii) Two 45-minute sessions per week for 8 weeks	(i) High intensity = 15 (ii) Distributed = 15 (iii) Control = 15	Improvements in measures of fatigue, working memory and information processing speed in both treatment groups independent of treatment dose.
Mattioli et al, [455] 2010 (Italy)	Quasi-experimental 2 group design	Rehacom (plan a day & divided attention)	Three 1 hour sessions per week for 3 months	Treatment group = 10 Control group = 10	Executive function, information processing & attention tests

Table 3.2 cont. Selected studies of computer assisted cognitive rehabilitation programs

Study	Design	Type of Computer training	Duration & Frequency	Sample	Outcomes
Sastre-Garriga et al [468] 2010 (Spain)	Controlled non-randomised	Attention, working memory & executive function training	Total of 15 computer training sessions & 5 group sessions over 12 weeks	N=59	Post treatment improvements seen in backward digit span test and on composite neuropsychological score. No correlation between improvements and specific regional activations on fMRI.
Shatil et al., [460] 2010 (Isreal)	Quasi-experimental 2 group design	Cogni-Fit Personal Coach	Three sessions per week for 12 weeks	Treatment group = 59 Control group = 48	Training group improved in measures of general memory, visual working memory & verbal working memory compared to controls
Filippi et al [454] 2012 (Italy)	Randomised controlled	Rehacom (plan a day & divided attention)	Three one-hour sessions per week for 12 weeks	N=20 (RRMS)	Improvement in attention, information processing and executive functions in treatment group. fMRI using the Stroop Test revealed increased activity in the posterior cingulate cortex and lateral prefrontal cortex.
Chiaravalloti et al [469] 2012 (Italy)	Double-blind, placebo-controlled RCT	Modified Story Memory Technique	45-60 minute sessions twice per week for 5 weeks	N=16	After treatment greater activations on fMRI in frontal, parietal, precuneus & parahippocampal regions.

Adapted from Amato, M.P., et al., *Treatment of cognitive impairment in multiple sclerosis: position paper.* J Neurol. **260**(6): p. 1452-68. [470]. Copyright 2013 Springer-Verlag with permission.

3.1.4 MRI outcomes

Few studies have examined the structural and functional basis of cognitive rehabilitation using advanced MRI techniques [454-456, 468].

A pilot study by Sastre-Garriga and colleagues recruited fifteen patients with MS and evidence of cognitive impairment along with five healthy controls [468]. Cognitive impairment among the patients with MS was defined as scores of <1.5 SD below the mean on at least two tests of six designed to examine for deficits in sustained attention, cognitive flexibility, working memory and information processing speed. Patients with MS underwent one-hour sessions of a combination of computerised and non-computerised game-like group activities thrice weekly for five weeks. The control group did not receive training.

Using the PASAT as the fMRI paradigm, participants were scanned at baseline, pre-rehabilitation and after five weeks of rehabilitation. Baseline and pre-rehabilitation scans were compared as a negative control to examine for practice effects and found no statistical differences in activation. After rehabilitation, MS patients showed significant improvement in performance on the backward version of the digit span test (baseline 54.73 ± 6.98, post-intervention 59.26 ± 4.28, $p = 0.007$) as well as a composite score of neuropsychological outcomes ($p = 0.01$). Neuropsychological outcomes however were not compared to the controls and may reflect a practice effect of repeat testing. Compared to controls, participants undergoing rehabilitation showed increased fMRI activity in the right cerebellum (p <0.001 uncorrected at voxel level). Conclusions from this small pilot study are restricted by its non-randomised design and limited descriptions of the non-computerised intervention.

Cerasa and colleagues used a double blind, randomised controlled study with 23 patients with RRMS and cognitive deficits limited to information processing speed, sustained attention and executive function as a means to focus a specific intervention [456]. Subjects were included if they scored <2 SD below the mean

on at least one of the SDMT, PASAT, Trail making test (A-B) or the Stroop word colour task. Patients were however excluded if they had evidence of severe cognitive impairment as defined as scoring <2 SD below the mean normative values in at least three tests on a more extensive cognitive battery of tests, mainly drawn from the BRBNT.

Patients were randomised to either the active treatment arm which involved structured cognitive rehabilitation using RehaCom in modules of "divided attention", "attention and concentration" and "vigilance", or the control group which performed visuomotor coordination tests with a timed response to presented stimuli. All participants met twice weekly for 1-hour sessions for six weeks. Following treatment, patients showed statistically significant improvement in the Stroop test compared to controls (p <0.007).

Using the paced visual serial addition test (PVSAT) as an fMRI paradigm, patients in the treatment group showed increased activity in *a priori* regions of interest (ROI) including the right posterior cerebellar lobule (p_{FWE} = 0.02) and left superior parietal lobule (p_{FWE} = 0.04) relative to controls at follow up. The increased activity in these regions was positively correlated with improvement in the Stroop Task on regression analysis (figure 3.3).

Figure 3.3 Group x Time Interaction of Cognitive Rehabilitation on fMRI activity
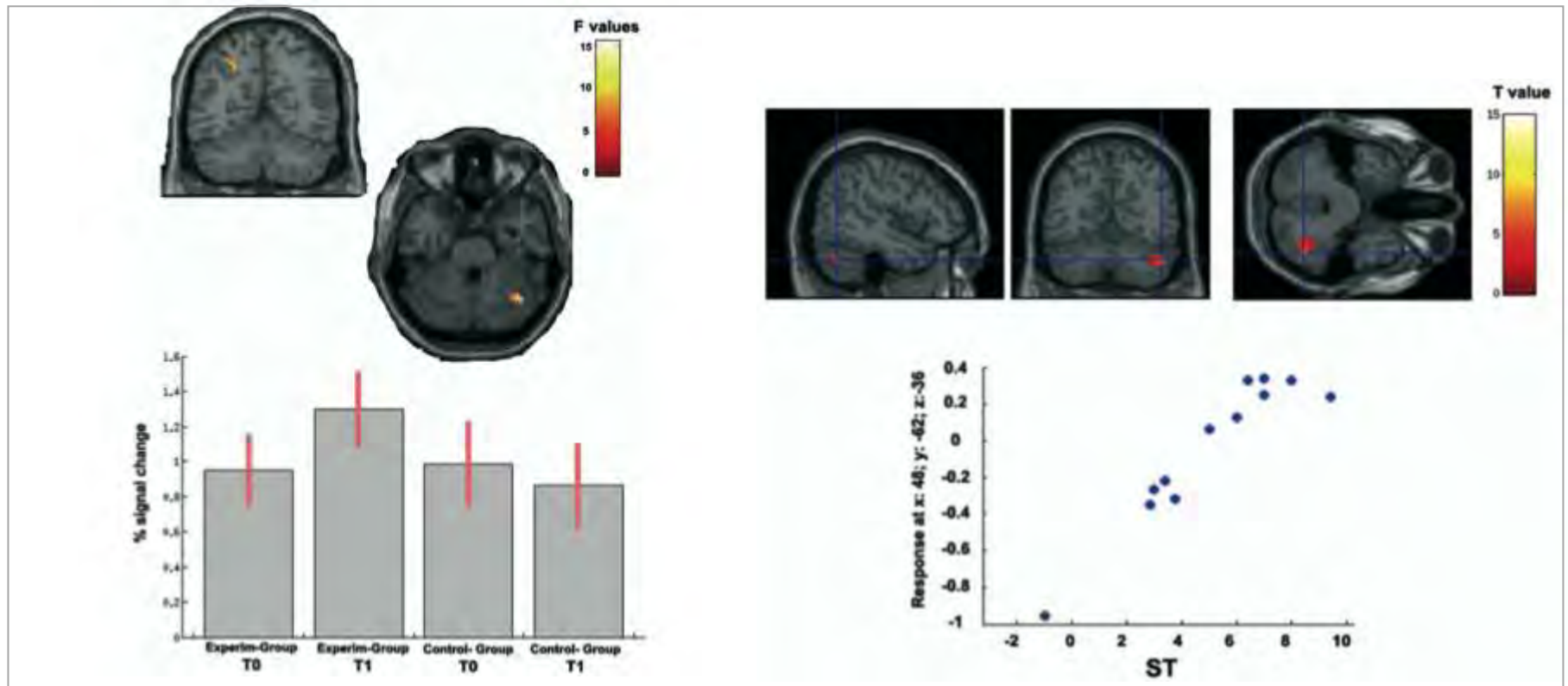
Treatment group showing significantly increased activity in right posterior cerebellar lobule (p_{FWE} = 0.02), left superior parietal lobule (p_{FWE} = 0.04) relative to control group after

Significant correlation between brain signal activity (in right posterior cerebellar lobule during fMRI) and behavioural performance during Stroop Task (delta scores) in experimental

Cerasa, A., et al., Computer-assisted cognitive rehabilitation of attention deficits for multiple sclerosis: a randomized trial with FMRI correlates. Neurorehabil Neural Repair, 2013. **27**(4): p. 284-95. Copyright 2013 with permission from Sage.

Also utilising RehaCom software, Filippi et al performed a randomised controlled trial with 20 patients with MS involving a supervised 12-week training program. The training primarily targeted executive function and attention through the "plan a day" and "divided attention" modules [454]. The control group did not receive any intervention. Cognitive impairment was defined as z scores of less than -1.5 in either the PASAT or any measure of the WCST.

The authors identified significant improvements in PASAT 2" (control group baseline 3.9±8.3, post-intervention 4.9±9.5, treatment group baseline 7.6±10.1, post-intervention 17.7±15.0, p = 0.03). In the PASAT 3" improvements were also seen in the treatment group relative to controls (p=0.001). At follow up, improvements were also seen in all measures of the WCST (total errors p = 0.02, perseverative responses p = 0.01 and perseverative errors p = 0.03) in the treated group compared to controls indicative of improvement in attention, information processing and executive functions.

Using the Stroop Test as the fMRI paradigm, a significant "treatment x time" interaction was seen with increased activity in the posterior cingulate cortex and dorsolateral prefrontal cortex bilaterally at follow up in the treatment group (figure 3.4). This study is also the only study to date to explore the potential structural basis of alterations of fMRI activity in cognitively impaired patients with MS, however no structural changes in relation to GM volumes or NAWM architecture on DTI were found.

This study has several limitations as it was limited to a small number of patients who were of were of relatively low disability levels (EDSS <4.0) and had not received DMTs in the preceding year suggestive of a milder disease course. It is unclear therefore, if the study conclusions are applicable to a wider population of MS patients. The mean PASAT 3" score in the control group was seen to decrease at month 3 (baseline 11.0±12.0, post-intervention 9.7±16.5). This is in contrast to the expected learning effects seen in most neuropsychological studies involving repeat testing.

Figure 3.4 Changes in fMRI activity during Stroop Task
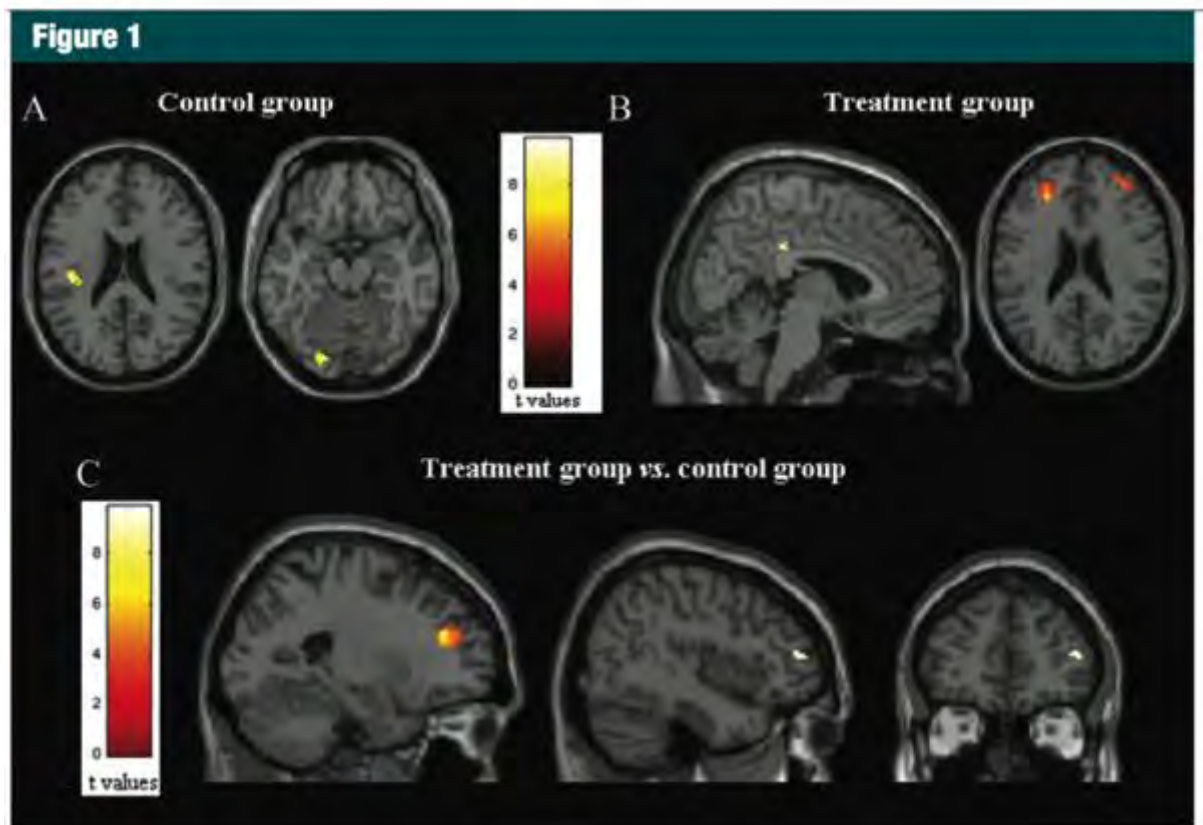
Statistical parametric mapping results showing changes between time 1 and time 2.

A: Control group showing increased activation in left insula and left lingual gyrus. B: Treatment group showing increased activation of the posterior cingulate cortex and bilateral dorsolateral prefrontal cortex. C: Between group comparison showing significant "group x time" interaction (analysis of variance, two-by-two factorial design)

with activation in left dorsolateral prefrontal cortex ($p_{FWE} = <0.05$).

Filippi, M., et al., *Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study.* Radiology, 2012. **262**(3): p. 932-40.

Copyright 2012 with permission from RSNA [454].

3.2 Summary

The effectiveness of cognitive rehabilitation in MS remains uncertain. It is clear however, that adequate identification and management of cognitive impairment in MS remains a significant unmet need for patients and their relatives.

Research that seeks to explore these questions further must have clear definitions of what constitutes cognitive impairment and the specific domains targeted by any intervention must be reflected in the outcome measures. Studies should be mindful of the most pertinent cognitive deficits in MS, which are known to be related to attention and speed of information processing which impact upon efficient working memory function and may be the most amenable to intervention. Previous studies have often been limited to patients with mild disability. It is unclear how generalisable findings from such studies are to the MS population as a whole.

With any intervention that may impact upon cognitive function in MS, determining the magnitude of improvement in neuropsychological tests that is clinically meaningful is difficult. Even having utilised appropriate cognitive tests to identify patients with cognitive impairment, such tests may prove to be insensitive to change over the short term. Advanced MRI provides a potentially more sensitive measure of learning potential and early identification of neuroplasticity may be fundamental for any rehabilitative strategies.

Limited fMRI studies illustrating plasticity with various interventions have established the potential for cognitive rehabilitation. There remains a need to undertake longitudinal studies and develop techniques that focus on the structural basis of brain plasticity. Effective cognitive rehabilitation is likely to involve plasticity over the longer term through the promotion of effective network remodelling. Detailed studies of resting state networks and the microstructural architecture of normal appearing brain tissues are lacking.

The remainder of this thesis will attempt to address some of these unanswered questions through identifying individuals with cognitive impairment attending MS clinic and further explore the potential for cognitive rehabilitation using detailed structural and functional MRI.

Through detailed description of a broad patient cohort, attempts will be made to identify additional characteristics that may discriminate those individuals with cognitive impairment from MS patients who are cognitively intact and provide a framework around which clinically meaningful improvement in cognitive performance might be defined.

Focus will be given to an experimental design that seeks to explore the feasibility and efficacy of a home-based, computer-assisted cognitive rehabilitation program and will utilise advanced structural and functional MRI techniques to better understand the basis of learning and thus the potential for cognitive rehabilitation in an MS population.

The following chapter will outline cross-sectional data examining the relationship between cognitive impairment, unemployment and QOL. Subsequent chapters will report longitudinal data exploring the efficacy of cognitive rehabilitation in patients with cognitive impairment with fMRI, cognitive and QOL measures.

4

Application of BICAMS in a UK Outpatient Clinic.

Description of a UK Patient Cohort

4.1 Introduction

There are a number of cognitive test batteries that can be used to identify cognitive impairment in MS [121, 202]. The Brief International Cognitive Assessment for MS (BICAMS) is a brief (15-minute) screening tool for practicing clinicians to identify cognitive impairment in. BICAMS comprises the first five learning trials of the California Verbal Learning Test II (CVLT-II), the first three recall trials Brief Visuospatial Memory Test Revised (BVMT-R) and the Symbol Digits Modality Test A (SDMT) [203].

As part of a longitudinal study exploring the efficacy and feasibility of home-based, computerised cognitive rehabilitation (see chapter 5), patients who consented to enrol in the trial first underwent screening with BICAMS to identify those with cognitive impairment eligible for the study.

In this chapter we present the data obtained during screening and examine how the presence of cognitive impairment relates to disability, employment and quality of life measures in our patient population. It provides the first UK data on the application of BICAMS in relation to many of these measures including employment status.

4.2 Subjects and Methods

4.2.1 Participants

Sixty-two patients (43 female, 19 male) were included in the study between February 2014 and February 2015. Participants were recruited through outpatients while attending for routine Neurology outpatient appointments at Brighton and Sussex University Hospitals NHS Trust (BSUH). All participants signed informed written consent before undergoing testing. The study was approved by the Northern Ireland Research Ethics Committee. Inclusion criteria were as follows: (a) age between 18 and 65, (b) clinically definite MS, according to the McDonald criteria [22]. All participants underwent a detailed neurological assessment including Kurtzke Expanded Disability Status Scale

(EDSS)[110] scoring by an EDSS certified neurologist (http://www.neurostatus.net).

Patients were excluded if they had a history of significant psychiatric disorders, alcohol or drug abuse, visual acuity less than 6/18 corrected, oscillopsia or diplopia that would interfere with testing. Patients were also excluded if they had had a MS relapse, received corticosteroids, changes in antidepressants or psychoactive medications within the previous month.

4.2.2 Cognitive and Behavioural Assessment

Participants underwent neuropsychological assessment and were defined as having cognitive impairment if they scored below the 5th centile for normative data (adjusted for age, sex and years of formal education) on one or more of the BICAMS tests.

MS specific measures
Patients completed the following assessments;

- Functional Assessment of MS (FAMS) a MS specific, self-reported, quality of life scale which comprises six subscales pertinent to QOL in MS and rated in a five-point Likert-scale: mobility (0-28 points), symptoms (0-28 points), emotional well-being (0-28 points), general contentment (0-28 points), thinking/fatigue (0-36 points) and social well-being (0-28 points). A higher score reflects better QOL [471].

- Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), a 15-item patient measure of perceived competency with activities of daily living and day to day cognitive tasks [472]. There are two parallel versions, the self-reported (MSNQ-S) and similar informant reported format (MSNQ-I). Positive MSNQ-S is defined as a score greater than 23. MSNQ-S has been shown to correlate with all three tests in the BICAMS battery [473] but is also influenced by depression [284, 474]. Therefore a positive MSNQ might therefore be considered to be a potential measure of neuropsychological and neuropsychiatric compromise rather than

cognitive impairment alone [284]. In this study due to patients often attending outpatients alone, only the MSNQ-S was administered.

- The Fatigue Severity Scale consists of nine items scored from 1 to 7 (1 = completely disagree, 7 = completely agree)[475]. It focuses primarily on the physical impact of fatigue with one item relating to the cognitive impact of fatigue. Scale scores are the mean of item scores.

- Unidimensional Self-Efficacy scale for MS (USE-MS), is a 12-item self-reported scale measuring an individual's self-efficacy i.e. belief in their abilities to enact change in their personal circumstances [476].

General disease outcome measures

- EuroQOL five dimension questionnaire (EQ-5D-L), is a generic health-related quality of life scale consisting of five questions assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression each on a five-point scale from 1 to 5 (denoting no problems to frequent problems) [477]. A second part of the questionnaire requires patients to highlight their perceived QOL on a visual analogue scale ranging from 0 to 100, with 0 representing the "worst health imaginable" and 100 denoting the best. Different weights are ascribed to the relevant components of the questionnaire yielding a providing a range of scores from -0.6 to 1.0. A score of less than zero is associated with a perception of QOL worse than death. EQ-5D has been recently utilised in MS [478] including one large scale study showing that all the domains assessed on EQ-5D were determinants of QOL in patients with MS providing validation of this tool in MS [479].

- The Hospital Anxiety and Depression Scale (HADS) [480] is a 14-item self-reported scale comprising two subscales of seven items each examining anxiety and depression. A score of 8-10 is considered borderline while a score of 11 or more indicates anxiety or depression. Although devised as a generic scale it has been validated in MS [481] showing a high degree of specificity and sensitivity [226].

- Patient Activation Measure (PAM-13) a 13 item generic scale for chronic illness management and a measure of patient "empowerment" which has been validated in MS [482].

- Data was also obtained on employment status.

4.3 Statistical Analysis

Analyses were performed using SPSS version 21 (Armonk, NY: IBM Corp). Descriptive statistics for continuous variables are expressed as mean and standard deviation, while categorical variables are expressed as frequency and percentage.

All tests were two-tailed; p values less than 0.05 were considered significant. Kolmogorov-Smirnov tests of normality were used to confirm normal distribution of the variables. Categorical variables were compared by Pearson χ^2 test or Fisher's exact test as appropriate. Continuous data were compared by means using independent samples t-tests (for normally distributed data) or the Mann-Whitney U test for non-normally distributed data.

In secondary analysis, binary logistic regression analyses were conducted to determine which factors were most predictive of employment status. Variables that significantly differentiated employment status were entered into the regression model.

4.4 Results

4.4.1 Demographic and Cognitive Outcomes

65 patients were consented for screening. Three patients were excluded on the basis of oscillopsia/diplopia that would potentially interfere with testing. 62 patients underwent clinical and neuropsychological assessment. 40 patients (65%) showed evidence of cognitive impairment as defined as scoring below the 5th centile for normative data on one or more of the BICAMS tests.

At entry 44 patients (71%) had relapsing remitting MS (RRMS) and 18 patients (29%) had secondary progressive MS (SPMS). Participants were aged between 31 and 63 years of age (mean 49.35, SD 8.88). The duration of MS from diagnosis to enrolment ranged from 12 months to 40 years (mean 12 years, SD +/- 8 yrs). Median EDSS was 4.0. 31 participants (50%) were on disease

modifying therapy (DMT) at enrolment (natalizumab n=7, beta-Interferon n=9, glatiramer acetate n=2, fingolimod n=11 and teriflunomide n=2).

Among the cognitively impaired patients, 21   (52.5%) failed one test, 11 (27.5%) failed two tests and 8 (20%) failed all three tests of the BICAMS test battery. The most frequently failed exam was the SDMT with 56% of all patients scoring below the 5th centile, 29% failed the CVLT-II and 23% failed the BVMT-R (figure 4.1).

Figure 4.1 Proportion of all patients scoring below 5th centile on BICAMS tests
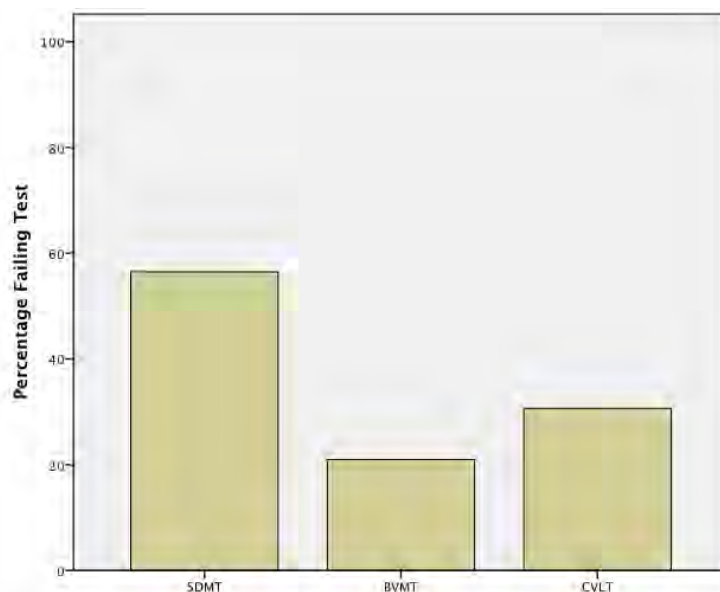
Baseline and demographic characteristics of the two groups (cognitively impaired versus non-cognitively impaired) are shown in table 4.1. Gender, age, education, duration of illness, treatment with disease modifying therapy and EDSS did not differ significantly between the groups. Overall 27 (44%) of patients were in employment however patients with cognitive impairment on one or more tests were significantly more likely to be unemployed (p = 0.007 χ^2), (OR 4.5, 95% CI 1.5 – 13.6), RR 2.1 (1.1 – 4.1). Increasing rates of unemployment were associated with increased number of tests failed (p=0.011)

(see figure 4.2). The odds of being unemployed with patients failing on 1, 2 and 3 tests increased to 4.3, 5.7 and 6.4 respectively.

Figure 4.2 BICAMS and Unemployment
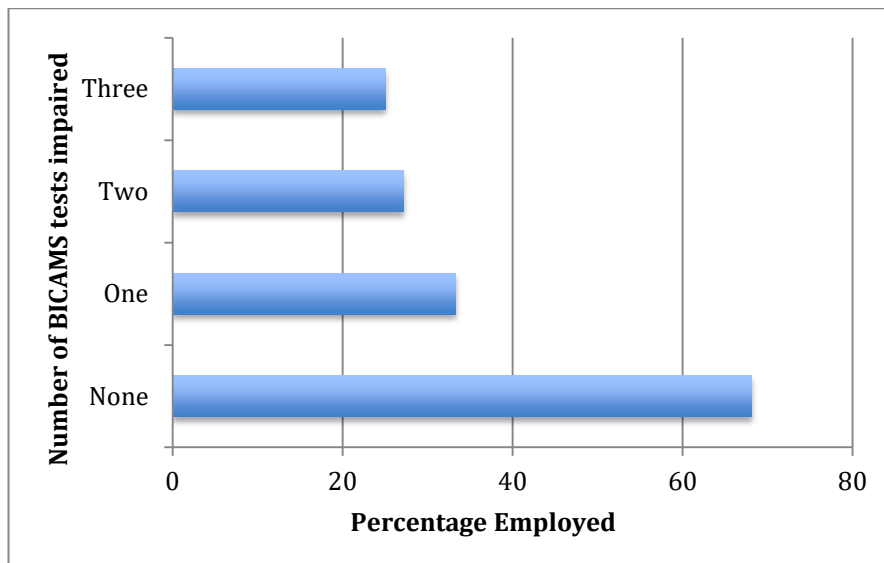
Rates of employment versus number of tests failed showing increasing rates of unemployment the more BICAMS tests that are failed.

In a binary logistic regression with employment status as the dependent variable, among the variables potentially relating to employment (disability, sex, duration of disease, disease course and cognitive impairment), the SDMT score and gender (female >male) were found to be the most significant predictors of unemployment accounting for between 44-59% of the variance (table 4.2). Rates of unemployment were seen to increase with lower performance on the SDMT (figure 4.3).

Table 4.1 Demographic characteristics by group

	Normal Cognitive Performance (n=22)	Cognitively Impaired (n=40)	
	Mean ± SD	*Mean ± SD*	*p-value*
Gender			
Female	15 (68.2%)	28 (70%)	.882(χ^2)
Male	7 (31.8%)	12 (30%)	
Age (years)	51.3 (9.7)	48.3 (8.33)	.210
Time since diagnosis (years)	10.8 (7.3)	12.7 (8.2)	.375
Disease subtype			
Relapsing-remitting	17 (77.3%)	27 (67.5%)	.417(χ^2)
Secondary-progressive	5 (22.7%)	13 (32.5%)	
EDSS median (IQR)^	4 (2.0; 4.5)	4 (3.3; 6.0)	.065**
Treatment at enrolment to study			
Yes	12/22 (54.5%)	19/40 (47.5%)	.596(χ^2)
Interferon*	3	6	
Glatiramer Acetate	2	0	
Fingolimod	6	5	
Natalizumab	0	7	
Teriflunomide	1	1	
Dimethly-Fumarate	0	0	
No DMTs			
Education (y)	14.05 (2.34)	13.80 (2.78)	.614
Employed			
Yes	15 (68.2%)	13 (32.5%)	.009 (χ^2)
No	7 (31.2%)	27 (67.5%)	
Driving			
Yes	18	32	.100 (Fisher's exact)
No	4	8	

^median

** Non-parametric Mann-Whitney U Test

*Includes IF-1b SC, IF-1A IM and IF-1A SC

Figure 4.3 Rates of employment with increasing performance on SDMT
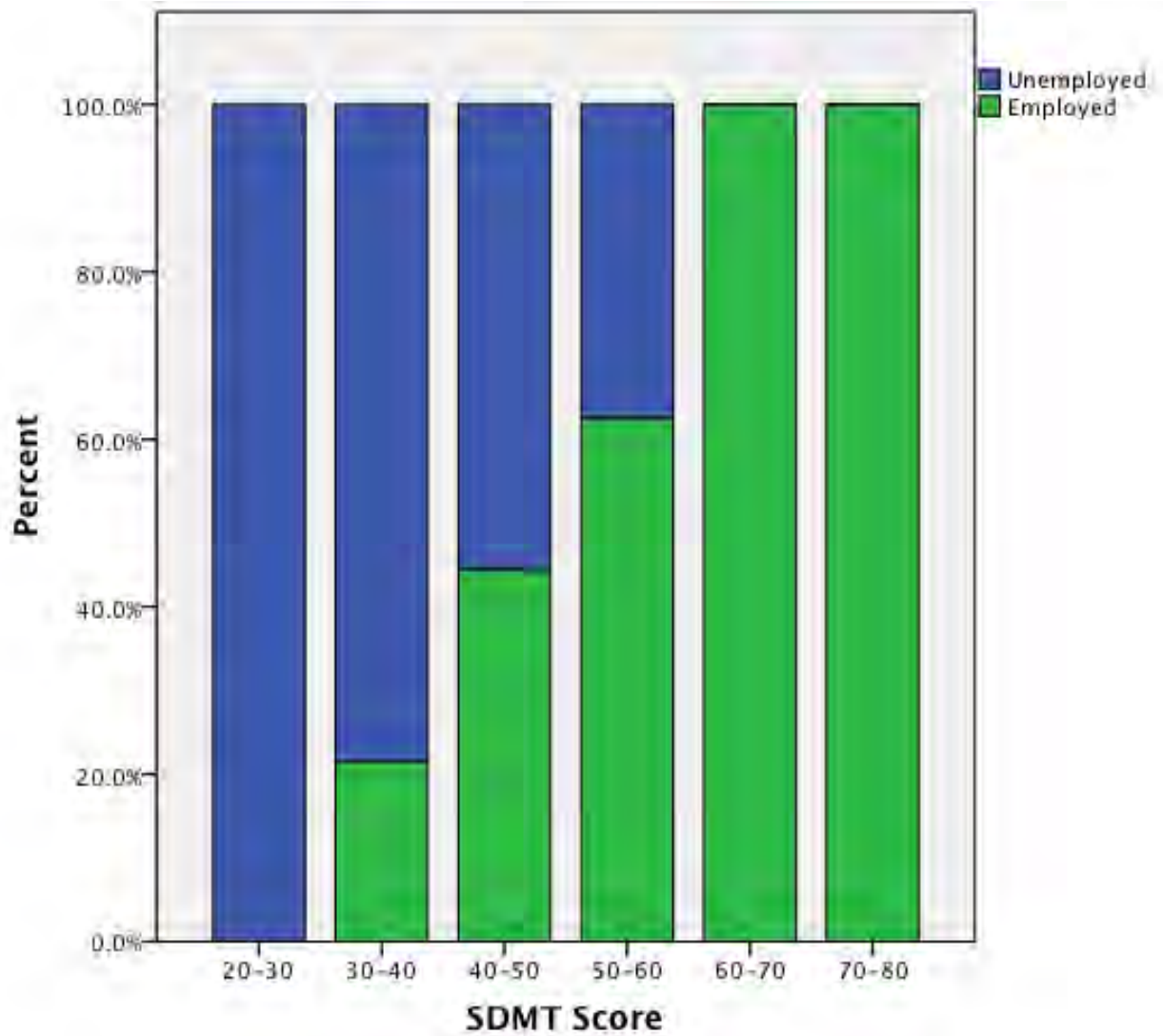
SDMT score versus rate of employment showing lower rates of employment with lower SDMT scores.

Table 4.2 Regression model (Employment as dependent variable)

Variables in Equation	Sig.	Exp(B)	95% C.I. for Exp (B)	
			Lower	Upper
Age	.732	.982	.888	1.087
Duration	.201	.916	.800	1.048
Type of MS	.872	1.217	.111	13.326
Education	.873	1.024	.768	1.364
EDSS	.996	.998	.575	1.734
Gender	.023	8.371	1.336	52.441
SDMT	.005	1.161	1.045	1.290
CVLT	.622	1.021	.940	1.109
BVMT-R	.831	.985	.856	1.133
Constant	.030	.000		

Model Summary

Step	Cox & Snell R Square	Nagelkerke R Square
1	.442	.592

4.4.2 Quality of life and behavioural data

Quality of life and behaviour outcome measures are shown in table 4.2. Patients with cognitive impairment had significant lower FAMS scores (p=0.001) (indicating lower QOL), higher EQ-5D scores (p<0.001) (indicating lower QOL) and higher MSNQ-S (p=0.004) scores in keeping with a greater subjective perception of cognitive impairment.

Of the three cognitive tests employed, the SDMT was found to correlate most closely with FAMS and EQ-5D QOL outcome measures (table 4.3). Quality of life measures were seen to improve with increasing performance on the SDMT (Figures 4.4).

Table 4.3 Quality of life and behavioural measures

	Normal Cognitive Performance (n=22)		Cognitively Impaired (n=40)		
	Mean	*± SD*	*Mean*	*± SD*	*t*
FAMS	117.05	23.72	90.93	30.86	.001
PAM-13	64.86	13.10	61.84	17.00	.471
EQ5D	8.59	2.61	11.78	3.29	<.0001
USE-MS	20.27	5.16	17.41	6.72	.089
MSNQ-S "Positive"	12/22	(54.5%)	33/40	(82.5%)	.018(χ^2)
HADS-D	7.23	3.56	9.03	3.29	.05
HADS-A	7.50	5.21	9.15	4.69	.208
FSS	45.81	9.47	50.35	11.90	.136

FAMS: Functional Assessment of MS; PAM-13: Patient Activation Measure; EQ5D: EuroQOL five dimension questionnaire; USE-MS: Unidimensional Self-Efficacy scale for MS; MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; HADS-D: Hospital Anxiety and Depression Scale (depression); HADS-A: Hospital Anxiety and Depression Scale (anxiety); FSS: Fatigue Severity Scale;

Table 4.4 Correlations between BICAMS and QOL outcome measures

	FAMS	EQ-5D	MSNQ-S
	Pearson's Correlation		
SDMT	.435 (*p*= <.001)	-.466 (*p*= <.001)	-.321 (*p*=.011)
CVLT-II	.359 (*p*=.004)	-.294 (*p*=.020)	-.417 (*p*=.001)
BVMT-R	.200 (*p*=.119)	-.196 (*p*=.127)	-.361 (*p*=.004)

Figure 4.4 SDMT score versus QOL measures
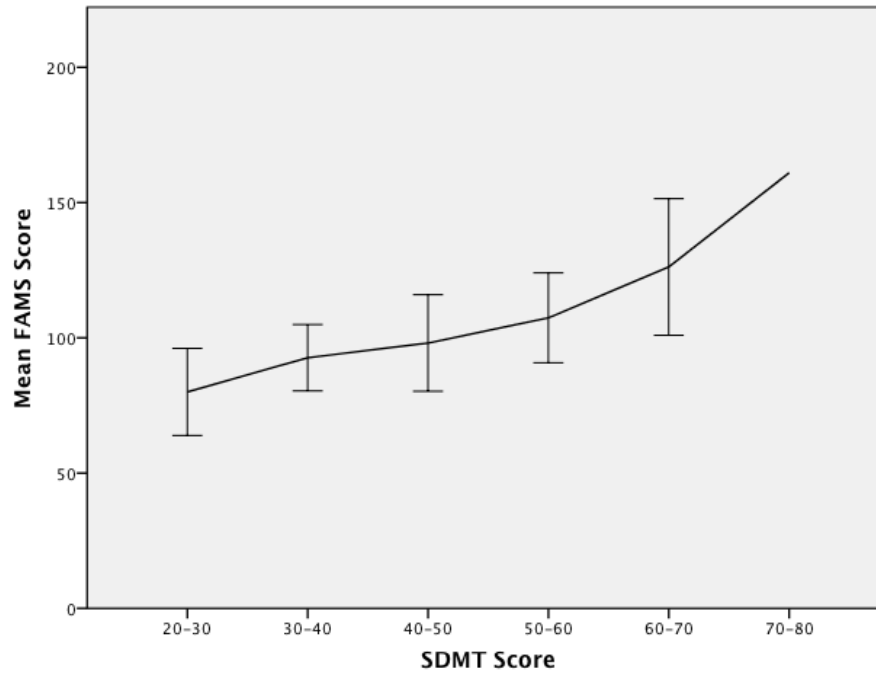
(a) Graph showing increase mean (95% CI) FAMS score (indicating better QOL) with increasing SDMT performance.
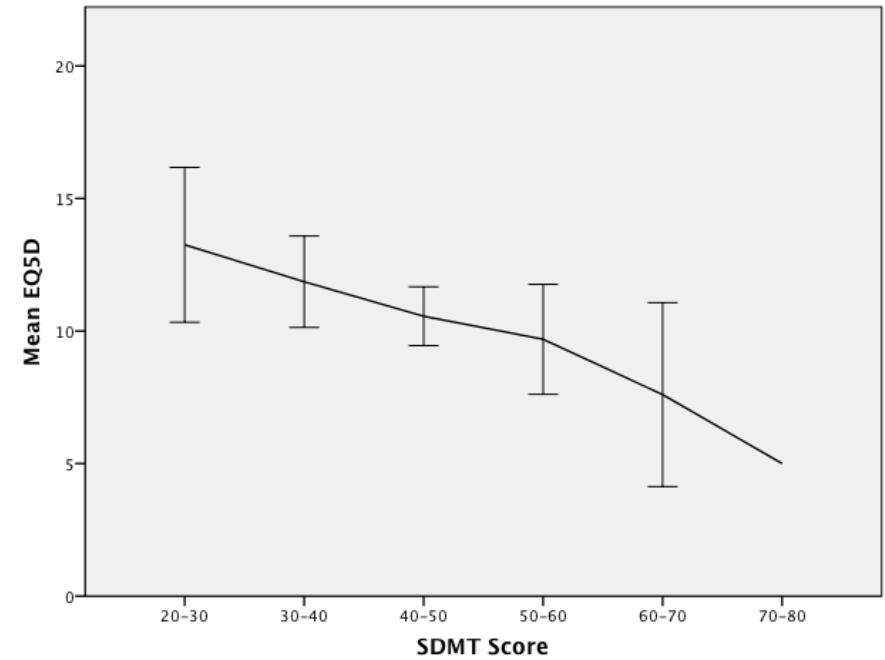
(b) Graph showing decreased mean (95% CI) EQ5D score (indicating better QOL) with increasing SDMT performance

4.5 Discussion

Cognitive impairment is common among patients with MS. The incidence of cognitive impairment in our cohort of MS patients attending outpatients at 65% was similar to that previously reported elsewhere. BICAMS provides a sensitive and easy to conduct means of identifying cognitive impairment in the outpatient setting and may provide a means for identification of patients with other, more complex psychosocial needs.

Rates of unemployment have been shown to increase over time in patients with MS and presents significant cost implications to the individual and society [483, 484]. Various risk factors for unemployment in MS have been identified including low education level, extent of disability, progressive subtype and personality as well as cognitive impairment [485, 486].

This study provides the first UK data pertaining to the use of BICAMS in relation to employment status within a UK cohort. Factors linked to unemployment in our study were advanced age and disease duration, increased disability and cognitive impairment. When included in a regression analysis, the only significant predictors of employment status were lower performance on the SDMT and female gender accounting for 59.2% of the variance.

Of the tests utilised within BICAMS, the SDMT may provide among the most sensitive measures of cognitive impairment in MS [172, 173]. Previous work examining cognitive impairment in relation to employment in MS had identified the SDMT to also be one of the main predictors of employment status [485, 487-489]; the CVLT-II has also predicted reduced employment status in a longitudinal study [485]. The SDMT, as a measure of information processing speed, may indicate competence at multitasking, a requirement of many employment situations [490]. Although simple strategies may overcome memory deficits, at least when they are mild, the "bandwidth" limitations of reduced information processing speed are less easy to manage.

Female gender has previously been associated with unemployment among patients with MS [85]. It one study it was reported that 60% of women cited an inability to meet the combined demands of home and work as the primary reason for leaving employment [491]. It is not clear, however if the gender difference observed here is reflected in the wider workforce within the local area.

Patients with MS have consistently been shown to have a reduced quality of life with multiple factors related to the disease such as disability, pain, fatigue, personality, depression and unemployment likely to be implicated [488, 492]. Cognitive impairment has been shown to negatively impact upon QOL independent of physical disability [28].

In our study there was a statistically significant difference in QOL between those patients with cognitive impairment compared to those without as measured on both the MS specific QOL scale, (FAMS) as well as a generic QOL scale (EQ-5D). Of the cognitive tests utilised in BICAMS, the SDMT was mostly closely correlated with both the FAMS and EQ-5D QOL measures.

Although some studies have found patient reports of subjective cognitive impairment to only modestly correlate with objective cognitive impairment [493, 494], a better understanding of the specific cognitive deficits in MS has led to more sensitive patient reported measures being developed, in which a closer correlation is seen between subjective measures of cognitive impairment and objective outcomes [472, 495]. However other factors such as mood need to be considered when interpreting patient reported symptoms [496]. Recent work has also suggested that patient reported perceptions of cognitive difficulties may be predictive of unemployment status independent of mood and objective memory performance [489]. This finding may reflect a relative insensitivity of standard tests to subtle cognitive impairments at a time when "sub-clinical" cognitive impairment may be beginning to cause difficulties with work.

To explore this, we utilised the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ-S), a patient self-reported measure perceived competency with activities of daily living and day-to-day cognitive tasks [472]. Cognitively impaired patients had significantly lower MSNQ-S scores than patients without cognitive impairment. There was moderate correlation with objective measures of cognitive impairment across the BICAMS test battery.

How best to manage cognitive impairment is, at present, far from clear [470]. However on a clinical basis, early identification of cognitive impairment allows identification of patients who are at risk of employment difficulties [497], which may enable support to be put in place that enables them to continue in their current employment with accommodations [498, 499]. This will extend their time in employment, potentially allow them to avoid having employment terminated for poor performance and, instead, achieve medical retirement which a better personal and financial outcome in most countries.

Limitations of this current study are that it involved a relatively small cohort and was cross-sectional in nature. The patients who had consented to undergo cognitive testing were those who had consented to participate in a longitudinal trial of home-based, computerised, cognitive rehabilitation outlined in the following chapters. The data presented here therefore may be subject to selection bias as some individuals in full time employment may have been less likely to participate due to potential time constraints.

Other limitations include the retrospective acquisition of the employment data, a lack of descriptive data pertaining to employment status (such as full-time versus part-time employment) and details pertaining to when an individual ceased to be in employment and how this relates to duration of illness. The type of employment (e.g. professional versus manual occupations) may also be impacted upon differently by cognitive impairment. Perhaps our conclusions should be tentative, because they rely on self-report data collected from a group over half of whom had demonstrated cognitive impairment. However, previous findings suggest this is unlikely to be a confounding factor [500]. Future work might examine these factors in detail.

5

Home-based, Computer-assisted Cognitive Rehabilitation.
An fMRI Study

5.1 Background and Aims

Cognitive impairment is common among patients attending MS outpatient clinic in BSUH. The structural and functional basis for this is unclear. This chapter seeks to explore the potential for cognitive rehabilitation in MS using a computer-assisted training program and to investigate the basis of learning and neuroplasticity in an MS cohort using a working memory fMRI paradigm.

5.2 Subjects and Methods

5.2.1 Participants

Details of screening, recruitment and inclusion/exclusion criteria are detailed in the previous chapter. Sixty-two patients were screened for eligibility and thirty-eight patients with evidence of cognitive impairment were invited to participate in the cognitive rehabilitation study between February 2014 and February 2015. The study was approved by the Northern Ireland Research Ethics Committee.

5.2.2 Study Design

An open-design randomised, controlled, exploratory trial was conducted. Neuropsychological and MRI data was obtained at baseline (time 1) as well as immediately following a 6-week intervention period and after an additional 12 weeks (time 2 and time 3 respectively).

5.2.3 Randomisation

Following baseline MRI, patients were randomised to either the treatment or control groups. Randomisation was performed using a random number generator and group allocations were placed inside sealed folders. Folders were opened following baseline MRI to reveal group allocation.

5.2.4 Cognitive and Behavioural Assessments

At entry all participants underwent a detailed clinical neurological assessment including EDSS scoring by an EDSS certified neurologist (http://www.neurostatus.net). At each time point participants also underwent cognitive assessment using the BICAMS cognitive test battery as well as a number of behavioural and QOL assessments.

Participants completed the following assessments at each time point; EuroQOL five dimension questionnaire (EQ-5D) [501], Functional Assessment of MS (FAMS) [471], Patient Activation Measure (PAM-13) [482], Unidimensional Self-Efficacy scale for MS (USE-MS) [476], the Hospital Anxiety and Depression Scale (HADS) [480], Multiple Sclerosis Neuropsychological Self Reported Questionnaire (MSNQ-S) [472], and the Fatigue Severity Score [502].

Details of these assessments are outlined in the previous chapter.

5.2.5 Intervention

The treatment group underwent six weeks of home-based, computer-assisted cognitive rehabilitation using RehaCom software (http://www.fixxl.co.uk). This consisted of 45-minute sessions, three times weekly. The control group was asked to watch a series of natural history DVDs of corresponding duration and frequency to the rehabilitation sessions performed by the treatment group.

Treatment sessions consisted of training in three specific modules involving working memory, visuospatial memory and divided attention. Deficits affecting these domains are among the most commonly identified in MS. The software involves minimal inputs via a keyboard and has detailed onscreen instructions to ensure understanding of the task before commencing training. In all tasks the level of difficulty is tailored to the individuals performance and increased only in line with satisfactory progress. Real-time data pertaining to performance, progress and compliance is transmitted to the investigator over the Internet during the intervention period.

In the divided attention task the patient is asked to drive a simulated car using keyboard inputs. Multiple distractions must be navigated and the speed and direction of the vehicle altered according to road conditions. As the complexity of the task increases more distractors are introduced with increased multitasking skills required.

The working memory task consists of remembering a series of playing cards presented briefly on screen. The participant is then asked to select which cards were presented from a longer series of options including distractor cards. As the complexity of the task increases participants are asked to remember only cards of a particular value or suit and the number of items to remember increases. Higher levels involve having to remember the cards in reverse order.

Visuospatial memory is a similar task involving various objects presented briefly on screen with the patient asked to remember the object as well as its position in

the sequence. As the complexity of the task increases the number of items on screen increases and more abstract shapes are introduced.

Figure 5.1 Flow Diagram of Assessment Schedule
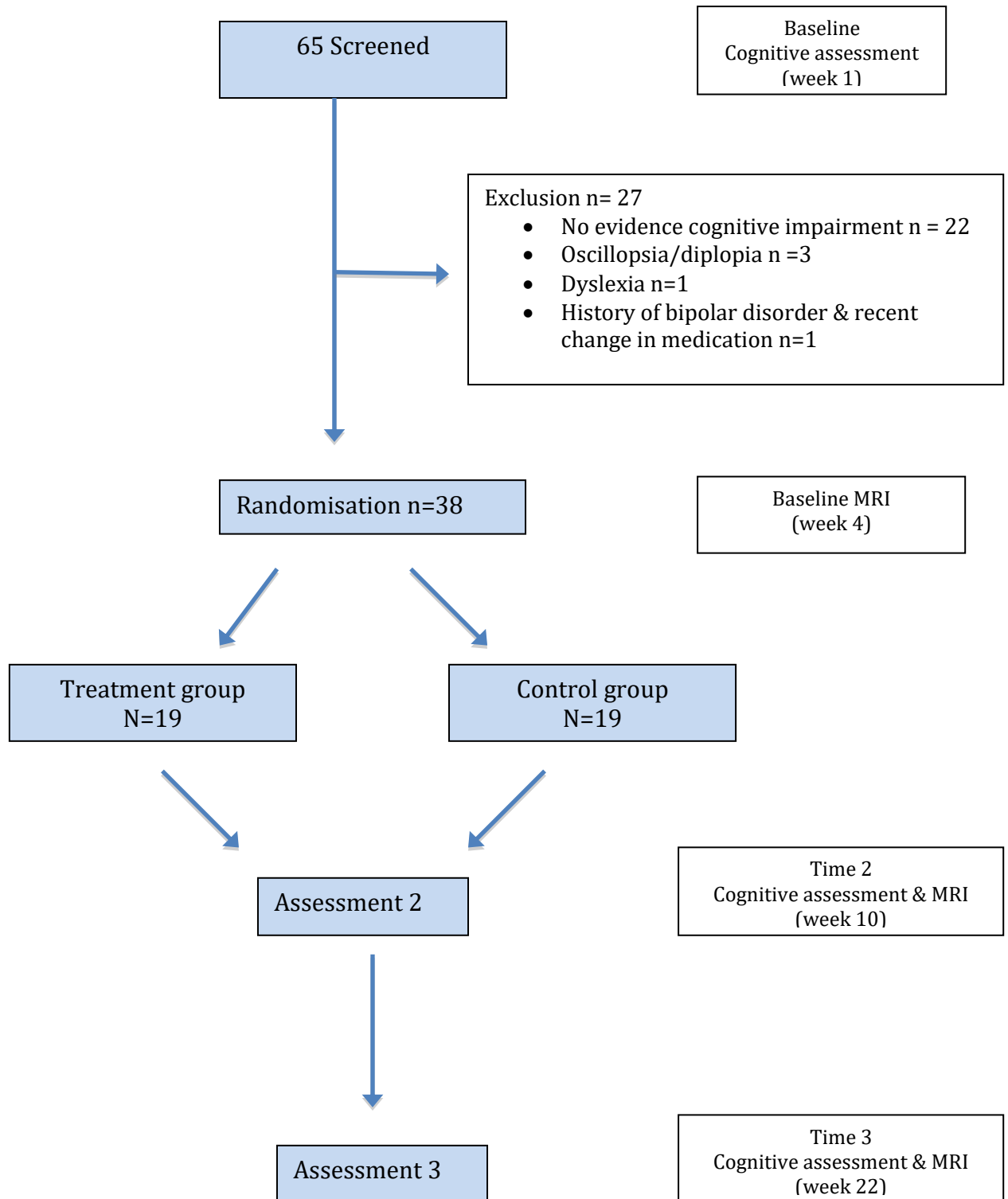
5.2.6 MRI Imaging Protocol

Detailed structural and function neuroimaging was carried out using a 1.5T Siemens Avanto (Siemens AG 8 Medical Solutions, Erlangen, Germany) equipped with a 32-channel head-coil and maximum gradient strength of 44 mT/m. The following were acquired in an order designed to minimise the potential for fatigue on the fMRI task.

- *PD/T2 Turbo spin-echo (TSE)*
    - Acquisition time, 3 minutes
    - TR = 3040, TE = 11ms (PD), 86ms (T2)
    - Slice thickness 5mm (voxel size 0.9x0.9x5mm)
- *T1-weighted high resolution scan using 3D-MPRAGE*
    - Acquisition time, 6 minutes
    - TR 27.3ms, TE 3.57ms
    - Slice thickness 1mm (voxel size 1x1x1). Flip angle 7degrees
    - Number of excitations 1. Number of slices 192.
- *Functional MRI.*
    - Single-shot gradient echo planar imaging (EPI) pulse sequence (three runs) during which patients performs an n-back task (see next section for details).
    - Acquisition time 9 minutes each run
    - TR= 2520, TE= 43
    - Slice thickness 3mm (voxel size 3x3x3). Flip angle 90 degrees
    - Number of volumes = 230, slices 34
- *Quantitative MT*
    - Performed using a balanced steady state free precession acquisition (bSSFP): [503]
    - Acquisition time, 13 minutes
    - TR = 3.66, TE =1.83
    - T1-map using two gradient echo scans: (acquisition time, 2 mins)
        - TR =30ms, TE = 5ms
        - Slice thickness 5mm
        - Slices per slab 32
    - Slice thickness 5mm
    - Field of view 240 x 240

N-back task

A visual n-back test was presented during functional imaging acquisition. This was adapted from Sweet et al [157] and involved three conditions; 0-back, 1-back and 2-back. The 0-back condition was designed to act as the baseline condition (vigilance state) and would provide the baseline activation for comparison in fMRI analysis. The 1-back and 2-back conditions provided increasing working memory demands.

Patients were asked to practice the n-back task outside the MRI scanner to ensure comprehension of the task and allow familiarity with the task. Patients were then asked to lie supine on the MRI scanner table and their head was placed in the head coil. Foam cushions were placed around the participant's head to ensure comfort and minimise movement.

Structural scans were obtained before the fMRI acquisition. Before the fMRI session participants completed a 6-minute practice session of the task while structural imaging (MPRAGE) was being performed. Different stimuli were presented during the practice task to the fMRI task.

A visual n-back task with different levels working memory load was then presented using (Cogent V and MATLAB 2013a). Stimuli were projected onto a mirrored screen inside the MRI scanner 45cm from a participants nose for participant viewing. Line of sight was checked and participants were permitted to wear contact lenses or MRI compatible glasses for viewing if required.

An MRI compatible button box was placed in the participant's right hand with two buttons to indicate (a) "yes" for target, (b) "no" for non-target. The non-target response was used to control for cortical
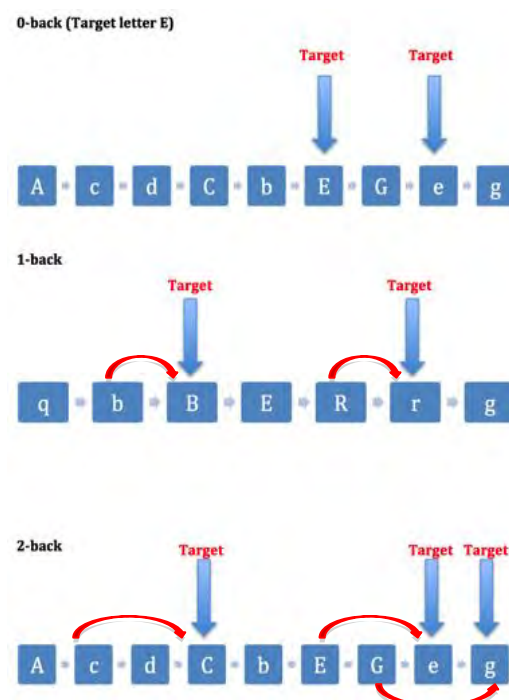
activations that may result from hand movements during the response. The response box was connected to a desktop PC in an adjacent room to record task response and performance.

White digits were projected onto a black background in bold size 200 Arial font. This involved of a series of pseudo-randomised consonants in both upper and lower case but excluding "L" due to the potential ambiguity of the lower case.

Participants were asked to indicate if the presented visual stimulus matched a defined letter presented prior to the sequence (0-back), presented immediately before ("1-back") or the second last letter in the sequence ("2-back") (figure 5.2). The stimulus duration was 1000ms with a between stimulus interval of 2000ms. Instructions were presented before each new n-back task for 3000ms. Between each n-back task a resting screen was presented for 2000ms consisting of a white cross.

fMRI data were acquired during three 9-minute runs. 0-back, 1-back and 2-back tasks were presented in a randomised manner resulting in six blocks consisting of 126 stimuli, one third of which were targets. Twice as many 0-back tasks were presented as 1-back or 2-back.

There was a rest period of 90 seconds between blocks. Reaction times, correct responses, incorrect responses and omissions were recorded.

5.3 Statistical Analysis

5.3.1 Behavioural data

Analyses were performed using SPSS version 21 (Armonk, NY: IBM Corp). Descriptive statistics for continuous variables are expressed as mean and standard deviation, while categorical variables are expressed as frequency and percentage.

Between groups comparisons were performed using independent samples t-tests, the Mann-Whitney U test and the Pearson χ^2 test as appropriate. Kolmogorov-Smirnov tests of normality were used to confirm normal distribution of the variables. Cognitive and behavioural measures were compared between the treatment and placebo groups. The primary outcomes were quality of life and cognitive performance.

Outcomes were compared between the two groups using a 2 x3 repeat measures analysis of variance (ANOVA) with "time" as the within subject factor and "treatment" as the between factor (placebo versus active rehabilitation). A paired samples t-test was used to assess any within group difference in behavioural outcomes before and after treatment. All statistical analyses had 2-tailed α levels of <0.05 for defining significance.

Analyses were based on an intention to treat basis. The final analysis therefore included those patients with baseline plus at least one other assessment.

5.3.2 Functional MRI analysis

fMRI data were analysed using SPM8 (Wellcome Department of Cognitive Neurology, UCL, London, http://www.fil.ion.ucl.ac.uk/spm).

For each time series, the first five EPIs were discarded to ensure steady state magnetisation. Individual EPIs were then realigned to the first remaining image of the series by rigid body transformation to correct for involuntary head movements during acquisition. fMRI data from the 3 sessions (time 1, 2 and 3) were realigned using a rigid body transformation before normalisation into a standard anatomical space (Montreal Neurological Institute [MNI]) using linear and non-linear transformations. Finally, images were smoothed with an 8mm^3 full-width-at-half-maximum (FWHM) 3D Gaussian kernel. High pass filtering (cut-off 120 seconds) was applied to each time series. Subjects with head movement greater than 2mm were removed from analysis.

First-Level Analysis

Data for all three n-back runs was pooled for each participant. The statistical modelling was based a mixed-effect analysis: each participant's data was first processed at the 1st level, modelling the 3 types of block (0-, 1-, and 2-back). The resulting contrast images were used for a group-level, or second level analysis.

For each participant, the difference in BOLD response between the 0-back, 1-back and 2-back conditions was estimated at every voxel across the whole brain using the general linear model (GLM). This produced a series of contrasts representing mean activation during each n-back condition minus the 0-back condition, which acted as the baseline activation. Group-by-condition interactions were calculated using the following contrasts: [(1b>0b) treatment > (1b>0b) controls] and [(2b>0b) treatment > (2b>0b) controls]. This produced statistical maps for the main effect of 1-back and 2-back tasks. The resulting contrast images were used in the second-level analysis for comparison between the two study arms.

Second-Level Analysis

Each contrast obtained at the first-level was entered into a second level general linear model to generate summary statistical parametric maps (SPMs). The generated SPMs acted as a dependent variable in hypothesis testing. Within group activations at a particular time point were assessed using one-sample t test while within group changes between time points were assessed using a paired t test.

For between group analysis of difference between the first two time points, we used a 2 x 2 ANOVA flexible factorial design with group (between-subject) and time (within-subject) as separate factors to examine the main effects on group (treatment versus control), time (pre- and post-treatment) and the interaction between them to evaluate areas of relative change in activity after cognitive training versus placebo at the first two time points.

The threshold for significance was set at an alpha of 0.05 corrected for multiple comparisons (family-wise error (FWE) corrected). Within each region of statistical significance, the location of local maxima of signal intensity increase is expressed as x, y, and z coordinates in MNI space.

5.3.3 Quantitative MT analysis

The MT data were analysed using SPM8 (Wellcome Department of Cognitive Neurology, UCL, London, http://www.fil.ion.ucl.ac.uk/spm). MT and T1 mapping data from all three sessions were first realigned to subject specific MPrage structural images using the SPM8 rigid-body registration function. T1 images were then segmented into white and grey matter and CSF to yield a parenchymal mask.

A T1 map was calculated for all datasets by fitting the theoretical spoiled gradient echo as a function of the flip angle to the signal measured by the 3D FLASH sequences. MT parameters were obtained by performing a voxel wise non-linear least squares fitting (Levenberg–Marquardt) to a binary spin bath model for bSSFP [503].

These methods yielded bound proton fraction (F), MT exchange rate constant (k_f), and T2 of the free water component (T_{2f}). The quantitative maps were masked to remove background noise, warped into standard MNI space using the segmentation deformation fields then smoothed using an $8mm^3$ FWHM Gaussian kernel.

Figure 5.2 Consort diagram

Assessed for eligibility (n= 65)

Enrolment &
baseline assessment

**Time 1 (Baseline)
Assessments**
Cognitive, behavioural, MRI

Excluded (n=27)
- ♦ Not meeting inclusion criteria (n=22)
- ♦ Oscillopsia/diplopia (n=3)
- ♦ History of bipolar disorder with recent change in medications (n= 1)
- ♦ Dyslexia (n=1)

Randomised (n=38)

Allocated to intervention (n=19)

Allocated to control (n=19)

Withdrawal (n=1)
- ♦ *Relapse of MS (n=1)*

Did not complete NP* assessment (n=1)
- ♦ *Time constraints (n=1)*

Did not complete NP* assessment (n=1)
- ♦ *Time constraints (n=1)*

Follow-up (time2)

Time 2 Assessments:
Cognitive, behavioural & MRI (*n=17*)

Time 2 Assessments:
Cognitive, behavioural & MRI (*n=18*)

Withdrawal (n=4)
- ♦ *Relapse of MS (n=1)*
- ♦ *Unable to tolerate MRI (n=1)*
- ♦ *Patient moved house (n=1)*
- ♦ *No reason given (n=1)*

Follow-up (time3)

Time 3 Assessments
Cognitive, behavioural & MRI (*n=17*)

Time 3 Assessments:
Cognitive, behavioural & MRI (*n=14*)

*NP; Neuropsychological

5.4 Results

5.4.1 Baseline characteristics

38 patients were included in the study. The majority of the participants were female (71.1%). At entry 27 patients (70.3%) had RRMS, and 11 patients (29.7%) had SPMS. Patients were aged between 32 and 62 (mean 47.37, SD 8.23). The duration of MS from diagnosis to enrolment ranged from 12 months to 40 years (mean 11.61 years, SD +/- 8.2 yrs). Median EDSS was 5.0 (3.5 – 6.0). 20 patients (52.6%) were on disease modifying therapy at enrolment (natalizumab n=6, beta-Interferon n=7, fingolimod n=6 and teriflunomide n=1).

After randomisation to either computer-assisted cognitive training (treatment group, n=19) or the control condition (n=19), there were no significant differences in terms of baseline demographic between the two groups (table 5.1). The treatment group had higher baseline cognitive scores on the BICAMS battery however these did not differ significantly from the control group (table 5.2). Mean T2 lesion load did not significantly differ between the groups [treatment 8.90cm^3, (SD+/- 6.35) controls 8.19cm^3, (SD +/- 10.81) p=0.812].

Baseline QOL measures are shown in table 5.3. The treatment group had lower mean FAMS scores (indicating lower QOL) and lower USE-MS scores (indicating lower levels of perceived self-efficacy) however the differences were not statistically significant.

Table 5.1 Baseline Demographic Characteristics

	Treatment group (n=19)			Control group (n=19)		
	Mean		*± SD/IQR*	*Mean*	*± SD/IQR*	*t*
Gender						
Female	12	(63.2%)		15 (78.9%)		.238 (χ^2)
Male	7	(36.8%)		4 (21.1%)		
Age (years)	46.6		7.2	48.1	9.3	.588
Time since diagnosis (years)	11.99		6.05	12.42	9.95	.598
Disease subtype						
Relapsing-remitting	13	(68.4%)		13 (68.4%)		.800(χ^2)
Secondary-progressive	6	(31.6%)		6 (31.6%)		
EDSS ^	5.0		(4.0-6.0)	5.0	2.0-6.0	.751*
Treatment at enrolment						
Yes	12/19 (63.2%)			8/19 (42.1%)		.165 (χ^2)
Interferon**	5			2		
Fingolimod	5			1		
Natalizumab	2			4		
Teriflunomide	0			1		
No DMT's	7/19			11/19		
Education (y)	14.47		2.88	13.21	2.64	.167
T2 lesion volume (cm^3)	8.90		6.35	8.19	10.81	.812
Employed						
Yes	6	(31.6%)		8 (42.1%)		.369 (χ^2)
No	13	(68.4%)		11 (57.9%)		

^median

* Non-parametric Mann-Whitney U Test

**Includes IF-1b SC, IF-1A IM and IF-1A SC

Table 5.2 Cognitive Performance at Baseline

	Treatment group (n=19)		Control group (n=19)		t
	Mean	*± SD*	*Mean*	*± SD*	
SDMT	42.76	7.11	37.83	11.60	.112
CVLT	45.94	9.85	44.78	9.2	.537
BVMT-R	20.53	5.90	18.44	7.37	.214

SDMT: Symbol Digits Modalities Test; CVLT: California Verbal Learning Test;
BVMT-R: Brief Visuospatial Memory Test Revised.

Table 5.3 Baseline Quality of life and other behavioural measures

	Treatment group (n=19)		Control group (n=19)		
	Mean	*± SD*	*Mean ±*	*± SD*	*t*
FAMS	87.26	23.00	101.06	31.98	.170
PAM-13	59.52	18.42	64.26	15.65	.398
EQ5D	0.52	0.18	0.61	0.19	0.18
USE-MS	48.26	18.01	59.74	19.96	.270
MSNQ-S	36.89	13.49	34.68	11.51	.590
HADS-D	9.47	3.55	8.47	3.21	.507
HADS-A	9.26	3.72	9.37	5.56	.946
FSS	52.37	10.40	48.84	13.59	.375*

FAMS Functional Assessment of MS, *MSNQ* Multiple Sclerosis Neuropsychological Questionnaire,

PAM-13, Patient Activation Measure *EQ-5D,* EuroQOL five dimension questionnaire

FSS Fatigue Severity Scale

USE-MS Unidimensional Self-Efficacy scale for MS,

HADS, Hospital Anxiety and Depression Scale (HADS-D = depression, HADS-A = anxiety subscale)

5.4.2 Compliance - computer-assisted cognitive training

Overall 88.9% of patients (16/18) in the intervention group completed at least 75% of the prescribed sessions with 66.7% (12/18) completing all the prescribed sessions (figure 5.4).

Figure 5.3 Compliance with prescribed cognitive training sessions
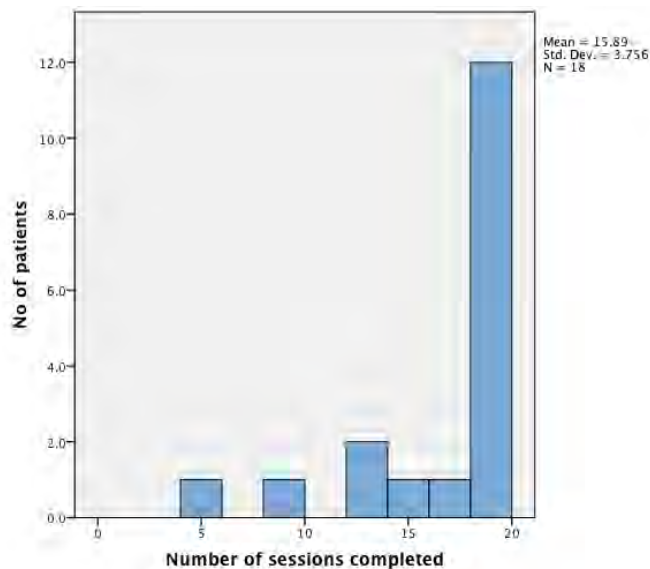
5.4.3 Functional MRI

Baseline

The n-back task was associated with robust activations of several cortical areas. The 1-back task was associated with activations involving the dorsolateral prefrontal cortex bilaterally as well as bilateral inferior parietal lobule, insular and cerebellar regions relative to the 0-back contrast. The same regions were activated in the 2-back condition but the spatial extent and magnitude of the responses was greater, particularly over the fronto-parietal regions (tables 5.4 & 5.5). The task main effects for all subjects (n=38) showing regions of significant change in activation (pFWE corrected <0.05) during (a) 1-back (b) 2-back task is shown in figure 5.5.

When comparing the 1-back and 2-back contrasts across all participants at baseline, there were no regions more active in the 1back>2 back task; however

there was a statistically significant difference in activations in 2-back>1-back in the left inferior frontal gyrus (pars triangularis), and right supramarginal gurus.

The reverse contrast in both instances (showing areas of deactivation when engaged in either 1-back or 2-back task) is shown in figure 5.6. Unsurprisingly these regions are known to mainly comprise the default-mode network; a "task-negative" region that is known to be active when not engaged in a particular cognitive focus. It primarily comprises the ventromedial prefrontal cortex, bilateral precuneus and posterior cingulate cortices.

Figure 5.4 Task main effects for all subjects
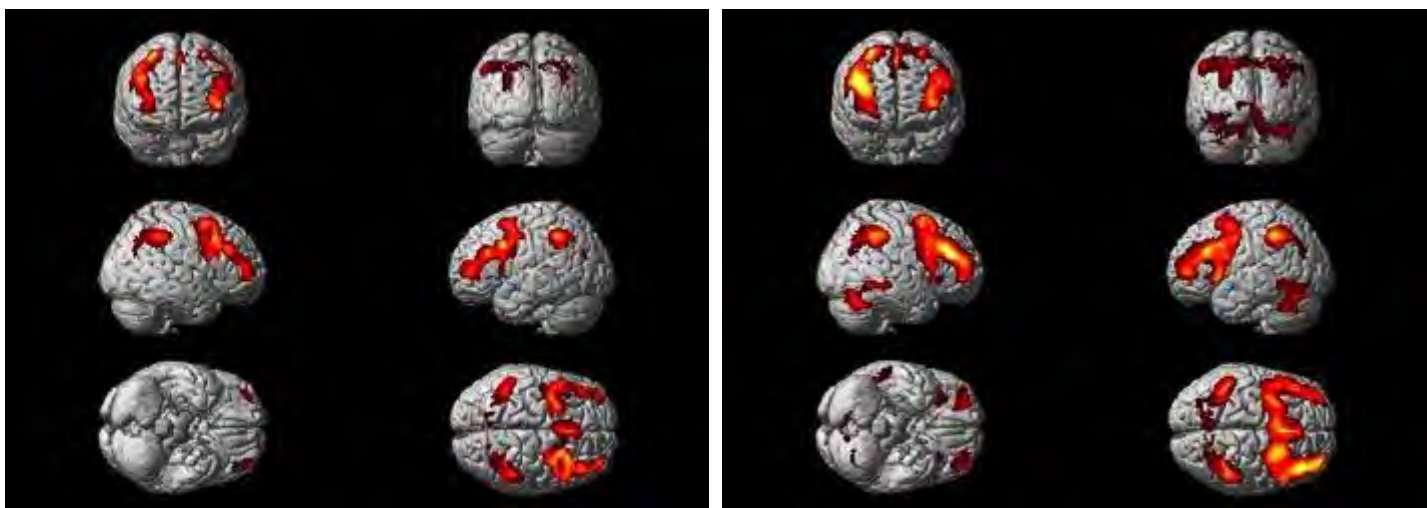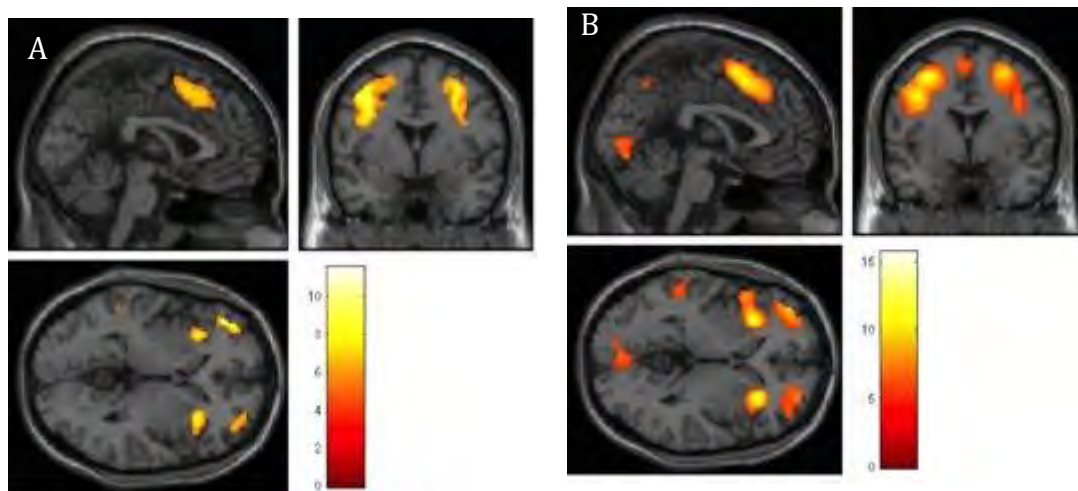
Task main effects for all subjects (n=38) showing areas of significant activation in: (a) 1-back, (b) 2-back (pFWE corrected <0.05) primarily involving the DLPFC, insula, inferior parietal lobules and occipital cortices.

Table 5.4 Areas of Significant Activation for 1-back> 0-back

Brain region	MNI Coordinates			
	x	*y*	*z*	*Max t-score*
Dorsolateral prefrontal				
Right middle frontal gyrus	28	8	58	11.49
Left middle frontal gyrus	-40	48	2	9.6
Left precentral gyrus	-36	0	42	9.6
Parietal (inferior parietal lobule)				
Right angular gyrus	34	-56	44	11.21
Right supramarginal gyrus	50	-40	42	10.82
Left supramarginal gyrus	-44	-46	46	10.27
Occipital				
Right superior occipital gyrus (lateral occipital cortex)	30	-64	38	11.56
Left superior occipital gyrus (lateral occipital cortex)	-24	-64	44	9.43
Insula				
Left insula	-30	22	2	8.54
Right insula	34	22	0	8.52
Cerebellum				
Left Cerebellum (crus)	-26	-64	-30	7.6
Right Cerebellum (crus)	30	-62	-32	7.51

Table 5.5 Areas of Significant Activation for 2-back>0 back task

Brain region	MNI Coordinates			
	x	*y*	*z*	*Max t-score*
Dorsolateral prefrontal				
Right middle frontal gyrus	44	34	28	15.72
Left inferior frontal gyrus (pars triangularis)	-46	30	28	12.72
Lateral Parietal (inferior parietal lobule)				
Right supramarginal gyrus	40	-44	38	13.93
Left supramarginal gyrus	-38	-44	40	13.57
Lateral Occipital				
Left middle occipital gyrus	-26	-68	36	13.19
Right occipital fusiform gyrus	38	-70	-20	8.83
Cerebellum				
Left cerebellum	-26	-66	-30	11.56
Right cerebellum	30	-64	-30	10.88
Insula				
Right insula	32	26	0	12.23
Left insula	-30	22	0	11.85

Figure 5.5 Regions of Decreased Activation During n-back task
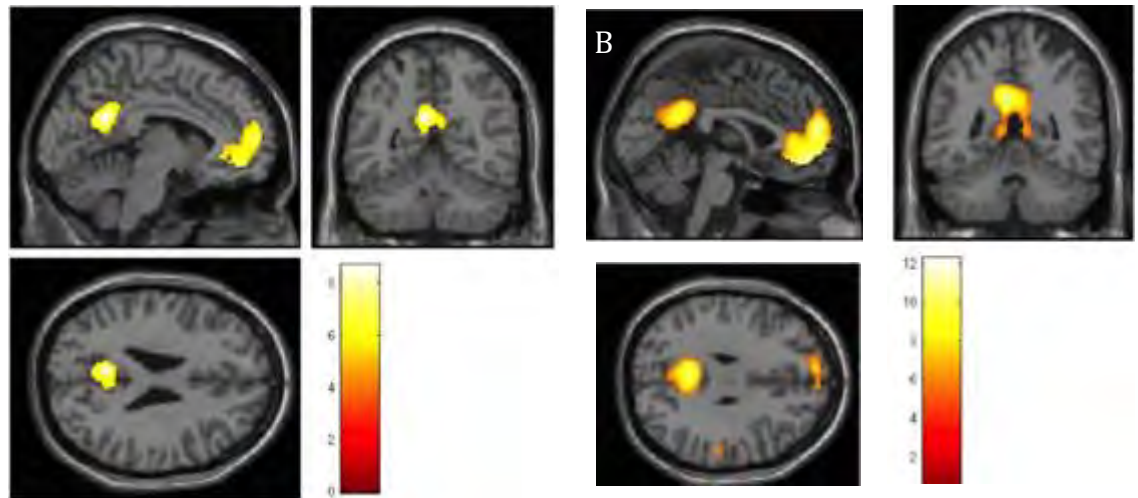
Regions of decreased activation when undertaking 1-back (A) and 2-back (B) tasks showing relatively deactivation of the ventromedial prefrontal, posterior cingulate cortex and precuneus when engaging in either the 1-back or 2-back condition relative to rest. Such regions are known to comprise the default-mode network.

5.4.4 fMRI Outcomes

Time 2

At time 2 (immediately following the intervention period), increased activation was seen in the right temporo-parietal regions (right supramarginal and angular gyri) in the 1-back only (figure 5.7) in the treatment group relative to controls (group-by-time interaction). No significant change was seen in the 2-back task.

| Brain region | *MNI Coordinates* | | | | | |
	x	*y*	*z*	*Max t-score*	*p (FWE) cluster*	*K_e Cluster*
Right inferior parietal lobule (Right angular gyrus)	44	-68	22	5.38	0.005	228

Figure 5.6 Increase in activation in the treatment group relative to controls
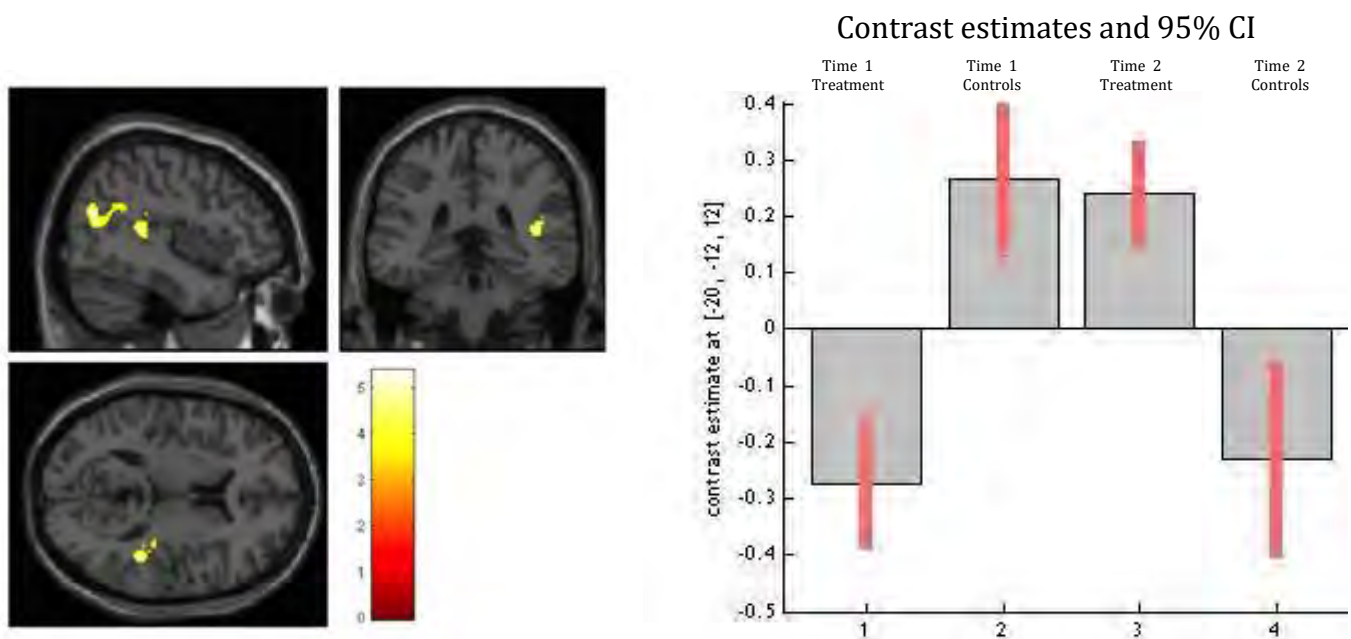
Increased activation was seen in the right temporo-parietal regions (right supramarginal and angular gyri) in the 1-back only at time 2 relative to time 1.

Time 3

At time 3 significant increases in activation were seen in both the 1-back and 2-back conditions in the treatment group relative to controls. In the 1-back task, increased activation was seen in the left frontal and right temporo-parietal regions. In the more demanding 2-back task, increases in activation were seen in bilateral prefrontal and right temporo-pariteal regions (table 5.7).

Table 5.6 Increased activations in treatment group during 1-back

	MNI Coordinates					
Brain region	*x*	*y*	*z*	*Max t-score*	*p (FWE) cluster*	*K_e Cluster*
Left inferior frontal gyrus	-48	28	18	4.85	0.001	294
Right temporo-parietal junction	56	-26	6	4.18	0.012	187

Figure 5.7 Increased activations in treatment group during 1-back
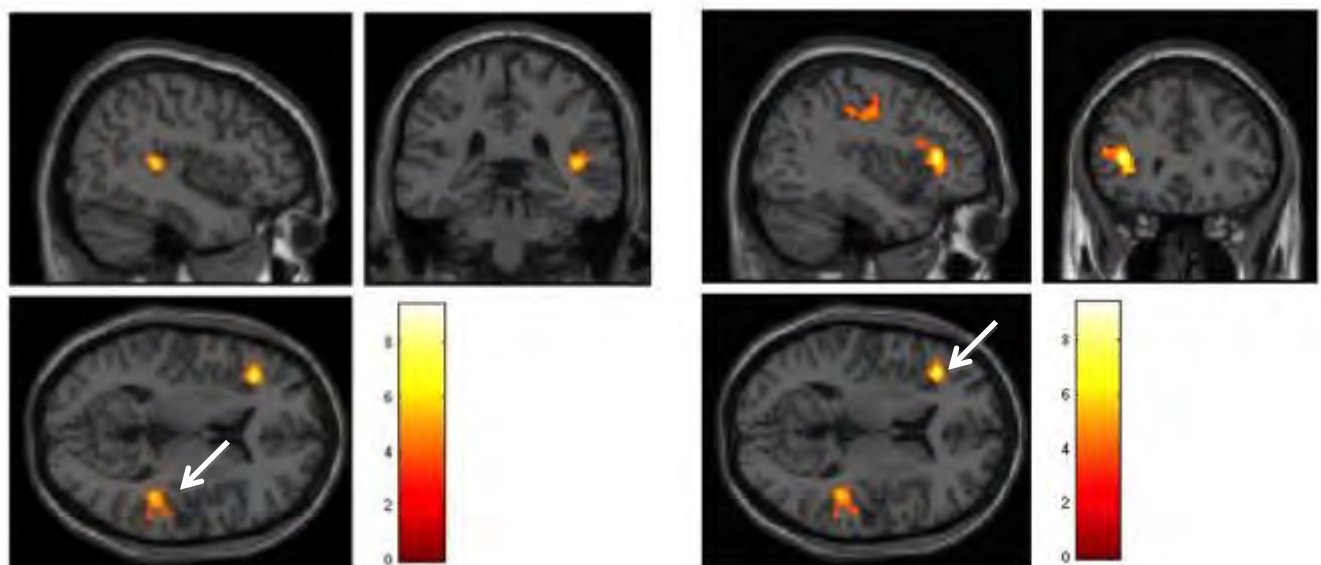
(a) Increased activation in treatment group in right parietal region (supramarginal gyrus)

(b) Increased activation in treatment group in the left prefrontal region

Table 5.7 Group x time interaction in 2-back at follow up (time 3)

MNI Coordinates

Brain region	*x*	*y*	*z*	*Max t-score*	*p (FWE) cluster*	*K_e Cluster*
Left middle frontal gyrus	-34	30	18	5.60	0.044	152
Right inferior frontal gyrus	40	28	26	4.64	0.013	206
Right superior temporal gyrus	58	-22	2	4.10	0.024	178

Figure 5.8 Significant group-by-time interaction at time 3 during 2-back
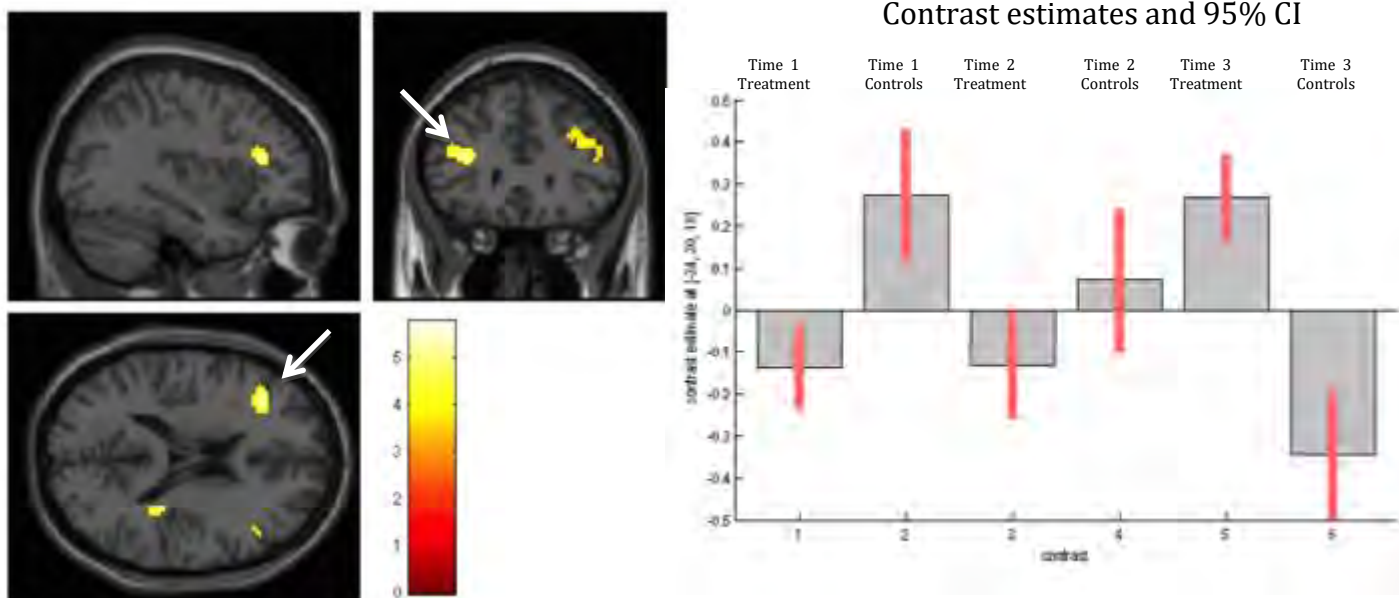
Bilateral frontal gyrus activation in treatment group relative to controls. Left MFG activation (arrow) significant at *p = <0.042* FWE-corrected *at cluster level (k=152).*

Figure 5.9 Fronto-parietal increases in activation
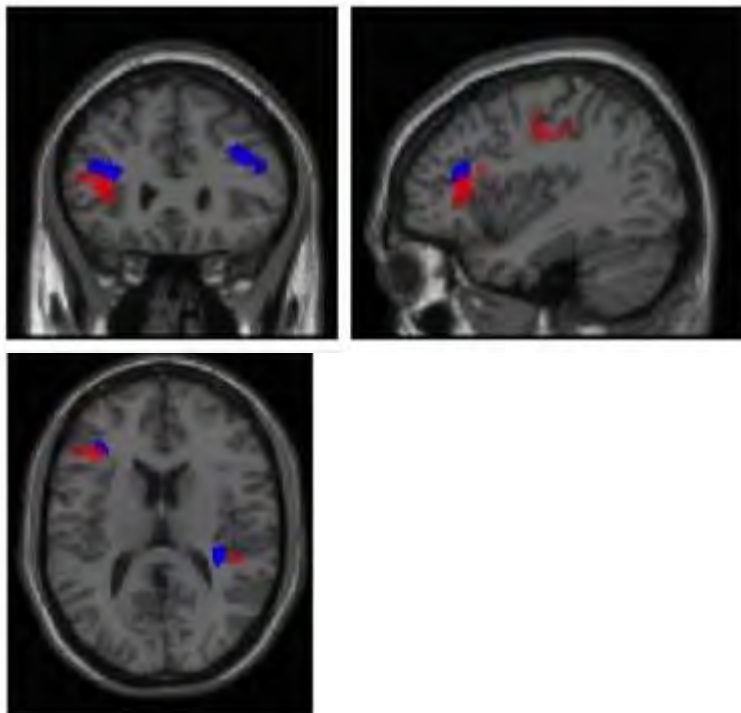
Increased activation patterns in fronto-parietal regions during
1-back (red) and 2-back (blue) tasks in treatment group
relative to controls at time 3.

5.5 N-back task

All participants engaged in the fMRI paradigm. Patients were given the opportunity to familiarise themselves with the n-back task prior to entering the MRI scanner. All participants were then asked to practice the n-back task for five minutes while structural imaging was being performed. There were no significant differences in error rate (omissions and false positive responses) between the treatment and control groups at baseline (table 5.8).

Across all participants there were significantly more errors on the 2-back test than the 1-back test (1-back mean no errors 3.14, SD 5.76, 2-back means no errors 5.08, SD 6.97, p=0.001). With repeated testing both groups showed significantly fewer errors at subsequent time points however there were no significant differences between the groups in overall error rate.

Table 5.8 Mean total errors on baseline fMRI task

Total Errors	Treatment group (n=19)		Control group (n=19)		
	Mean	*± SD*	*Mean*	*± SD*	*T*
0-back	1.53	1.70	1.69	2.17	.809
1-back	2.61	3.40	3.63	7.41	.597
2-back	5.22	4.67	4.95	8.75	.907

Table 5.9 Mean n-back errors at baseline, time 2 and time 3

	Treatment (n=17)		Control (n=14)		*ANOVA p-value*
	Mean	*± SD*	*Mean*	*± SD*	
0-back 1	1.53	1.70	1.69	2.17	
0-back 2	1.83	1.17	1.21	1.47	0.940
0-back 3	1.30	1.94	1.32	1.25	
1-back 1	2.61	3.40	3.63	7.41	
1-back 2	1.44	2.12	1.95	1.47	0.234
1-back 3	3.27	3.43	2.14	1.99	
2-back 1	5.22	4.67	4.95	8.75	
2-back 2	4.22	3.47	5.11	4.31	0.256
2-back 3	3.27	3.43	2.14	1.99	

5.6 Quantitative Magnetisation Transfer

No significant between-group changes were seen in the QMT at time 2 or time 3. Overall QMT measures (macromolecular bound fraction and forward exchange rate) showed stability over time. A representative image of whole brain MT parameter estimation is shown in figure 5.11.

Figure 5.10 Example of whole brain MT parameter estimation
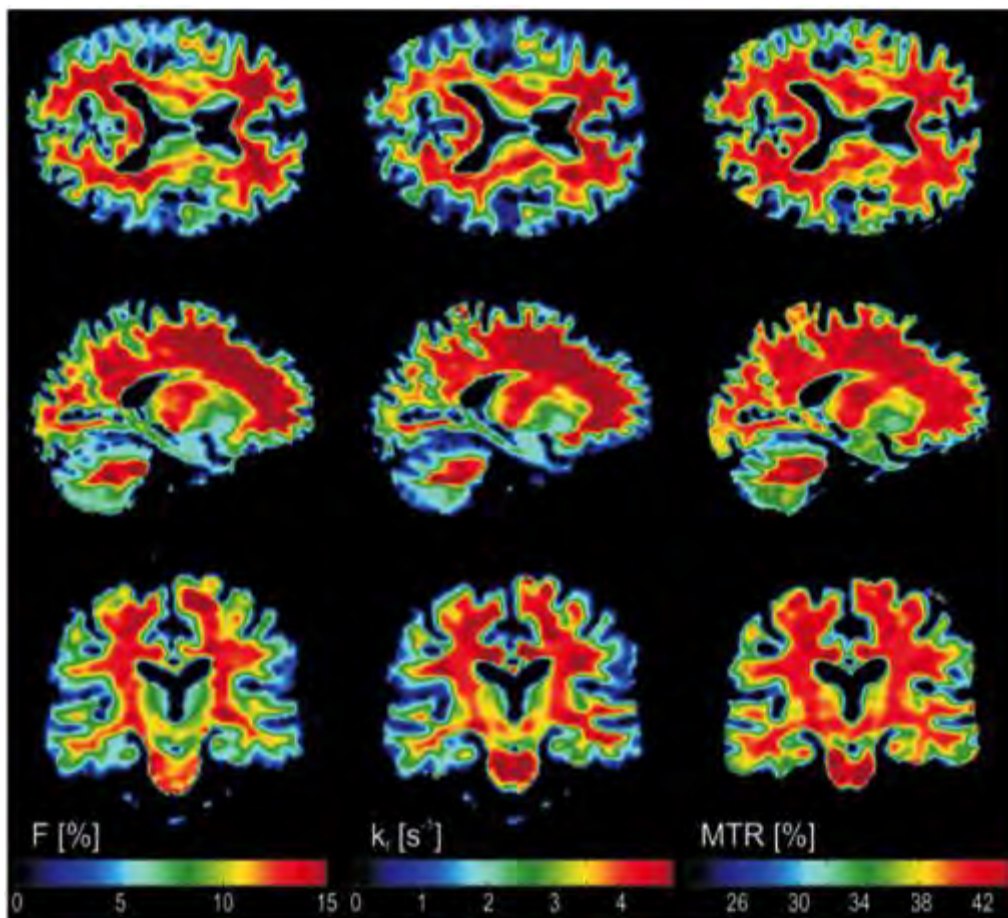
Axial, sagittal and coronal sample images of a healthy volunteer showing 3D 1.3mm isotropic high-resolution MT parameter estimates for the restricted pool fraction F and the magnetisation exchange rate kf as derived from the two-pool model.

From: *Gloor, M., K. Scheffler, and O. Bieri, Quantitative magnetization transfer imaging using balanced SSFP. Magn Reson Med, 2008.* **60***(3): p. 691-700*

Copyright 2008, with permission from John Wiley & Sons [503].

5.7 Discussion:

The n-back fMRI paradigm in our study cohort was associated with robust cortical activations and revealed a fronto-parietal pattern of activation (in particular the DLPFC and posterior parietal cortex) in keeping with known working memory networks [151-153].

Negative task responses in our n-back paradigm (relative deactivation of certain regions when instigating the active task) were seen in the ventromedial prefrontal regions, the posterior cingulate cortex and precuneus. Such regions are known to be highly metabolically active regions at rest and key components of the default mode network (DMN) [384, 504]. It is therefore unsurprising that a shift in activation away from such regions is seen when engaging in a higher demand cognitive task.

Overall, these findings suggest our n-back paradigm is an appropriate model for assessing working memory networks in our patient population and provides a template upon which changes in cortical activity related to learning and plasticity might be assessed.

Changes in activation following treatment

In line with previous work [454], in the patients in our cohort undertaking cognitive rehabilitation showed significant changes in cortical activation at follow-up within the bilateral prefrontal and temporo-parietal regions relative to controls.

The fact that, in this study, such changes appeared to evolve over the course of the follow-up period suggests that such functional changes may be as a result of alterations occurring at the cellular level that take time to manifest functionally as new or enhanced connections. Additionally, the fact that the evolution of such changes continues after the active intervention phase, one might hypothesise that mechanistically, learning techniques acquired during the training phase continue to be exercised.

Prefrontal cortex

Comprising the superior, middle and inferior frontal gyri, the prefrontal cortex was seen to be one of the main areas active during the 1-back and 2-back conditions across all subjects.

It has been shown that the lateral prefrontal cortex is also critical in the executive control of working memory and has a role in response inhibition [146, 188-190]. Bor et al showed that structured sequences, although easier to remember than unstructured sequences, were associated with greater activation of the lateral frontal cortex indicative of executive processes that involve organisation of information into higher-level "chunks" [146]. The authors suggest that effective reorganisation in this manner attenuates task difficulty resulting in improved working memory performance. The ability to recruit the DLPFC has also been shown to be associated with maintained cognitive performance in CIS over the course of 12 months [437].

Executive control of working memory in this manner to increase task performance is clearly useful during the n-back task [505]. The activation of frontal executive centres during the n-back task is likely to reflect that participants are actively having to decide whether or not to ignore irrelevant stimuli while responding only to a relevant stimulus. Involvement of ventral language areas meanwhile, might suggest subvocal rehearsal of the presented letters [190].

With respect to the alterations in fMRI activity seen in our treatment cohort at follow up, it is postulated that cognitive training results in improved executive control of working memory. The working memory computer training module involved remembering playing cards often of a particular suit or colour and is therefore heavily reliant on executive abilities such as set shifting and response inhibition. Once acquired such executive skills may be transferable to other cognitive processes such as efficiency of information processing [506, 507]. Such skills may therefore be seen to persist after cessation of formal training.

Temporo-parietal regions

Significant temporo-parietal activations were seen across all subjects participating in the n-back task however, a significant increase in activation was seen at follow up in the treatment group relative to controls particularly in the right inferior parietal lobule.

The inferior parietal lobule in consists of the supramarginal gyrus rostrally and the angular gyrus caudally and lies at the junction of the primary auditory and somatosensory cortices. In the dominant hemisphere it is considered a key area in the processing of both written and spoken language due to it possessing interneurons to both Broca's and Wernicke's areas [508]. The non-dominant inferior parietal lobule may also contribute to language processing [509-511] and may be particularly important in providing additional cortical resources in MS patients with cognitive impairment compared to those without impairment [156].

Several key attention networks have been shown to involve bilateral temporo-parietal regions. A right hemisphere dominant "ventral attentional network" consisting of the temporo-parietal junction, ventral prefrontal cortex and anterior insula is thought to be responsible for directing attention to salient events [153, 194, 195]. Similarly a "dorsal attention network" is thought to exist consisting of the superior parietal lobule and the dorsal frontal cortex and is responsible for linking stimuli and responses [196].

Figure 5.11 Anatomy of temporoparietal junction
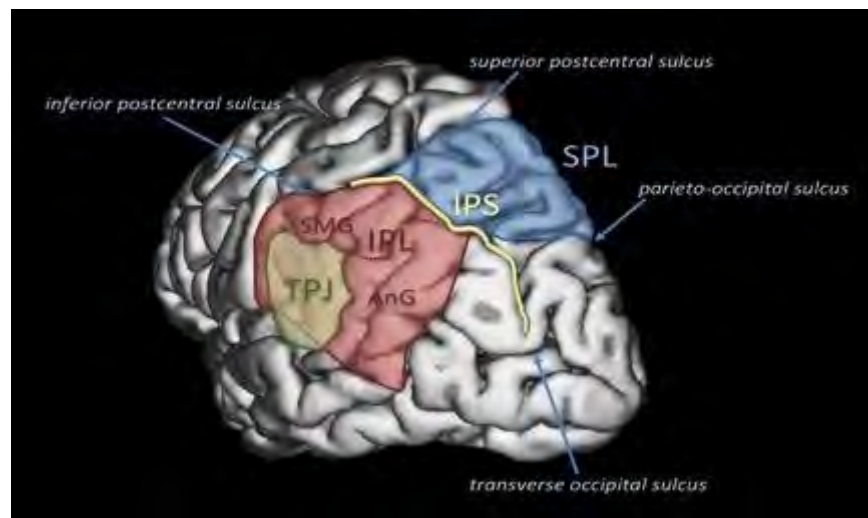
Posterior parietal cortex separated into dorsal and ventral portions by the intraparietal sulcus (IPS). Dorsal PPC includes the superior parietal lobule (SPL) and IPS. Ventral PPC includes inferior parietal lobule (IPL) and its subregions: supramarginal gyrus (SMG), temporoparietal junction (TPJ), and angular gyrus (AnG). Hutchinson et al. Learn. Mem. 2009;16:343-356. Copyright 2009 Cold Spring Harbor Laboratory Press with permission.

Many of the computer-training tasks involve sustained attention and it might be postulated that the increased activation seen at follow up in the treatment group is as a result of improved efficiency of the ventral attention network. Significant attentional demands are required for the n-back task and thus improved efficiency of attention networks may be reflected in a greater relative activation in those patients practised in such methods. Previous work in MS has indicated that attention may be one of the domains most amenable to rehabilitation [452, 454].

In our study, limited functional changes were seen in the right ventral attention network only in the 1-back task at time 2. The spatial extent of these changes was, however, greater at time 3 and present in both the 1-back and 2-back conditions. This further supports the hypothesis that functional adaptation occurs over time as a result of on-going utilisation of techniques acquired during formal training. This clearly has implications for when to assess the benefits of such an intervention.

Conversely, we did not detect any structural change after training on QMT. Due to the short duration of follow up, this is not entirely surprising. Functional alterations in cortical activity may subsequently modulate brain structure at the microstructural level through enhanced synaptic activity and ultimately through the formation of new connections but such changes in structural brain architecture might only be detectable over the longer term.

Some studies have identified structural changes as a result of training and rehabilitation mainly in the context of physiotherapy [512-515]. Most of these studies utilised DTI rather than magnetisation transfer imaging. Increased callolsal FA and reduced MD have been identified at follow up in a group of MS patients receiving physiotherapy compared to healthy controls in several studies [512, 514].

Our study attempted to explore the role of myelin in rehabilitation and repair. It was hypothesised that increased structural integrity would ultimately be associated with increased myelin density (potentially as a result of increased fibre density). Such changes may take longer to develop but may be confounded by on-going demyelination in patients with more active MS.

5.8 Summary

In this study it has been shown that cognitive rehabiliation can result in significant alterations to patterns of cortical activations in patients with MS. Such alterations are shown to develop over time and progress even following the cessation of formal rehabiliation. It may be the case that techniques aquired through training are applicable to more diverse cognitive tasks and therefore continue to be utilised for everyday tasks.

This study adds weight to the argument that cognitive rehabiliation leads to modifications in functional activity which may impact upon cognitive performance. In keeping with previous work and it is hypothesised that it is the executive function and attention that are the most responsive to training as identified by modifications in typical frontal executive and attentional network areas.

It is postulated that alterations in fMRI activity result from microstructural changes. The lack of significant change on in QMT measurements however, suggests that the microstructural changes thought to underpin learning and adaptive responses, may, at present, be beyond the resolution of even the most advanced MRI techniques or that they do not manifest in the timescale of this study. Cognitive rehabilitation may result in relative *stability* of pertinent networks and longer-term follow up may be required to identify such changes.

Although the fMRI paradigm utlised a n-back task as a proxy for working memory, the actual error rate on the n-back task did not significantly differ between groups. This suggests such a measure is not in itself sufficently sensitive to reflect subtle changes in functional activations. It remains to be seen if other clinical and neuropsychological outcomes are sensitive to such changes.

6

Neuropsychological, Cognitive and Quality of Life Outcomes

6.1 Cognitive and Behavioural Outcomes

6.1.1 Baseline characteristics

Baseline characteristics, QOL measures and cognitive performance of the study group have been previously outlined. There were no significant differences at baseline in patient demographics (age, gender, educations, EDSS), QOL measures or cognitive performance between the groups. Patients were reassessed immediately following training (time 2) and after an additional 12-week period (time 3).

6.1.2 Cognitive outcomes – Time 2

Compared to time 1, significantly more patients in the treatment group showed an improvement in the SDMT slope, defined as ≥10% improvement in time 2 compared to time 1 ($\chi2$ = 0.008) see figure 6.1. Similar gain scores in the CVLT and BVMT-R were not significantly different between the groups.

Table 6.1 BICAMS outcomes in Treatment versus Control Groups at time 2

	Treatment (n=17)		Control (n=18)		*p-value* (χ^2)
SDMT gain ≥10%	9/17	(53%)	2/18	(11%)	.008
CVLT gain ≥10%	9/17	(53%)	9/18	(50%)	.862
BVMT gain ≥10%	11/17	(65%)	9/18	(50%)	.380

Figure 6.1 Improvement in SDMT slope immediately post-intervention
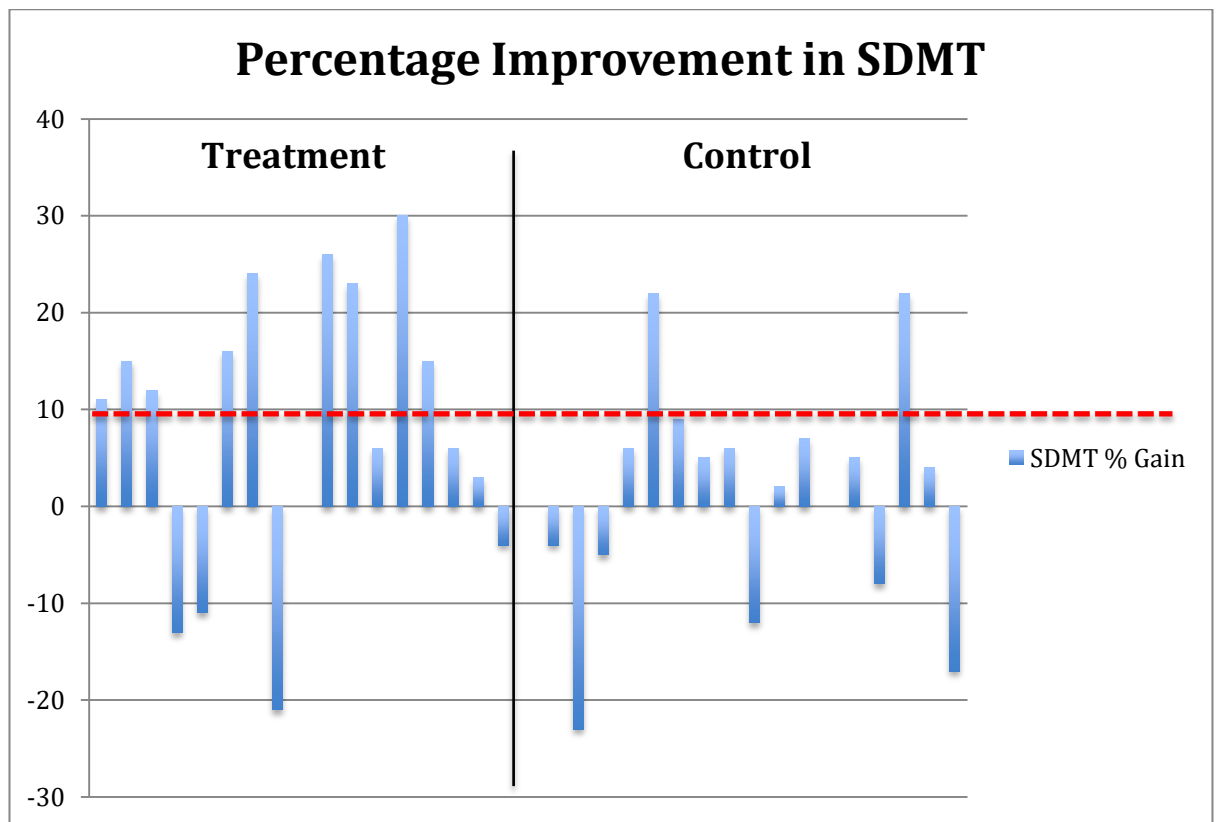
Proportion of patients showing greater than 10% improvement in SDMT immediately post-intervention by group ($\chi2 = 0.008$).

6.1.3 Cognitive outcomes - Time 3

Overall, there was an improvemnet in BICAMS performance across participants at follow up. The proportion of patients showing an increase of ≥10% in the SDMT was maintained at time 3 however an increasing proportion of patients in the control group also showed a similar improvement by this stage making the difference between the groups non-significant at follow up.

	Treatment (n=17)	Control (n=14)	*p-value* (χ^2)
SDMT gain ≥10%	9/17 (52.9%)	6/14 (42.9%)	0.815
CVLT gain ≥10%	9/17 (52.9%)	9/14 (64.3%)	0.542
BVMT gain ≥10%	14/17 (82.4%)	8/14 (57.1%)	0.124

SDMT: Symbol Digits Modalities Test; CVLT: California Verbal Learning Test; BVMT: Brief Visuospatial Memory Test.

In the BVMT-R there was a trend towards greater improved performance in the treatement group relative to controls but this did not reach significance (table 6.3 & figure 6.2).

Table 6.2 BICAMS performance at follow-up

	Treatment (n=17)		Control (n=14)		
	Mean	*± SD*	*Mean*	*± SD*	*p-value*
SDMT 1	42.76	7.11	37.83	11.60	
SDMT 2	45.82	7.29	39.06	11.72	0.429
SDMT 3	46.12	7.63	41.14	13.85	
CVLT 1	45.94	9.85	44.78	9.2	
CVLT 2	52.71	11.80	48.83	11.13	0.394
CVLT 3	52.88	10.98	52.29	10.78	
BVMT 1	20.53	5.90	18.44	7.37	
BVMT 2	25.18	4.44	20.39	6.60	0.266
BVMT 3	27.82	4.20	21.21	7.127	

SDMT: Symbol Digits Modalities Test; CVLT: California Verbal Learning Test; BVMT: Brief Visuospatial Memory Test.

Figure 6.2 Performance on BICAMS across three time points
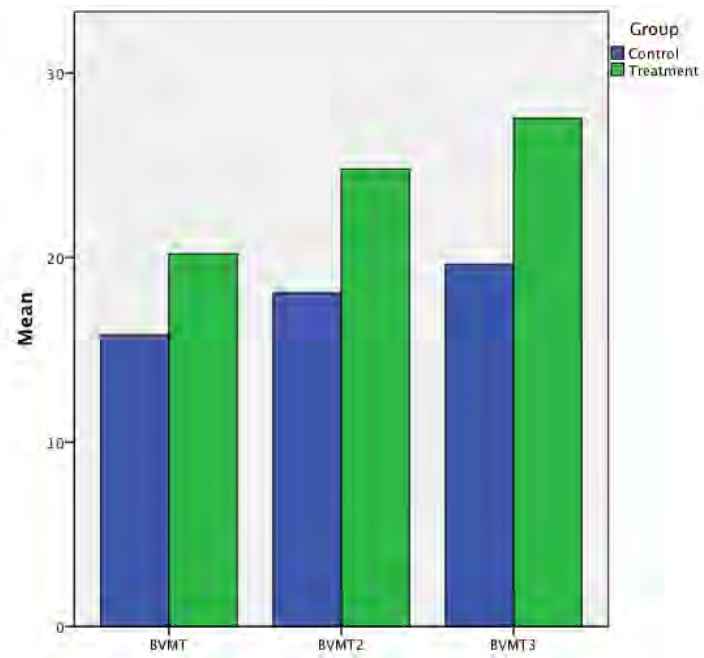
6.2 QOL outcomes

At time 2 and time 3 there were no significant differences in QOL outcome measures, measures of self-efficacy or subjective cognitive performance between the two groups (table 6.4). Subjective perceptions of improvement in cognitive performance was seen to improve across all participants at follow up (p = <0.001) however no significant between group changes were seen.

Table 6.3 Quality of Life outcomes at follow up, by treatment group.

	Treatment (n=17)		Control (n=14)		
Scores at Time 1, Time 2 & Time 3	*Mean*	*± SD*	*Mean*	*± SD*	*p-value*
FAMS 1	85.24	22.61	102.79	35.06	
FAMS 2	82.18	25.09	99.14	36.89	0.719
FAMS 3	89.00	30.99	101.00	32.40	
PAM-13 1	54.62	17.13	65.58	14.66	
PAM-13 2	59.15	13.65	64.15	13.81	0.158
PAM-13 3	58.79	15.52	62.10	15.90	
EQ-5D 1	0.49	0.13	0.61	0.22	
EQ-5D 2	0.49	0.23	0.53	0.26	0.388
EQ-5D 3	0.53	0.20	0.57	0.27	
MSNQ-S 1	35.65	13.56	34.79	12.34	
MSNQ-S 2	32.76	13.81	31.36	15.83	0.892
MSNQ-S 3	29.18	15.14	28.93	13.13	
HADS-D 1	9.82	3.38	9.21	3.38	
HADS-D 2	9.82	3.34	9.50	4.35	0.921
HADS-D 3	9.35	2.85	8.79	4.21	
HADS-A 1	9.18	3.80	9.86	5.74	
HADS-A 2	9.29	4.47	8.21	5.06	0.334
HADS-A 3	8.53	4.38	6.86	4.93	
FSS 1	52.12	10.89	49.43	14.18	
FSS 2	52.53	13.21	48.57	15.64	0.912
FSS 3	52.53	11.47	49.29	15.50	
USE-MS 1	16.00	5.85	19.00	6.72	
USE-MS 2	15.76	5.62	18.69	6.60	0.996
USE-MS 3	16.47	5.70	19.31	8.70	

FAMS: Functional Assessment of MS; PAM-13: Patient Activation Measure; EQ5D: EuroQOL five dimension questionnaire; USE-MS: Unidimensional Self-Efficacy scale for MS; MSNQ: Multiple Sclerosis Neuropsychological Questionnaire; HADS-D: Hospital Anxiety and Depression Scale (depression); HADS-A: Hospital Anxiety and Depression Scale (anxiety); FSS: Fatigue Severity Scale;

6.3 Discussion

The SDMT is known to be the most sensitive tests for cognitive impairment in MS [172, 173]. It has also been shown to exhibit minimal practice effects even when conducted over the short term [516]. In a study by Benedict et al, patients with MS undertaking the SDMT monthly for 6 months exhibited practice effects amounting to only to 0.2 SD for the duration of the study.

In our study, at time 2 a greater proportion of patients in the treatment group were seen to improve in the SDMT by ≥10%. Both the CVLT and BVMT-R did not show any significant group difference over time. The proportion of patients showing improvement in the SDMT at time 3 was unchanged (representing maintenance of improvement) however between time 2 and time 3 a number of patients in the control group showed improvement in the SDMT possibly representative of practice effects. Overall this may suggest that, although there is a practice effect associated with repeat testing, those patients undergoing cognitive rehabilitation may have more efficient learning associated with practiced tasks. The more efficient information processing seen in the treatment group (as represented by improvement in SDMT) may be as a result of the increased activation of the bifrontal executive networks seen on fMRI.

QOL measures used did not change significantly over time or exhibit between group differences. FAMS is a composite score of QOL measures across multiple domains and it is perhaps unsurprising that it did not reflect what may be otherwise small changes in cognitive performance. QOL is a complex construct influenced by a multitude of factors such as employment status, social networks, perceptions of self-worth and self-efficacy. It is possible that cognitive rehabilitation has a positive impact on a number of these factors but such changes in such factors take time to manifest as improvements in QOL.

7

Limitations, conclusion &

future work

7.1 Limitations

This work has several limitations. Firstly, as the study was largely exploratory in nature, it utilised an open design and is therefore subject to a number of limitations inherent to this type of design. The primary drawback relates to the fact that participants were not blinded to the nature of the intervention.

Patients who had invested time and effort in the cognitive training may have expected to see an improvement in performance at follow up and may therefore have exerted a greater "subconscious" effort during both the cognitive testing and fMRI n-back tasks than the control group. A sham intervention is generally considered preferable to having no intervention in an attempt to ensure blinding. However devising an adequate sham intervention in non-pharmacological trials is often difficult. An ideal sham intervention is sufficiently similar to the treatment condition that participants are unable to "guess" the group allocation but ought to be sufficiently different so as to not introduce additional confounders. In assessing the efficacy of computerised cognitive rehabilitation, where patients otherwise known to have insight into their deficits, an adequate sham intervention of this nature was not thought possible. The fact patients were unblinded has the potential to lead to a greater placebo response among the treatment group. However the fact that fatigue and other QOL indices such as mood patient reported measures of cognitive impairment did not differ significantly between the groups, is evidence against a significant placebo response. Functional MRI activations would also not expected to show a significant placebo response.

For pragmatic reasons blinding of the treating neurologist was not established due to the necessary interaction between patient and investigator, who was available to help to install software etc. This does present the potential for observer bias, particularly where repeat testing is required. BICAMS however provides objective measures of cognitive performance relatively immune from potential bias. SPM analysis of MRI data offers objective, largely automated measures independent of assessment bias. Investigator blinding was

maintained for any methods such as assessment of white matter lesion volumes that involved manual interpretation.

Using alternative forms of a test can offset learning effects. In this case of BICAMS, only the original testing forms have been validated and thus were used in this study. In view of these potential practice effects, a control group was therefore required to highlight any possible beneficial effects of the intervention offered. The randomisation procedures resulted in groups that were matched across demographics and disease characteristics and could be expected to control for practice effects between groups.

The choice of an active control condition (natural history DVDs) was an attempt to control for the potential effect of introspection involved with being involved in a clinical trial. Focused awareness on one's cognitive abilities may have an effect on cognitive performance and other QOL outcome measures. There exists a potential confounding effect of focused attention in the control condition however such attention is required for a multitude of everyday tasks and was not considered to present a significant confounding influence.

Although data is available on patient compliance with the active intervention by means of data collected via the software, patient compliance with the control condition is reliant on patient report and was not considered entirely reliable.

The numbers of patients recruited to the study were relatively small and hampered by patient drop out between time 2 and time 3. This potentially limits the ability to detect subtle changes that may be clinically meaningful in the longer term.   It also does not allow for subgroup analysis to see which group of patients may benefit most from cognitive rehabilitation.

Although a broad group of patients were recruited to the study, for practical reasons, non-ambulant patients were excluded from the study. The absence of such patients may limit the generalizability of this study. However these are patients that already may have the greatest degree of cognitive impairment and

exhibit limited potential for rehabilitation. Conversely, there may have been a reluctance on the behalf of the recruiting neurologist to approach patients with a recent diagnosis of MS who were perhaps still coming to terms with the diagnosis.

Throughout this thesis multiple comparisons were performed in the analysis of the behavioural and cognitive data (all MRI analysis used the family-wise error correction). This does raise the prospect of a type I error in the interpretation of statistical significance. However, it is known that many of the comparisons are highly correlated and formal correction likely to compound the risk of a type II error in this relatively small sample.

Finally, much of the change in activations seen in the fMRI task relates to areas known to be responsible for executive functions. Executive function and attention maybe most amenable to training but is not specifically assessed in the BICAMS.

7.2 Conclusion

Our work demonstrates the potential beneficial effect of cognitive rehabilitation in MS. Such beneficial effects are likely to be underpinned by adaptive functional changes in executive centres and attention networks.

Out study highlights that, following cognitive rehabilitation, improvements may be seen in information processing speed which are thought to reflect alterations within attentional and executive networks. The more efficient information processing seen in the treatment group on SDMT may be as a result of the increased recruitment of these networks.

We have also shown that the incidence of unemployment is much higher among patients with cognitive impairment and that such patients exhibit much lower measures of QOL. In addition to minimising physical disability, one of the major goals in MS therapeutics is to preserve cognitive function thereby maintaining QOL and employment for individuals. Cognitive rehabilitation may have significant cost-saving implications for the individual and society. Although not all cognitive deficits in MS may benefit from rehabilitation, identification of modifiable elements would be key to an efficient and cost effect approach to rehabilitation in the future.

7.3 Future work

This work has shown that home-based computerised cognitive rehabilitation may lead to alterations in functional connectivity that underpins learning. Improvements in cognitive performance were observed in a significant number of patients at early follow up. The promotion and encouragement of compensatory strategies and focused awareness on the presence of cognitive impairment may lead to behavioural adaptation that leads to maintenance of cognitive improvements after cessation of therapy.

In future, further studies might address the issue of an adequate sham intervention and in so-doing, attempt to ensure a double-blind design. In addition, clearly a larger study would offer a greater statistical power to detect subtle change. As executive function may be amenable to rehabilitation, outcome measures that include assessment of executive function may also be desirable.

Future work might also examine the role of cognitive impairment in unemployment in more detail. The type of employment (e.g. professional versus manual occupations) may also be impacted upon differently by cognitive impairment. Data pertaining to employment status such as full-time versus part-time employment and details pertaining to when an individual ceased to be in employment and how this relates to duration of illness may be of interest.

There is very limited data on the effect of cognitive rehabilitation in the longer term. Most of the published studies have follow up of less than six months. There is some limited evidence that improvement on cognitive measures may be maintained long-term following even a brief period of cognitive training [451, 517]. The role for repeated sessions is untested and the required frequency of such interventions is unknown. Such factors may be of interest in future work.

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Appendices

i   **Symbol digits modalities test A**

⊢	>	⊣	÷	+	Γ	)	÷	(
1	2	3	4	5	6	7	8	9

(	⊣	÷	(	⊢	>	÷	Γ	(	>	÷	(	>	(	÷

Γ	>	(	÷	⊣	>	⊢	Γ	(	÷	>	÷	Γ	⊢	)

Γ	⊣	+	)	(	⊢	+	Γ	)	⊣	÷	÷	⊢	Γ	+

÷	Γ	⊣	(	>	Γ	(	⊣	>	+	÷	)	⊢	>	Γ

÷	⊣	)	⊢	>	+	Γ	⊣	÷	⊢	+	÷	÷	)	(

>	÷	+	÷	⊢	>	Γ	÷	(	+	÷	⊣	>	)	Γ

÷	)	+	÷	⊢	+	)	⊣	(	÷	÷	(	Γ	⊢	>

⊣	÷	(	>	Γ	÷	(	>	÷	+	⊢	⊣	Γ	)	÷

ii   ***Brief Visuospatial Memory Test***

iii   California Verbal Learning Test

List A Immediate Free Recall Trial 1

I'm going to read a list of words to you. Listen carefully, because when I'm through, I want you to tell me as many of the words as you can. You can say them in any order, just say as many of them as you can. Are you ready?

Read List A at an even pace, taking slightly longer than one second per word, so the entire list takes 18 to 20 seconds. Then say: Go ahead.

Trial 2

I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order. Be sure to also say words from the list that you told me the first time.

Trials 3 and 4

I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

Trial 5

I'm going to read the same list one more time. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

Record all responses verbatim, in the order recalled. Prompt only once (e.g., Anything else?) at the end of each free and cued recall trial (i.e., after 15 seconds with no response or when the examinee says he/she cannot remember more words).

List A	Trial 1	Resp Type	Trial 2	Resp Type	Trial 3	Resp Type	Trial 4	Resp Type	Trial 5	Resp Type
truck	1		1		1		1		1	
spinach	2		2		2		2		2	
giraffe	3		3		3		3		3	
bookcase	4		4		4		4		4	
onion	5		5		5		5		5	
motorcycle	6		6		6		6		6	
cabinet	7		7		7		7		7	
zebra	8		8		8		8		8	
coach	9		9		9		9		9	
lamp	10		10		10		10		10	
celery	11		11		11		11		11	
cow	12		12		12		12		12	
desk	13		13		13		13		13	
boat	14		14		14		14		14	
squirrel	15		15		15		15		15	
cabbage	16		16		16		16		16	
	17		17		17		17		17	
	18		18		18		18		18	
	19		19		19		19		19	
	20		20		20		20		20	

Total Correct C	Total Correct C	Total Correct C	Total Correct C	Total Correct C
Total Repetitions R	Total Repetitions R	Total Repetitions R	Total Repetitions R	Total Repetitions R
Total Intrusions I	Total Intrusions I	Total Intrusions I	Total Intrusions I	Total Intrusions I

183

iv   *Functional assessment of multiple sclerosis*

FAMS (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	MOBILITY	Not at all	A little bit	Some-what	Quite a bit	Very much
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GF1	I am able to work (include work at home)	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
ITU3	I have to limit my social activity because of my condition	0	1	2	3	4
CNS5	I have strength in my legs	0	1	2	3	4
MS1	I have trouble getting around in public places	0	1	2	3	4
MS2	I have to take my condition into account when making plans	0	1	2	3	4

	SYMPTOMS	Not at all	A little bit	Some-what	Quite a bit	Very much
GP2	I have nausea	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BRM1	I have pain in my joints	0	1	2	3	4
MS3	I am bothered by headaches	0	1	2	3	4
MS4	I am bothered by muscle pains	0	1	2	3	4

FAMS (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE3	I am losing hope in the fight against my illness..................	0	1	2	3	4
GF3	I am able to enjoy life..	0	1	2	3	4
MS5	I feel trapped by my condition	0	1	2	3	4
MS6	I am depressed about my condition...................................	0	1	2	3	4
MS7	I feel useless	0	1	2	3	4
MS8	I feel overwhelmed by my condition	0	1	2	3	4

	GENERAL CONTENTMENT	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF2	My work (include work at home) is fulfilling....................	0	1	2	3	4
GF4	I have accepted my illness..................................	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
MS9	I am frustrated by my condition	0	1	2	3	4
Sp5	I feel a sense of purpose in my life	0	1	2	3	4
HI6	I feel motivated to do things...	0	1	2	3	4

FAMS (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	THINKING AND FATIGUE	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
MS10	I need to rest during the day	0	1	2	3	4
HI9	I have trouble remembering things	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
MS11	My thinking is slower than before	0	1	2	3	4
MS12	I have trouble learning new tasks or directions	0	1	2	3	4

	FAMILY/SOCIAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
MS13	My family has trouble understanding when my condition gets worse	0	1	2	3	4
MS14	I feel "left out" of things	0	1	2	3	4

FAMS (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
GS7	I am satisfied with my sex life	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
MS15	Heat worsens my symptoms	0	1	2	3	4
BL1	I have trouble controlling my urine	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
MS16	I am bothered by muscle spasms	0	1	2	3	4

v   *Hospital anxiety and depression scale*

Hospital Anxiety and Depression Scale

~ Scoring Sheet ~

	Yes definitely	Yes sometimes	No, not much	No, not at all
1. I wake early and then sleep badly for the rest of the night.	3	2	1	0
2. I get very frightened or have panic feelings for apparently no reason at all.	3	2	1	0
3. I feel miserable and sad.	3	2	1	0
4. I feel anxious when I go out of the house on my own.	3	2	1	0
5. I have lost interest in things.	3	2	1	0
6. I get palpitations, or sensations of 'butterflies' in my stomach or chest.	3	2	1	0
7. I have a good appetite.	0	1	2	3
8. I feel scared or frightened.	3	2	1	0
9. I feel life is not worth living.	3	2	1	0
10. I still enjoy the things I used to.	0	1	2	3
11. I am restless and can't keep still.	3	2	1	0
12. I am more irritable than usual.	3	2	1	0
13. I feel as if I have slowed down.	3	2	1	0
14. Worrying thoughts constantly go through my mind.	3	2	1	0

Anxiety   2, 4, 6, 8, 11, 12, 14

Depression   1, 3, 5, 7, 9, 10, 13

Scoring   3, 2, 1, 0 (For items 7 & 10 the scoring is reversed)

GRADING: 0 - 7 = Non-case   8 – 10 = Borderline case   11+ = Case

vi   *Unidimensional self-efficacy scale for Multiple Sclerosis*

USE-MS

Date:

Instructions: For each statement, tick ✓the box which best sums up your response as to how you have been feeling in the past **two weeks**.

---

1. I am confident when meeting new people and going to new places

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

2. I find that the things I do in the day make me feel happy and satisfied

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

3. I can keep my MS from interfering with time spent with my friends and family

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

4. I have as much independence as I feel I need

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

5. Sometimes I feel inadequate as a person because of my condition

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

6. There are many things that I can do to help control my fatigue

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

7. I feel that my social life would be better if I did not have MS

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

8. I rely on others to help me make decisions

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

9. I worry about how I will cope in the future

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

10. Despite my difficulties, I can still manage to cope with daily life

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

11. There is really no way I can solve some of the problems I have with my MS

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

12. Despite my MS, I can do anything I set my mind to

Strongly Disagree	Disagree	Agree	Strongly Agree
☐	☐	☐	☐

vii   *Fatigue Severity Score*

Fatigue Severity Scale (FSS)

Your Name_____

Date:_____Date of birth: _____

This questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

***A low value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates strong agreement.

During the past week, I have found that:	Disagree ⟷ Agree
1. My motivation is lower when I am fatigued	1 2 3 4 5 6 7
2. Exercise brings on my fatigue.	1 2 3 4 5 6 7
3. I am easily fatigued.	1 2 3 4 5 6 7
4. Fatigue interferes with my physical functioning.	1 2 3 4 5 6 7
5. Fatigue causes frequent problems for me.	1 2 3 4 5 6 7
6. My fatigue prevents sustained physical functioning.	1 2 3 4 5 6 7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1 2 3 4 5 6 7
8. Fatigue is among my three most disabling symptoms.	1 2 3 4 5 6 7
9. Fatigue interferes with my work, family or social life.	1 2 3 4 5 6 7

Total Score: _____

viii   Multiple sclerosis neuropsychological screening questionnaire

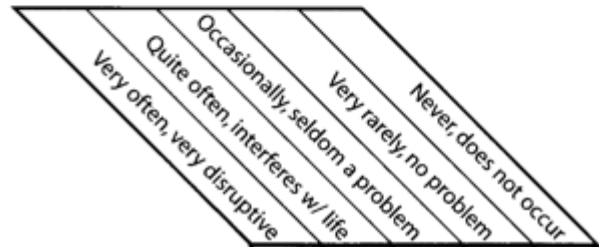**MSNQ Patient**

Name: _____

Date: _____

Circle one: MALE / FEMALE

INSTRUCTIONS:
The following questions ask about
problems that you may experience. Rate
how often these problems occur **AND**
how severe they are. Base your ratings
on how you have been over the **last
three months**.

Please check the appropriate box.

	Very often, very disruptive (4)	Quite often, interferes w/ life (3)	Occasionally, seldom a problem (2)	Very rarely, no problem (1)	Never, does not occur (0)
1. Are you easily distracted?					
2. Do you lose your thoughts while listening to somebody speak?					
3. Are you slow when trying to solve problems?					
4. Do you forget appointments?					
5. Do you forget what you read?					
6. Do you have trouble describing shows or programs recently watched?					
7. Do you need to have instructions repeated?					
8. Do you have to be reminded to do tasks?					
9. Do you forget errands that were planned?					
10. Do you have difficulty answering questions?					
11. Do you have difficulty keeping track of two things at once?					
12. Do you miss the point of what someone is trying to say?					
13. Do you have difficulty controlling impulses?					
14. Do you laugh or cry with little cause?					
15. Do you talk excessively or focus too much on your own interests?					

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ix   *Patient Activation Measure – 13 item questionnaire*

Below are some statements that people sometimes make when they talk about their health. Please indicate how much you agree or disagree with each statement as it applies to you personally by circling your answer. Your answers should be what is true for you and not just what you think others want you to say.

If the statement does not apply to you, circle N/A.

1.	When all is said and done, I am the person who is responsible for taking care of my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
2.	Taking an active role in my own health care is the most important thing that affects my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
3.	I am confident I can help prevent or reduce problems associated with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
4.	I know what each of my prescribed medications do	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
5.	I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
6.	I am confident that I can tell a doctor concerns I have even when he or she does not ask	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
7.	I am confident that I can follow through on medical treatments I may need to do at home	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
8.	I understand my health problems and what causes them	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
9.	I know what treatments are available for my health problems	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
10.	I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
11.	I know how to prevent problems with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
12.	I am confident I can figure out solutions when new problems arise with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
13.	I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A

x   ***EQ-5D-5L Health Questionnaire***

Under each heading, please tick the ONE box that best describes your health TODAY

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 ❑

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 ❑

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 ❑

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 ❑
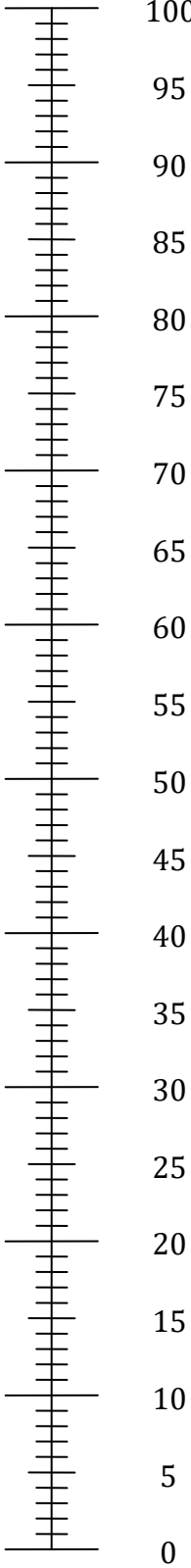
I have extreme pain or discomfort ❑

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 ❑

- We would like to know how good or bad your health is

  TODAY.

- This scale is numbered from 0 to 100.

- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

The best health
you can imagine

YOUR HEALTH TODAY =

| 100 |
| 95 |
| 90 |
| 85 |
| 80 |
| 75 |
| 70 |
| 65 |
| 60 |
| 55 |
| 50 |
| 45 |
| 40 |
| 35 |
| 30 |
| 25 |
| 20 |
| 15 |
| 10 |
| 5 |
| 0 |

The worst health
you can imagine

xi   *Expanded disability status scale*

Score	Description
0	Normal neurological examination
1	No disability, minimal signs in 1 FS*
1.5	No disability, minimal signs in >1 FS
2	Minimal disability in 1 FS
2.5	Mild disability in 1 FS or minimal disability in 2 FSs
3	Moderate disability in 1 FS, or mild disability in 3 or 4 FSs. Fully ambulatory.
3.5	Fully ambulatory but with moderate disability in 1 FS and more than minimal disability in several others
4	Fully ambulatory without aid, self-sufficient, up and about ~12 h/day despite relatively severe disability; able to walk without aid/rest for ~500 m
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability; able to walk without aid or rest for ~300 m
5	Ambulatory without aid or rest for ~200 m; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for ~100 m; disability severe enough to preclude full daily activities
6	Intermittent or unilateral constant assistance (stick, crutch, brace) required to walk for ~100 m with or without resting
6.5	Constant bilateral assistance (stick, crutches, braces) required to walk for ~20 m without resting
7	Unable to walk beyond ~5 m, even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair for ~12 h/day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels him-/herself, but cannot carry on in standard wheelchair for a full day; may require motorised wheelchair
8	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arms, retains some self-care functions
9	Confined to bed; can still communicate and eat
9.5	Totally helpless bed-bound patient; unable to communicate effectively or eat/swallow
10	Death due to MS

FS = functional system; FSs = functional systems; MS = multiple sclerosis.

*Each system (visual, pyramidal, etc.) has a separate FS scale; scores are compiled to assist designation of the overall score.