Early diagnosis, monitoring, subjective performance and predictors of subclinical cognitive decline in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is a demyelinating, degenerative disease for which the etiology remains unknown. Cognitive impairment (CI) is common in MS with up to 65% of patients experiencing cognitive dysfunction in one or more cognitive domains. The most common cognitive domains affected in MS include information processing speed, memory and attention. Subtle impairment in these areas has been shown to cause significant impacts on a patients' ability to function in many aspects of their lives. Brief and reliable methods to measure changes in cognitive functioning remains an unmet need in the MS outpatient clinic. Traditional neuropsychological assessment relies on highly skilled neuropsychologists and whilst effective at measuring CI, is inefficient and insensitive to subtle changes in function. Given the high prevalence and pervasive nature of changes in cognitive functioning, monitoring all MS patients for changes in their cognitive functioning from a previous state is crucial and a priority in the field. New technologies may provide innovative ways to measure cognitive functioning in the MS outpatient clinic.

This thesis follows the journey from implementation and feasibility, to validation, to a prognostic use case of a web-based computerised reaction time battery, MSReactor. MSReactor consists of three reaction time tasks measuring the broad cognitive domains of psychomotor processing speed, attention and working memory. We report on the feasibility of implementing MSReactor into busy outpatient clinics and investigate important psychometric properties of the tool. We found that administration of MSReactor was highly scalable, well accepted and persistence of testing remained high. The MSReactor tasks displayed minimal practice effects and were reliable. In addition, the tasks correlated moderately with a validated and widely used tool, the Symbol Digit Modalities Test (SDMT). In chapter two, we further investigated the criterion-related validity of the MSReactor tasks. We found that the MSReactor tests could moderately predict scores on an electronic version of the SDMT, suggesting they measure some overlapping cognitive domains.

We report on the relationship between perceived cognitive performance and objective changes on the MSReactor tasks. Subjective cognitive functioning is an important aspect of management of MS, as clinicians often rely on a patient reporting cognitive changes to make clinical decisions. We found weak correlations between objective changes on some tasks, depression, and the subjective rating of performance. Our results suggest people living with

MS do not reliably perceive changes in function as measured with a computerised battery. Finally, we modelled and identified discrete longitudinal trajectories of MSReactor data. We identified a group of participants who were more likely to experience worsening of reaction times; and importantly, more likely to experience a disability progression event.

The findings from this work demonstrate that a computerised reaction time battery is a scalable and reliable method to screen large numbers of patients for changes in broad cognitive functions. The battery can measure longitudinal worsening trajectories in cognitive function, and these trajectories were associated with greater risk of sustained cognitive change and disability worsening. The introduction of cognitive monitoring into clinical practice could result in earlier detection of cognitive dysfunction, at a time when it is potentially modifiable.

Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals, one accepted paper and one submitted publication. The core theme of the thesis is the development and validation of a new technological tool to measure changes in cognitive function in people with multiple sclerosis. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Central Clinical School, Department of Neuroscience under the supervision of Associate Professor Anneke van der Walt.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters one through four, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** (published, in press, accepted or returned for revision, submitted)	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
1	The feasibility, reliability and concurrent	Published	80%. Concept, collecting data, statistical analysis and	1) David Darby, concept, input into manuscript 5%	No

	validity of the MSReactor computerized cognitive screening tool in multiple sclerosis		writing first draft	2) Tomas Kalincik, input into manuscript 5% 3) Helmut Butzkueven, concept, input into manuscript 5% 4) Anneke van der Walt, concept, input into manuscript 5%	
2	The MSReactor computerized cognitive battery correlates with the processing speed test in relapsing-remitting multiple sclerosis	Published	50%. Concept, collecting data, statistical analysis and writing and editing first draft	1) Charmaine Yam. Statistical analysis, writing and editing first draft 40% 2) Anneke van der Walt, Jim Stankovich. Concept, statistical analysis and manuscript input 5% 3) All other authors. Access to patients, input into manuscript 5%	No
3	Subjective versus objective performance in people with multiple sclerosis using the	Submitted	80%. Concept, collecting data, statistical analysis, writing and editing first draft.	1) Anneke van der Walt, Helmut Butzkueven. Concept, manuscript input. 10% 2) All other authors. Access to patients,	No

	MSReactor computerised cognitive tests			manuscript input. 10%	
4	Computerised cognitive measures can detect reaction time slowing and predict disability progression in relapsing remitting multiple sclerosis	Accepted	80%. Concept, collecting data, statistical analysis, writing and editing first draft.	1) Anneke van der Walt, Helmut Butzkueven, Tomas Kalincik. Concept, statistical advice, manuscript input. 10% 2) All other authors. Access to patients, manuscript input. 10%	No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

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I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Anneke van der Walt

Main Supervisor signature: **Date:** 10 June 2021

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Preface

This thesis is submitted as a 'thesis including published work'. This work was done under the supervision of Associate Professor Anneke van der Walt (primary), Professor Helmut Butzkueven, Associate Professor David Darby and Associate Professor Tomas Kalincik. All relevant Human Research Ethics Committee approvals and written informed consent for all participants was obtained prior to any data collection.

Introduction: This chapter reviews the prevalence, presentation, and management of cognitive dysfunction in MS and appraises the current traditional neuropsychological tools as well as modern technological advances in computerised testing used to assess cognition. A new computerised cognitive battery is introduced and described in the context of existing literature. The steps taken to determine the feasibility, usability and validity of the computerised cognitive battery in the clinic and home settings form the basis for chapters one and two of this work. Perceived cognitive performance and the identification of longitudinal cognitive change trajectories using the computerised tests and the predictors of these trajectories form the basis for chapters three and four of this work.

Chapter 1: is a reproduction of the journal article "*Merlo, D, Darby, D, Kalincik, T, Butzkueven, H & van der Walt, A. The feasibility, reliability and concurrent validity of the MSReactor computerized cognitive screening tool in multiple sclerosis*" published in Therapeutic Advances in Neurological Disorders in July 2019 (see Appendix). The study design was undertaken with A/Prof Anneke van der Walt, Prof Helmut Butzkueven and A/Prof David Darby, who also edited the manuscript. I enrolled all participants and collected all data with the computerised cognitive battery. I performed all statistical analyses and drafted the manuscript and revisions. Routine clinical data was collected via MSBase, an international longitudinal registry, to which participants had provided independent consent for their treating neurologist to contribute pseudonymised clinical data. All authors contributed to revision of the manuscript.

Chapter 2: is a reproduction of the journal article "*Daniel Merlo[1], Charmaine Yam[1], Jim Stankovich, et al. The MSReactor computerized cognitive battery correlates with the processing speed test in relapsing-remitting multiple sclerosis"* published in Multiple Sclerosis and Related Disorders in May 2020. As shared first author of this manuscript, I was responsible

for conceptualisation of and design of the study and analyses, establishing the methodology, statistical analysis and drafting of the manuscript. I edited the initial manuscript draft and subsequent revisions. Data was collected at six sites, led by principal investigators Dr Tomas Kalincik, Dr Trevor Kilpatrick, Dr Jeannette Lechner-Scott, Dr Bruce Taylor, Dr Michael Barnett, Dr Helmut Butzkueven and Dr Anneke van der Walt. Routine clinical data was collected via MSBase, an international longitudinal registry, to which participants had provided independent consent for their treating neurologist to contribute pseudonymised clinical data. All authors contributed to revision of the manuscript.

Chapter 3: is a reproduction of the journal article *"Daniel Merlo, Tomas Kalincik, Chao Zhu, Melissa Gresle, Jeanette Lechner-Scott, Trevor Kilpatrick, Michael Barnett, Bruce Taylor, Katherine Buzzard, David Darby, Helmut Butzkueven and Anneke van der Walt. "Subjective versus objective performance in people with multiple sclerosis using the MSReactor computerised cognitive tests"* which was submitted for publication to Multiple Sclerosis Journal on 9 June 2021. I was responsible for conceptualising and design of the study, study implementation, all data analysis and drafting the manuscript. Data was collected at six sites, led by principal investigators Dr Tomas Kalincik, Dr Trevor Kilpatrick, Dr Jeannette Lechner-Scott, Dr Bruce Taylor, Dr Katherine Buzzard, Dr Michael Barnett, Dr Helmut Butzkueven and Dr Anneke van der Walt. All authors contributed to revision of the manuscript.

Chapter 4: is a reproduction of the journal article *"Daniel Merlo, Jim Stankovich, Claire Bai, Tomas Kalincik, Chao Zhu, Melissa Gresle, Jeanette Lechner-Scott, Trevor Kilpatrick, Michael Barnett, Bruce Taylor, David Darby, Helmut Butzkueven and Anneke van der Walt. Computerised cognitive measures can detect reaction time slowing and predict disability progression in relapsing remitting multiple sclerosis"* which was accepted for publication in Neurology on 28th August 2021. I was responsible for conceptualising and design of the study, study implementation, all data analysis and drafting the manuscript. Data was collected at six sites, led by principal investigators Dr Tomas Kalincik, Dr Trevor Kilpatrick, Dr Jeannette Lechner-Scott, Dr Bruce Taylor, Dr Michael Barnett, Dr Helmut Butzkueven and Dr Anneke van der Walt. Routine clinical data was collected via MSBase, an international longitudinal registry, to which participants had provided independent consent for their treating neurologist to contribute pseudonymised clinical data. All authors contributed to revision of the manuscript.

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Merlo D[1], Yam, C[1], et al. The MSReactor computerized cognitive battery correlates with the processing speed test in relapsing-remitting multiple sclerosis. *Multiple Sclerosis and Related Disorders.* 2020; 43. doi: 10.1016/j.msard.2020.102212.

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Govier-Cole, A. E. et al. Inhibiting Bone Morphogenetic Protein 4 Type I Receptor Signaling Promotes Remyelination by Potentiating Oligodendrocyte Differentiation. *eNeuro.* March/April 2019, 6(2). doi: 10.1523/ENEURO.0399–18.2019.

Thesis platform presentations

Merlo D et al. Factors that affect computerized cognitive screening in people with multiple sclerosis: diurnal variation, location and practice effects. Eastern Health Research Forum, 2017, Melbourne, Australia.

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Merlo D et al. Worsening longitudinal reaction time trajectories using the MSReactor computerised battery predicts confirmed EDSS progression. Australian and New Zealand Association of Neurologists (ANZAN) conference, selected to present in May 2021, virtual.

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Abbreviations

AIC	akaike information criterion
ANAM	Automated Neuropsychological Assessment Metrics
ARCS	Auditory Recorded Cognitive Screen
BIC	bayesian information criterion
BICAMS	Brief International Cognitive Assessment in Multiple Sclerosis
BRB-N	Brief Repeatable Battery – Neuropsychology
BVMT-R	Brief Visuospatial Memory Test-Revised
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBB	Cogstate Brief Battery
CCC	concordance correlation coefficient
ChRT	choice reaction time test
CI	cognitive impairment
CI	confidence interval
CIS	Clinically Isolated Syndrome
CNS	central nervous system
CR	cognitive reserve
CRT	choice reaction time test
CTIP	Computerized Test of Information Processing
CVLT-II	California Verbal Learning Test II
DMN	default mode network
DMT	disease-modifying therapy
EDSS	Expanded Disability Status Scale
FST	Faces Symbol Test
GM	grey matter
HC	healthy controls
HR	hazard ratio
HR-QoL	health-related quality of life
IFNB	interferon-beta
IQR	interquartile range
LCMM	latent class mixed models
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis
MCCB	Mindstreams Computerized Cognitive Battery

MDT	Manual Dexterity Test
MN	multinomial
MRI	magnetic resonance imaging
MS	multiple sclerosis
ms	milliseconds
MSFC	Multiple Sclerosis Functional Composite
MSPT	Multiple Sclerosis Performance Test
MSR	MSReactor
MusiQoL	Multiple Sclerosis Quality of Life
NEDA	no evidence of disease activity
NPSBMS	Neuropsychological Screening Battery for Multiple Sclerosis
OBK	one back
OR	odds ratio
PASAT	Paced Auditory Serial Addition Test
PHQ-9	Patient Health Questionnaire 9
PPMS	primary-progressive multiple sclerosis
PRO	Patient Reported Outcome
PST	Processing Speed Test
PSWQ	Penn State Worry Questionnaire
pwMS	people with multiple sclerosis
PVSAT	Paced Visual Serial Addition Test
QoL	quality of life
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	randomised controlled trial
RIS	radiologically isolated syndrome
RRMS	relapsing-remitting multiple sclerosis
RT	reaction time
SD	standard deviation
SEFCI	Screening Examination for Cognitive Impairment
SiRT	simple reaction time test
SPART	Spatial Recall Test
SRT	simple reaction time test
SDMT	Symbol Digit Modalities Test
WM	white matter

Introduction

Multiple Sclerosis

Epidemiology and disease course

Multiple sclerosis (MS) is the most common debilitating neurological disease seen in young adults. MS is a global disease with now more than 2.3 million people affected worldwide and incidence cases of 33 per 100,000. The distribution of MS globally is heterogeneous with incidence rates between 2.2 per 100,000 in Sub Saharan Africa and 186 per 100,000 in Sweden. MS disease onset typically occurs in young adults between 20 and 40 years of age, and females are more commonly affected than males with a ratio of almost 3:1 (Female:Male) reported in most developed countries (1). Recent studies have demonstrated a changing epidemiological landscape of MS over the past few decades including increasing and heterogeneous incidence of disease globally, a delay in disease onset and changing sex-specific incidence, which may in part be attributed to increased general longevity, access to more effective therapies and technologies enabling more accurate diagnosis (2, 3).

Between 80% and 90% of MS patients will present with a relapsing-remitting (RRMS) disease of the central nervous system (CNS) (4), typically preceded by a clinically isolated syndrome (CIS). In some cases, radiologically isolated syndrome (RIS), an incidental finding of asymptomatic lesions fulfilling dissemination in time criteria suggestive of MS may be detected where one-third of patients will progress to CIS (5). RRMS is hallmarked by discrete neurological episodes, or relapses of many clinical presentations most commonly optic neuritis, brainstem and spinal cord syndromes, followed usually by seemingly complete recovery. As the disease progresses, relapse recovery is increasingly incomplete and, in some people, a "secondary" progressive disease (SPMS) emerges around 10-15 years following onset, leading to persistent and progressive neurological deficits (6). In 5%-15% of cases, patients will present with primary progressive onset (PPMS), characterized by accrual of progressive disability over many years usually involving one dominant neuronal system (commonly a progressive spastic paraparesis but sensory ataxia, cerebellar ataxia and cognitive symptoms are not uncommon).

The natural history of MS is changing due to increased early disease modifying therapy (DMT) use, leading to delayed and a lower proportion of RRMS patients converting to SPMS (7). There has also been a decrease in the proportion of patients diagnosed with PPMS (8) likely due to the unavailability of therapy for PPMS and patients being labelled as RRMS to access treatment (6). Paediatric MS is rare (2.9/100,000 (9)) and presents unique challenges in diagnosis and management of symptoms and will not be covered in this review.

Etiology and pathophysiology

Although the cause of MS remains elusive, widely referenced environmental factors such as smoking, obesity, Epstein-Barr virus infection and exposure to ultraviolet light or vitamin D levels (10), have been implicated. In addition, several large genome-wide association studies have identified over 100 common polymorphisms in genetic regions supporting the central role of the immune system in the etiology of MS (11). Hence, the etiological basis of the disease is likely to be multifactorial, with environmental factors interacting with 'risk' genotypes in susceptible individuals.

The primary target of the autoimmune attack in MS is the myelin sheath of CNS axons, but axonal death is common within areas of acute inflammation. Furthermore, progressive loss of neurons occurs from the earliest stage of the disease (12). These neurodegenerative and demyelinating processes contribute to the loss of whole brain volume, seen at all stages of multiple sclerosis (13). This loss of brain volume can be attributed to diffuse damage in both grey matter (GM) and white matter (WM) tissue and is likely to contribute to the development of neurological disability in MS (14, 15). Recently, authors have suggested a continuum of MS rather than clinical phenotypes, extending from the inflammatory dominant presentation seen in relapsing onset MS to the neurodegeneration dominant presentation seen in progressive forms of the disease (6).

Treatment of MS: a brief overview

Therapies available for use in MS management vary from immunomodulatory (interferon beta, glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, natalizumab), targeted immunodepleting therapies (such as ocrelizumab) or pulsed immune reconstitution therapies

(alemtuzumab, cladribine). These DMTs all have described mechanisms of action, targeting different aspects of the peripheral immune system with different efficacy on suppressing disease activity measures as clinical relapses and evidence of inflammatory magnetic resonance imaging (MRI) activity (new T2-hyperintense lesions or gadolinium enhancing lesions). Therapies are typically defined as "high" or "low" efficacy based on trial results when compared to placebo or an active comparator with further confirmation about differential efficacy from observational cohort studies. "High-efficacy" therapies are more potent, yet come with a higher risk of serious adverse events (16). Active management with "high-efficacy" therapies can reduce relapse rate, disability accrual and brain atrophy to a greater extent than "low-efficacy" therapies (17, 18).

Goals of treatment have expanded over the last five years and increasingly aims to achieve a state of 'no evidence of disease activity' (NEDA). The most commonly used definition of NEDA involves absence of clinical relapse, absence of disease progression (as measured by the Kurtze Expanded Disability Severity Scale (EDSS)) and absence of MRI activity (no new or enlarging T2 lesions or no gadolinium enhancing lesions). Although this definition of NEDA, also called NEDA-3 (19), reflects what is most commonly used in MS clinical practice to monitor disease activity, it is recognized as a limited definition. The inclusion of absence of brain atrophy (NEDA-4) (20), cerebrospinal fluid markers and absence of cognitive decline (NEDA-5) represent more comprehensive assessments of neurological function (21). The aim to achieve these benchmarks has led to earlier treatment with highly active therapies (6), however the evidence of whether or not patients rendered NEDA on DMT have an improved long-term outcome than patients who do not achieve NEDA is not yet available (21). The concept of NEDA in clinical practice remains controversial, perhaps reflecting the immaturity of the definitions and/or the overly strict definitions. A major additional factor is the lack of standardized, feasible and cost-effective methods to measure brain atrophy (21). Giovannoni et al. propose that the NEDA concept is reflective of a larger issue – the need to identify and monitor the treatment response for every individual patient treated with DMT (21). Sensitive biomarkers and tests of clinical change, which are feasible and cost effective, are required for use in clinical practice. This is particularly true for cognition, which is not frequently part of the clinical conversation or included in decision making around treatment response.

Clinical nature of cognitive impairment in MS

Cognitive impairment (CI) in MS was noted by Charcot more than a century ago when he described "conceptions that are formed slowly" and "marked enfeeblement of the memory", yet it is only relatively recently that research into the pathogenesis, prevalence and management of cognitive symptoms has gained renewed attention. The understanding of the impact of the neuropsychological impairments seen in people with MS (pwMS) has changed dramatically over this time from the belief that CI was only present in highly disabled patients to understanding that CI only weakly correlates with physical disability (22) and can be a pervasive and debilitating symptom at all stages of MS. The first work in the recent era by Rao et al (23) in the early 1990's reported the frequency of cognitive dysfunction in pwMS of up to 65%. Since that seminal report, many groups have published figures for prevalence rates of CI in different MS populations using various neuropsychological evaluation tools with frequencies in the range of 45% to 70% (22, 24-27).

The clinical presentation of cognitive dysfunction in MS is characterized by considerable interpatient variability. In studies investigating attention and the speed taken to process information, authors have attempted to separate the relative contributions of pure motor speed from decision time and have consistently found a slowing in the mental processing speed in pwMS (28-30). Executive functions are a group of basic cognitive processes that are responsible for the control, selection and monitoring of behaviours taken to achieve chosen goals. Higher order executive functions require the simultaneous use of multiple basic cognitive processes and can include planning, problem solving and reasoning (31). Impairments in higher order executive functions, such as planning (32, 33) and conceptual reasoning (34) have been identified in pwMS. Memory impairments are common in pwMS and extensively studied. Studies of memory in pwMS often involve tests of primary (short-term or working) or secondary (recent, long-term) memory (24). In studies involving secondary memory mechanisms, pwMS can perform poorly on tasks involving recall of verbal or non-verbal stimuli (35, 36) and further studies have suggested that this is due to deficits in the retrieval of memory rather than the encoding of memories (37). In contrast, studies on primary memory mechanisms (working memory) suggest a slowing in the speed or efficiency at which novel information is encoded (35, 38). Other studies of working memory in pwMS have suggested deficits in articulatory rehearsal, a component of the working memory model responsible for the retrieval of memory form their short-term store (36). Visuospatial

perception, or the ability to process and interpret visual information of objects and the space in which they exist; and verbal fluency, requiring information retrieval from secondary memory, utilize executive controls and can also be disrupted in pwMS (23).

Cognitive impairment across the clinical spectrum of MS

Radiologically Isolated Syndrome

CI can be present across the spectrum of MS clinical phenotypes. In a study investigating the association between MRI metrics and cognitive impairment, Amato and colleagues found around 30% of patients with RIS were cognitively impaired when compared to healthy subjects (39). These studies found that the pattern of cognitive dysfunction was similar to that seen in a RRMS cohort, predominantly with impairments in speed of information processing, sustained attention, phonetic verbal fluency and working memory (39, 40). A few limitations are noted with these studies. The sample sizes are relatively small and the study populations were enrolled through MS specialists clinics so the cohorts may not be representative of the wider RIS population. Although only two trials used a healthy comparator group, these results demonstrate CI can be present as early as pre-clinical RIS. Regardless, further research with larger cohorts and enrolment of all incidental RIS presentations, not just those suggestive of MS, should be conducted.

Clinically Isolated Syndrome

A number of controlled studies have investigated the prevalence of CI in CIS. Whilst mostly relatively small trials, between 12.3% and 57% CIS patients were found to be impaired when compared to healthy subjects or normative values derived from the assessment tool used (41-46). The wide range of frequencies reported in these studies likely reflect differences between the studies in the definition of CIS, assessment tools, patient characteristics such as disease duration and indeed even differences in the definition of CI. The presence of CI during CIS may also be important for conversion to clinically definite MS. In a prospective study, CIS suggestive of MS patients underwent cognitive assessment and were followed for 3.5 (+/- 2.3) years. The authors found that 88% of those who were cognitively impaired (according to their study definition of CI) went on to a formal diagnosis of MS, suggesting the cognitive impairment holds prognostic value in conversion to MS (43). CI in CIS is characterized by information processing speed slowing, working memory, verbal fluency and verbal and visuospatial memory deficits (46-50).

Relapsing Remitting MS

Many studies have reported the frequency of CI in RRMS. In the larger controlled trials, estimates range from 31% to 45% of RRMS patients being cognitively impaired compared to healthy subjects (51-53). In two controlled studies of patients recently diagnosed with RRMS or having an EDSS of 4 or under, found the prevalence of CI in early RRMS was 45% and 34.9% respectively (51, 52). Although the frequencies of CI are similar between CIS and RRMS, in studies that compared them directly the frequency of CI in RRMS was consistently higher than in CIS albeit not significantly (42, 44, 45). In one longitudinal study, Amato and colleagues found that pwMS who were cognitively impaired at baseline (in verbal memory and reasoning) evolved additional cognitive dysfunction after 4.5 years follow up (verbal fluency and comprehension) and again after ten years of follow up (attention and spatial memory) (54). In another recent longitudinal study Damasceno et al found that over six years, around 62% of RRMS patients cognition deteriorated most prominently in processing speed and memory. This study also found that cognitive impairment at baseline was the strongest predictor of both cognitive and clinical deterioration after six years (55). The cognitive profile seen in RRMS is similar to that seen in CIS, predominantly information processing speed slowing, working memory, verbal fluency and verbal and visuospatial memory deficits with the addition of verbal learning (42).

Progressive MS

The prevalence of CI in SPMS is an area requiring more study due to a limited number of controlled studies with small number of participants. In one study comparing CI across MS phenotypes, almost 83% of 29 SPMS patients were found to be CI which was double the proportion of the RRMS cohort measured as impaired using the same assessment tool (42). Another study, using a computerised cognitive test, found 80% of 30 SPMS patients were CI (56). Other studies have found frequencies of CI in between 56% and 79% of SPMS patients and were more frequently impaired than CIS or RRMS patients (45, 57, 58). The cognitive profile in SPMS are similar to that in RRMS, although more severe (59) with a two-fold increase in impaired processing speed, executive function, verbal fluency, episodic memory, working memory and visuospatial construction (60).

Early studies assessing cognition in PPMS patients concluded that CI was less prevalent than in other clinical phenotypes of MS. In 1995, Comi et al. found that just 7% of PPMS patients

had cognitive deficits (61). Another large study of 158 PPMS patients published at around the same time found that, when compared to a cohort of 63 matched healthy subjects, 28.6% of PPMS patients were impaired (according to their study definition of impairment) (62). More recently however, Potagas et al (42) and Ruano et al (45) have reported frequencies of CI in PPMS similar to those seen in SPMS, 56% and 91% respectively. In one study, PPMS patients performed more poorly on a wider range of cognitive abilities than RRMS, including information processing slowing, attention, working memory, executive function, verbal episodic memory (63).

Considerations in defining and measuring cognitive impairment

Methodological considerations

Although age and disability drive CI across MS clinical phenotypes (64), there exists significant heterogeneity in the reported frequencies of CI across the disease course. Much of this variability could be attributed to the range of populations studied, from highly controlled MS clinic and hospital based samples where prevalence may be over-estimated to population-based samples more reflective of the wider MS population (65). In addition to the population studied, there is considerable heterogeneity in the classification of CI found in the literature and this may have an impact on the reported prevalence rates of CI in MS. The classification of CI is based on the comparison of the test score to the mean of a normative sample. Commonly, the criteria used to determine CI is defined as performance below one, one and a half or two standard deviations (SD) of the normative mean. By this definition, studies using more conservative criteria will detect a lower prevalence of CI and those using a more liberal definition will detect higher prevalence rates of CI, respectively (66). Typically, a neuropsychology assessment will utilize a battery of tests (rather than a single test) and this can also impact on the prevalence of reported CI as an increasing number of test scores obtained increases the likelihood of impaired results (67). In addition, the threshold of abnormal tests required to define CI also differ. For example, a diagnosis of CI using a comprehensive battery may require two or more (68) domains to be dysfunctional, where a shorter battery may be less rigorous and require just one (or more) (69). Together with hospital-based samples, less stringent criteria are likely to overestimate the frequency of CI in these studies and an effort should be made by the scientific community to standardize the definition of CI. To this effect, Fischer and colleagues (66) investigated the reliability of different criteria to classify CI by applying 20 distinct approaches found in the literature to cognitive data from early and late

stage pwMS. As expected, the authors found a substantial effect of classification criteria on the prevalence rate of CI and concluded that the approaches are not fully comparable and highlighted the need for standardization.

Another methodological consideration for the measurement of CI in MS is the selection of the normative sample used. Normative data (norms) are used to compare the raw test result of a pwMS with data for the average test of a reference group of people without MS with the same demographics such as age, sex and education. To accurately define CI, a normative sample must be well described and most importantly, be representative of the population being studied (excluding the disease of interest). Many neuropsychological tests may not even have a normative sample, whereas others have significant limitations in their normative data which must be considered for their use. These limitations will be discussed further here using the Symbol Digit Modalities Test (SDMT) example. The SDMT is considered as one of the most sensitive measures of information processing speed (but also additional cognitive processes which are discussed in detail in later sections) in MS and is routinely included in neuropsychological test batteries. Despite this, historical SDMT norms hinder its use in contemporary cohorts (70, 71). It has been hypothesized that the Flynn effect, a phenomenon where cognitive performance in a population increases over time, is evident in the SDMT data (72). Hence, the use of norms developed approximately 40 years ago risk the overestimation of pwMS cognitive performance and underestimation of CI. Further, since the development of the historical normative age data, associations between information processing speed and both sex and education have been identified (73, 74). Sex was not accounted for in the original norms and education only stratified very crudely, leading to the recent update to the SDMT normative data by Strober and colleagues (71). In summary, a normative sample must be representative of the population being studied and current to provide clinicians and researchers accurate CI assessment.

There are other methodological and practical considerations in neuropsychological assessment which may limit its use for cognitive measurement in regular and routine clinical management of MS. Existing neuropsychological assessment is time and resource intensive, limiting the practicality of the incorporation of regular cognitive testing into MS outpatient clinics. Some limitations, such as ceiling/floor measurement effects or practice effects where there is improvement of test scores in the absence of neurological change, can mean an assessment tool is unsuitable for use in longitudinal cognitive testing where increased fidelity of testing is

required to enable early detection of cognitive changes. In addition, there is a need to identify and understand clinically meaningful change of quantitative cognitive scores to provide a useful metric in monitoring treatment response or disease progression, and to integrate these with existing medical record systems.

Cognitive Reserve as a confounder of cognitive impairment

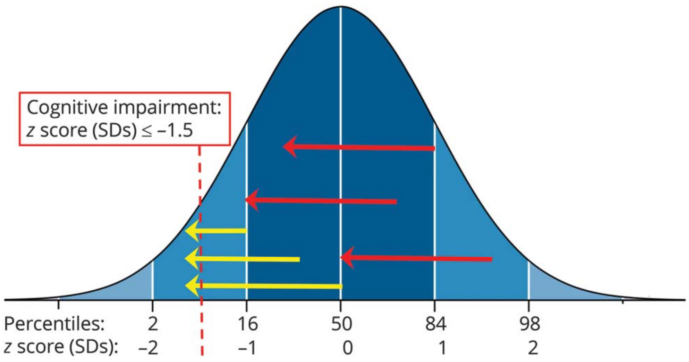
Another source of variability in cognitive data comes not from methodological design of studies or the definitions used to determine impairment, but from some patients' inherent ability to withstand considerably more disease burden than others. This remarkable ability, termed cognitive reserve (CR), comes from the combination of inherited and environmental factors of larger lifetime brain growth and intellectual enrichment, respectively (75). A larger lifetime brain growth, measured by head size or intercranial growth, in theory protects against cognitive decline by providing more brain volume that is able to be lost before reaching some critical threshold (76). One recent study in MS demonstrated the protective role of larger lifetime brain growth and its association with cognitive efficiency (77). Intellectual enrichment is the more commonly used definition of CR and in theory states that enriching experiences protect against cognitive decline by offering the use of new and existing compensatory mechanisms (78). Although the CR provided by intellectual enrichment cannot be measured directly, common proxies used in studies include educational attainment (years of education, level of education), occupational attainment, leisure activities (79) or a survey based composite of these proxies (79, 80). In MS, studies have shown that CR, as measured by educational level (81, 82), vocabulary knowledge (81, 83) and/or employment (84) status can protect against disease related cognitive decline. In a recent longitudinal study, Rocca et al. (85) found that CR was able to mitigate the effect of structural damage on cognitive performance and that the protective effect diminished with disease progression, presumably as a result of progressive degeneration reducing the brain volume and the amount of CR available. Furthermore, a recent study showed that preserved network functional connectivity could attenuate the effects of white matter tract damage and provided support by way of CR (86).

Measuring cognitive change versus cognitive impairment

It is clear from the studies above that MS leads to dysfunction in multiple cognitive domains, however the studies discussed mostly present only group-level data and little is known about the variability of cognitive trajectories at an individual level over their disease course. Intra-

individual variation (IIV), or how much an individual's performance on cognitive tasks varies over serial testing, may provide a more robust measure than mean level data. This may then provide unique insights into individual cognitive functioning and underlying pathology (87-89), as well as being more applicable in MS clinical practice.

The measurement of cognitive impairment using neuropsychological batteries is a static assessment, relative to a reference population. This implies that an individual's cognitive functioning has decreased from some earlier, higher level over time. Cognitive change, however, is a longitudinal process with reference to a patients' premorbid cognitive performance or functioning. These cognitive changes can occur even before a diagnosis of confirmed MS and in the early stages of disease individuals may still remain within the normal ranges of the tests (**Figure 1)**. To identify these individuals, more longitudinal designs with brief cognitive assessments of all new patients are needed to improve the knowledge of disease-related cognitive decline relative to baseline (90). Early cognitive changes are difficult to detect, both by clinicians (91) and standard neuropsychological tests (92), and tests that are sensitive to cognitive change rather than CI are needed in clinical practice.



About half of persons with multiple sclerosis are considered cognitively impaired in prevalence studies, which is based on performance below a chosen threshold (yellow arrows crossing −1.5 SDs). As illustrated, however, patients may experience and report notable decline from previous function without crossing the threshold into impairment (red arrows), although such decline likely affects real-world functioning. For example, the uppermost red arrow represents a person with above average cognition prior to disease onset (84th percentile). Despite a decline of 1.5 SD, this person's current performance is within the average range (dark blue shaded area), and she or he would be categorized as cognitively intact in research studies. Clinically, this person may be told that he or she does not have impairment, which conflicts with his or her real experience of decline.

Figure 1: Cognitive decline from previous functioning. Adapted from Sumowski et al. (2018)

Subjective cognitive impairment

How a person perceives CI or changes in their cognitive functioning has been fairly well studied in Alzheimers disease where subjective cognitive decline is recognized as a preclinical stage of dementia and mild cognitive impairment (93). Less is known about the clinical relevance of subjective cognitive concerns in the MS field. One study showed correlations between subjective cognition and mild impairment in objective measures of processing speed and immediate recall (94). Other studies have shown a discrepancy between subjective cognitive reporting and objective measures (95, 96). These studies often find a stronger relationship between subjective CI and depression and/or fatigue (97, 98). Subjective cognitive difficulties in pwMS has also been associated with sexual dysfunction (99), reduced thalamic and cortical gray matter volumes (100) and work capacity (101). Perceived CI may also play an important role in monitoring for cognitive changes in the clinical practice setting. Cognitive impairment is difficult to ascertain from the neurologists clinical judgement (91) however more literature on the accuracy of patients perception of decline is needed. To date, there is no literature on the relationship between subjective cognitive performance and objective measures using a computerised cognitive monitoring battery.

Functional, social and quality of life consequences of cognitive impairment in MS

Cognitive impairment can have a significant impact on the quality of life of a person living with MS, especially as disease onset is typically during the transformative young adult years of establishing a career and family. Health related quality of life (HR-QoL) is a subjective measure a person's quality of life with respect to disease and pwMS have significantly lower HR-QoL than controls (102).

Health Related-Quality Of Life

CI in MS has been consistently associated with a reduced HR-QoL (103, 104) and in one study, CI at MS diagnosis could predict worsening HR-QoL prospectively (105). In contrast, Benedict et al. (106) found that HR-QoL was more strongly predicted by measures of depression and fatigue than cognitive functioning. In the same study, the authors found vocational status was predicted by cognitive functioning.

Vocational status

Cognitive changes, even when subtle, can impact many aspects of a person's normal functioning including employment. There are a number of studies investigating the effect of CI on vocational outcomes. Rao et al. (107) found that cognitively impaired pwMS were more likely to be unemployed than cognitively preserved pwMS, independent of depression, anxiety or physical disability. This was subsequently supported by other studies (108, 109) which additionally found associations between absenteeism with CI and clinical phenotype in MS. Vocational status is often included in studies of cognitive functioning (68, 106) and CI was able to predict employment performance following a ten year interval (110). Maintaining employment is, of course, important and highly valued by pwMS and qualitative research has shown that cognitive changes and fatigue present a significant barrier to employment for pwMS. Although pwMS were aware of the costs associated with being employed, the consequences of unemployment or changing jobs were considered negative and stressful (111). Morrow and colleagues (112) investigated whether declining performance on serial tests of information processing speed and verbal memory could predict change in vocational status and found that a decline in cognitive performance could predict a deterioration in vocational status with high probability (87%).

Functional activities

In addition to the impacts on vocational status, pwMS who are cognitively impaired subjectively report fewer social activities, more sexual dysfunction and greater difficulty in performing household tasks than cognitively intact pwMS (107). In an objective measure of everyday functioning, Kalmar and colleagues (113) found that deficits in executive function, learning and information processing speed were associated performance on the Executive Functions Performance Test, comprising of tasks such as medication management, bill paying, handwashing and cooking. In another study, impairments in information processing speed and visuospatial skills was associated with poorer driving performance (114).

Social functioning

Decreased social functioning is commonly reported as a consequence of CI in MS. Where many studies report dysfunctions in processing speed, attention and memory, relatively little is known about social cognition in MS. Social cognition refers to the "mental operations that underlie social interactions" (115) and has been well described in a range of disorders including

autism and schizophrenia. Theory of mind, or the ability to interpret the intentions, feelings and beliefs of others; and facial emotion recognition, the ability to identify and distinguish the emotional states of others, have been the subject of recent work in MS. In a comprehensive review and meta-analysis, Cotter et al. (116) explored the relationship between social cognition and clinical, cognitive and demographic factors. The authors found significant and large deficits in both theory of mind and emotion recognition in pwMS compared to healthy subjects (effect size g=-0.64 and -0.71, respectively). Both of these components of social cognition have been associated with deficits in other cognitive domains and the relationship with depression and fatigue are still unclear (116). The vast majority of articles included in the systematic review study only patients with early RRMS and the authors emphasize the need for more generalizable studies in this important area of cognition which underpins social functioning in pwMS.

Comorbidities and confounders of cognitive impairment in MS

Psychological comorbidities

Depression

Depression is a common comorbidity in pwMS and occurs more frequently than in the general population (117). The lifetime prevalence of depression in MS, whether formally diagnosed or based on validated self-report surveys, is reported to be 25%-50% (117) in clinical based cohorts. In community, registry and health record-based studies, depression prevalence was similar with ranges between 32 and 50% (118-121). The etiology of depression in pwMS remains the topic of recent work with cerebral atrophy (122, 123), abnormalities in the hypothalamic-pituitary-adrenal axis (124, 125) and inflammation (126-128) accounting for significant variance in depression in MS.

Regardless of the etiology of depression in pwMS, it is clear that depression plays an adverse role in aspects of cognitive functioning. Studies have shown that in pwMS with mild-moderate depression perform more poorly on tasks of working memory, attention, information processing and executive functioning (129-132). In a recent study using a computerised cognitive battery, depression was measured with a validated survey and only weakly correlated

with measures of information processing speed, attention and working memory (133). In another study, after controlling for age, disease duration disability and fatigue, the Beck Depression Inventory score in pwMS was a significant predictor for most neuropsychological tasks including attention, information processing speed and verbal memory (134).

Few studies have investigated the pathophysiological link between depression and cognitive dysfunction in pwMS, however changes in hippocampal volume (135) or functional links in the default mode network (DMN) (136) may explain the comorbidity. It is unclear whether treatment of depression may positively impact cognitive functioning in pwMS, however positive effects on both depression and cognitive functioning (attention, information processing, verbal fluency) were seen in pwMS on treatment of fampridine (137) and natalizumab (138).

Anxiety

Anxiety is commonly reported in pwMS and occurs more frequently than in the general population (139). The prevalence of anxiety in pwMS ranges from around 19% in clinic based studies (140) to between 45 and 54% in population-based cohorts (120, 139). In the largest of these population studies (120), anxiety was proportionally more common in females with RRMS than other phenotypes of MS, or males. Interestingly, another population-based study found that the prevalence of anxiety in females with RRMS decreased by 8% for each year of follow up, relative to males (139). In the same study, a younger age at entry was also associated with anxiety. In a study investigating social anxiety in pwMS, it was found that the prevalence of social anxiety was twice that of general anxiety (141).

The development of anxiety in MS may share common pathways with depression and fatigue with dysregulation of the hypothalamic-pituitary-adrenal axis (142) and inflammation implicated (128), although one study found MRI changes in depression but not anxiety (143).

Few studies have investigated the role of anxiety in MS related cognitive dysfunction. In a study using a computerised cognitive battery (133), anxiety was not associated with measurements of information processing speed, attention and working memory. A recent study found anxiety was associated with slower processing speed, impaired verbal learning and

impaired working memory in pwMS and other immune-mediated inflammatory conditions (144).

Fatigue

Fatigue is one of the most commonly reported symptoms, affecting between 50%-80% of pwMS (145, 146). Theoretically, the origins of fatigue in MS may be either primary fatigue, caused by the MS pathology itself; or secondary fatigue, caused by motor function, test performance, pain, medication or other comorbidities. In reality, the subjective nature of fatigue and the significant congruities between primary and secondary fatigue means it may be hard for the clinician to determine the precise basis of fatigue (147). The etiology of fatigue in MS is unclear but current hypotheses support a role for cerebral atrophy (148) and lesion localization (149, 150) with inconclusive data on the role of inflammation (151).
The relationship between fatigue and cognition in MS from published studies are conflicting and is further limited by the lack of prospective work. Diamond et al. (132) found that physical fatigue influenced information processing speed and word learning and recall tasks, whereas Parmenter and colleagues (152) found no difference in performance on learning, attention or executive function tasks in pwMS during periods of high and low fatigue. In one study using a computerised cognitive battery, physical fatigue was not associated with performance on tests of information processing speed, attention, working memory or learning (153). Hanken et al. (149) asked if there was a cognitive signature for MS-related fatigue and concluded that only tasks assessing vigilance were related to fatigue.

In contrast to physical fatigue, another aspect of fatigue that is of increasing interest is the concept of cognitive fatigue. Although there is no universal definition of cognitive fatigue, one definition is that it is 'a decrease in, or inability to sustain, task performance throughout the duration of a sustained attention task' (154-156). However, Berard and colleagues note that although this is a commonly taken definition to operationalize cognitive fatigue, it is more likely a reflection of underlying deficits including slowed information processing speed and attention deficits (157). Indeed, earlier research into cognitive fatigue identified associations with impaired processing speed and sustained attention (158, 159). Reliable measurement of cognitive fatigue remains elusive and Kluger et al (160) argue for the objective measurement of cognitive fatigue over subjective patient reports of fatigue, between which there is often a lack of correspondence (161). Recent studies have focused on the objective measurement of

cognitive fatigue over sustained cognitive tasks, its pathophysiological correlates and associations with daily functioning, sleep quality, depression and quality of life (157, 162-165). One pilot study assessed the effectiveness of a potassium channel blocker in improving cognitive fatigue and found promising but non-significant results (166). Commonly in these studies, the Paced Auditory Serial Addition Test (PASAT), the SDMT and simple reaction time tasks were used as the sustained cognitive tasks. Typically, outcomes varied between comparing the responses in the latter part of the tests to the earlier responses or were compared pre- and post-completion of the sustained cognitive task. In 2017, Harrison and colleagues reviewed the cognitive fatigue literature and recommended the development of a guiding theory of cognitive fatigability. Further work is needed to examine the ecological and construct validity of the existing measures, where continuous attention measures show greatest promise (167).

Pathophysiology of cognitive impairment in MS

MRI-detected white matter lesions and cognitive impairment

The pathological changes that underpin CI in MS are still unclear. Many cross sectional studies (92) have investigated the role of WM lesions in CI in MS although longitudinal data is limited. Overall, most (not all) have found associations between brain T2 hyperintense and T1 hypointense lesion volumes and scores on neuropsychological testing however the data is quite heterogenous. Early studies (168-170) found robust correlations between total lesion area and memory, abstract reasoning and word fluency. More recently Papadopoulou et al. (171) found strong correlations between WM T2 lesion volume and SDMT scores. In contrast, a number of studies have found no associations between WM lesions and cognitive dysfunction as measured with the Minimal Assessment of Cognitive Function in MS (MACFIMS) (172) or Brief Repeatable Battery – Neuropsychology (BRB-N) (173) batteries, or by individual neuropsychological tests (174, 175).

In CIS patients, baseline T1 hypointense WM lesions predicted slowing of executive function speed after seven years and T2 hyperintense lesions were associated with information processing speed slowing (176). In RRMS, baseline T1 hypointense lesions could predict performance on attention tasks after five years although in this study T2 lesions did not predict cognitive performance (177). Whereas in PPMS patients, T2 hyperintense lesions could predict

CI after five years (178). The heterogeneity seen across the results of these studies is likely due to the different populations of MS phenotypes studied (some mixed, RRMS, SPMS etc), differing definitions of CI, different lesion quantification methods and different numbers of subjects in each study.

The location of the lesion in the WM is also important. Spatial distribution of these WM lesions in key white matter tracts have been shown to be associated with deficits in specific cognitive abilities (179-182). This loss of WM integrity has led MS to be termed by some as a disconnection syndrome and may result in impairment in information processing speed (183) and a functional disconnection between deep grey matter structures (174). To support this, a recent study found the efficiency of the DMN, a functional interconnected brain network comprising of many 'hubs' involved in many brain functions, was involved in CI in MS and that connectivity to the DMN of the cerebellum plays an important role in information processing speed decline (184).

Grey matter lesions and cognitive impairment in MS

Imaging of low contrast GM lesions has posed a problem with conventional MRI techniques and scanners with up to 91% of cortical lesions seen at autopsy missed by earlier imaging (185, 186). Despite this, several studies have shown associations between GM lesions and cognitive dysfunction in MS. In one, pwMS who are cognitively impaired had more cortical lesions than pwMS who were cognitively intact, despite having comparable WM lesion loads (173). Other studies have shown relationships between specific cognitive functions and GM lesions, both cortical and non-cortical. One group demonstrated associations between delayed recall and both cortical and hippocampal lesions, as well as an association between processing speed and cortical lesions (187, 188). Another study showed an association between juxtacortical lesions and processing speed (189).

Cerebral atrophy

Given the current limitations in detecting GM lesions, research has focused on reliable and reproducible measurements of GM volume and longitudinal atrophy. In addition to this, studies have shown that WM lesions are only partially responsible for cognitive impairment in MS, when compared to damage to GM (92). In one longitudinal study, the rate of atrophy in WM

remained constant across clinical phenotypes whereas GM atrophy rates increased from CIS (3-fold increase) through to SPMS (14-fold increase) (190). In studies of CIS and very early RRMS, the total GM volume can be reduced and was shown to be associated with impaired executive function (176), whereas whole brain volume (as measured by width of the third ventricle) was associated with impairment in information processing speed and attention (191). In one longitudinal study over 2.5 years, early grey matter loss was a sensitive biomarker of future cognitive dysfunction (192).

Several studies have combined MRI imaging for GM lesions with other MRI sequences or ultra high-field scanners and have suggested that mixed grey and white matter lesions may provide a robust biomarker for severity of cognitive dysfunction (193). Indeed, the spatial relationship between WM and GM lesions is important with greater GM loss in regions that are in close proximity to T2 hyperintense lesions in the WM (194, 195) and confirmed longitudinally several years later (196). This was explained eloquently by Benedict and colleagues (197) as WM damage initially leads to local GM damage, which then grows into an independent pathological process further affected by network connected damaged cortical or deep GM and leading to an increasing atrophy rate (198). This may explain findings of regionally specific GM atrophy such as early volume loss in the thalamus (199-202), putamen (203) and hippocampus (204), which can be strongly involved in CI such as rapid forgetting memory deficits and memory retrieval (205-208).

Summary

The pathophysiological correlates of CI in MS are yet to be elucidated. Results from cross-sectional studies are mixed, with WM T1 hypointense and T2 hyperintense lesion volumes and locations associated with CI in some, but not all, of the literature. In longitudinal studies of the role of WM in CI, T1 hypointense and T2 hyperintense lesion could predict CI in CIS patients. Whereas in RRMS patients, only T1 hypointense lesions were associated with impaired cognitive performance. Relatively few studies have examined the role of GM lesions in CI due to the limitations in conventional imaging. Despite this, several studies have shown associations between cortical, juxtacortical or hippocampal lesions and cognitive dysfunction in processing speed and memory. Cerebral atrophy shows promise as a biomarker for cognitive dysfunction in MS. Losses in volume of the whole brain, total GM and specific GM structures such as the thalamus and hypothalamus are strongly associated with various memory deficits.

In summary, although the findings remain heterogenous, studies to date have identified some promising insights into the pathophysiological etiology of CI in MS. However, more longitudinal work with well-defined cohorts of patients, standardized CI definitions and improving imaging and analysis techniques are required.

Treatment of cognitive impairment in MS

Treatment of cognitive impairment in MS with repurposed agents

Studies on the **symptomatic treatment** of cognitive dysfunction in MS provide inconclusive evidence of effectiveness of the therapies tested. Many of these studies have methodological limitations such as no randomization or control group, not including cognitively impaired subjects, sample sizes and variability in outcomes, meaning that the results should be interpreted with caution. Geisler et al. (209) conducted a randomized controlled trial (RCT) of amantadine (used for fatigue in MS) and pemoline with a placebo control arm. Outcomes included traditional measures of attention, processing speed (SDMT) and verbal and non-verbal memory measured at baseline and six weeks. No differences were seen between the groups, likely attributed to the low power of the study with just 16 patients treated or practice effects associated with the short retest interval. There have been numerous studies assessing modafinil for cognitive dysfunction in MS with mixed results. Wilken et al. (210) found improvement in cognitive outcomes in an uncontrolled study with modafinil adjunct therapy. Only one RCT found an improvement in cognitive function (attention) in the treated arm relative to placebo controls (211). Two cross over trials (212, 213) found improvements in single cognitive functions (working memory and delayed memory respectively) however only one was placebo controlled and both had short retest intervals, meaning practice effect improvements were likely. Two RCT's found no effect of modafinil on cognitive functioning (214, 215). Many other studies have been conducted on agents including acetylcholinesterase inhibitors including rivastigimine (216-218) and donepezil (219, 220) with mixed results. Limitations in some of these studies included a lack of control group, inadequate blinding, small sample sizes and even subjective self-reported cognitive outcomes. Other studies have looked at l-amphetamine (221-223), fampridine (224-226), cannabis (227) and gingko biloba (228-230) with inconclusive results.

Treatment effects of MS Disease Modifying Therapies

Evidence for the efficacy of treatment of CI in MS must come from RCTs where confounders of treatment effect, both known and unknown, are balanced across treatment and placebo control groups. **Disease modifying therapies** used to reduce inflammatory exacerbations and ultimate neurodegeneration in MS could potentially delay cognitive decline but is an area lacking in evidence. Although cognitive outcomes are rarely reported in clinical trials in MS, brain volume changes are often included and volumetric brain MRI techniques can assess drug-dependent changes in cerebral volume loss trajectories in MS patients (231, 232). A recent meta-analysis by Branger and colleagues (233) found that the immunosuppressant and immune reconstitution therapies, the highly effective options, offered neuroprotection over placebo or immunomodulatory therapies by slowing the rate of neurodegeneration as measured by brain volume loss (-0.14%/year vs -0.56%/year and -0.46%/year, respectively). The same beneficial properties may also potentially apply to cognition. The effect of DMTs on cognitive functioning in MS are summarized in **Table 1**.

In the BENEFIT trial, a five year study of outcomes of early versus late intervention with interferon beta 1b (IFNB-1b) in CIS patients, the PASAT was included as a secondary outcome as part of the Multiple Sclerosis Functional Composite (MSFC). The results showed an improvement in PASAT score over the five years, even when scores were in the normal range at baseline. Those in the early treatment group showed significantly greater improvements on the PASAT than the delayed or late treatment group, providing evidence to support earlier intervention to preserve cognitive function (234, 235). In a study of 166 RRMS patients randomized to interferon beta 1a (IFNB-1a), Fischer et al. (236) found beneficial effects on tests of information processing speed, learning and memory when measured with the MSFC battery. Improvements were also seen in the placebo control arm, indicating a degree of learning effect despite the two year retest interval, however the treatment groups improvements remained relatively more pronounced. In an analysis of the FREEDOMS and FREEDOMS II trials (237), RCT's of oral fingolimod compared with placebo, scores on the PASAT3 (as part of the MSFC) improved in fingolimod treated patients compared to placebo at 6, 12 and 24 months. In addition, lower baseline PASAT scores correlated with higher disability, lower brain volume and greater T2 lesion volume. In a phase III trial of glatiramer acetate versus placebo control (238) cognition was measured using the BRB-N and both groups showed significant improvement in cognitive performance after one to two years indicating potential practice effect improvements. In a RCT of glatiramer acetate in PPMS, the PASAT was

included as part of the MSFC and baseline scores reported however changes in cognitive function was not (239). In a pooled analysis of the AFFIRM and SENTINEL trials, investigating the efficacy of natalizumab in comparison to an active control or placebo in RRMS patients, Weinstock-Guttman et al. (240) found a reduced risk of cognitive decline in the AFFIRM study (placebo controlled) but not in the SENTINEL trial (vs active comparator). Both trials used the PASAT as part of the MSFC. In the OPERA I and II (241) trials of ocrelizumab in RRMS patients, the MSFC composite score improved in OPERA II but not OPERA I. Although contributing to the MSFC composite score, changes on the PASAT alone were not reported. No cognitive functioning measures were reported in the ORATORIO (242) trial, a phase III trial of ocrelizumab in PPMS. In a similar vein, just the MSFC composite score was reported for the phase III trial of Alemtuzumab versus active comparator trial (IFNB-1a) (243). Although an improvement in MSFC composite was seen in the alemtuzumab arm, cognitive outcomes (PASAT) were not reported.

There are numerous observational and post-marketing studies investigating the effect of DMT's on cognitive functioning, although most are affected by methodological limitations which can limit the validity of the results. Of note however is the COGIMUS study (244, 245), an Italian multicenter, prospective cohort including 459 early RRMS patients treated with high (44mcg) or low (22mcg) IFNB-1b in usual clinical practice. Subjects were tested with the BRN-B at baseline and then every 12 months for three years. The authors found that at three years, high dose IFNB-1b conferred a 32% reduction in risk of CI in three or more neuropsychological tasks. In addition, high dose IFNB-1b stopped progression of CI over three years, relative to the lower dose cohort. As noted by the authors however, the absence of a non-treated group is a limitation in assessing practice effects. Limitations in observational studies can include low sample sizes with heterogenous patient characteristics, subjective reporting of cognition (246), non-randomized single arm designs (247) and heterogenous outcomes.

A recent systematic review and meta-analysis by Landmeyer and colleagues (248) synthesized evidence from 44 longitudinal studies (including both RCTs and observational) assessing the efficacy of available DMT's to improve cognitive functioning. In this analysis the authors assessed improvements in information processing speed in both platform therapies (β-interferon, glatiramer acetate, dimethyl fumarate, teriflunomide) and escalation therapies (natalizumab, fingolimod, alemtuzumab). They found that although DMT's in general had a

positive effect on cognitive test performance, there were no differences in improvements of processing speed between platform therapies and the higher efficacy escalation therapies. A finding that is surprising given the superior efficacy in escalation therapies to reduce disease severity when measured by EDSS or relapse rates. An explanation for this discrepancy may lay in the fact that the mode of action of the majority of high efficacy DMTs are to reduce the inflammatory processes involved in RRMS pathology. Whereas recent evidence suggests that CI may indeed be largely driven by neurogenerative processes resulting in global and regional atrophy as discussed previously. There is, however, limited evidence that DMTs are able to moderate brain volume loss (233, 243) and potentially provide a beneficial effect in reducing the impact of CI. These findings, however, should be interpreted with caution as highlighted by Amato and Krupp (249) who reminded us of the limitations of the current literature including the inclusion of only early RRMS patients where cognitive changes may be subtle and not detected, brief trial durations and lack of stratification on baseline cognitive abilities. Another area of importance that should be considered for future trials is the timing of high efficacy DMT treatment. Even prior to diagnosis of MS, the accumulation of neurogenerative processes across the disease course leads to the inevitable collapse of network efficiency and ultimate reduction of cognitive function (250). This may or may not be immediately apparent, depending on the premorbid cognitive reserve status of the individual (251). Given that the processes underlying cognitive decline occur so early in the disease course, Cerqueira et al suggest the DMT therapy should begin as soon as it is evident (252). The majority of randomized clinical trials of DMT in MS are not appropriately designed to detect cognitive changes and future RCT's should use appropriate cognitive measures and designs to avoid practice effects; and be powered to assess cognition as a primary outcome measure if we are to properly understand the potential benefits of the new therapy on cognitive functioning.

Table 1: Effects of disease modifying treatments on cognitive dysfunction in MS. Adapted from Comi, G. (2010) (253)

Treatment	1-2 yr follow up	Comment
Glatiramer acetate	GA vs placebo: Word list generation test better in GA group.	Subgroup followed up at 10 years – decline in PASAT in both groups
Natalizumab	AFFIRM/SENTINEL: no cognitive outcomes	Some improvement in the MSFC (includes PASAT)
Fingolimod	Pooled analysis of FREEDOMS and FREEDOMS II shows improved PASAT-3 at 6, 12 and 24 months in treated group	
Dimethylfumarate	Post-hoc analysis of DEFINE and CONFIRM - MSFC	Improvement in PASAT-3 in treated group over 24 months
Teriflunomide	Improvements in patient reported outcomes of cognition and fatigue.	MSFC not assessed
Alemtuzumab	CARE-MSI, CARE-MSII	Improvements in MSFC over 2 years cf. IFN Beta
Ocrelizumab	OPERA I, OPERA II: improvement in MSFC above IFN-beta.	PPMS: not assessed

Comi, G. (2010). Effects of disease modifying treatments on cognitive dysfunction in multiple sclerosis. Neurological Sciences, 31(2), 261–264.
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Cognitive rehabilitation

Another approach to treatment of cognitive loss in MS is **neuropsychological rehabilitation**. Cognitive rehabilitation generally involves 'drill and practice', repetitive cognitive training tasks to restore cognitive skills that may have been lost. Results from early studies of cognitive rehabilitation in pwMS were inconsistent, attributed to methodological issues such as non-blinding and broad cognitive training rather than a cognitive skill targeted approach (254). Traditional approaches where patients attend in person for the training session can be expensive and difficult to administer and maintain patient compliance, however some have some benefits of the intervention. One RCT examined the efficacy of a ten session intervention to improve learning and memory abilities in pwMS (255), with improvements immediately after the ten one-hour face to face sessions and subjectively maintained six months later. Another intervention to improve memory in pwMS combined eight weekly group sessions focused on compensatory techniques with a computer assisted rehabilitation program and found benefits and increase in the use of the compensation techniques following the intervention (256). More recently, computer-based rehabilitation has enabled training programs that are adaptive in real time to an individuals performance and can be self-administered in the patients' home (257).

Emerging evidence from recent trials suggest that cognitive rehabilitation using technology may also be beneficial. Several studies using a computerised intervention to train processing speed and working memory found significant improvements of the cognitive measures following the intervention (258-260). Conversely, some computerised game-based training programs found improvements in only some of the cognitive skills trained (261). Several recent reviews into cognitive training in MS found low level evidence that rehabilitation can reduce cognitive symptoms in MS, however have highlighted the methodical limitations and heterogeneous outcome measures and findings of the current literature (262, 263). Given the heterogeneous responses to cognitive training observed, several recent studies have sought to determine the differences in treatment efficacy between individuals. In one, the authors found that beneficial response to cognitive rehabilitation was predicted by lower white matter tract disruption and increased functional connectivity in the default mode network areas of the precuneus and posterior cingulate (264). In another, better treatment response was predicted by baseline factors including RRMS phenotype, better cognitive performance and higher GM volume (265).

In summary, although in its infancy, targeted skill-specific rehabilitation offers promise in treating some cognitive impairments. Cognitive training is time and resource intensive, with many interventions requiring weeks or months. Computerised programs that can be delivered in a patients home may ease the burden on the patient. Early detection of subtle cognitive impairments, before functional and structural collapse, is crucial for the efficacy of restorative cognitive intervention.

Cognitive impairment in MS - Summary

Cognitive impairment is common in MS and its presentation is heterogeneous, although functions including information processing speed, attention, working memory and executive are often impacted. Cognitive dysfunction can be present at all stages of the MS disease course and can result in reduced social functioning, loss or reduction of employment and difficulties in performing everyday activities. The pathophysiological basis of CI in MS is unclear, with inflammatory focal lesions in the white and grey matter likely to precede degenerative global and regional atrophy of GM regions. Comorbid depression can have an adverse effect on cognitive functioning in MS, although the evidence around anxiety and fatigue is still unclear.

Although there is no evidence of efficacy of symptomatic treatment of CI with repurposed dementia therapies, the evidence of the beneficial effect on cognition of DMTs used in the management of MS is promising. There is however a need for higher level evidence from the inclusion of primary cognitive endpoints in pivotal RCTs.

Neuropsychological assessment in MS

Single neuropsychological tests

Coinciding with the renaissance of the interest in cognition as a symptom of multiple sclerosis, the development and validation of batteries of neuropsychological tests sensitive and specific to the pattern of CI in MS began in earnest. The neuropsychological tests that comprise many of the following batteries discussed here range from the well validated and commonly-used individual tests developed as early as the 1970's through to modern, computer-based tests that require further validation in MS yet offer promise in overcoming some of the limitations of traditional pen and paper testing. A summary of commonly used neuropsychological tests used in MS clinical practice to assess CI is provided in **Table 2**.

Table 2: Summary of common neuropsychological tools used to assess cognitive impairment in MS clinical practice.

Test	Cognitive domain measured	Batteries	Advantages	Disadvantages
SDMT	Processing speed, working memory, executive function	MACFIMS, BRB-N, BICAMS, MSFC	- Excellent sensitivity. - Good to excellent reliability. - Alternate forms. - Brief and well-tolerated.	- Performance can be affected by incidental learning of stimuli and impairments in visual scanning. - Limited to cultures that use Arabic numerals.

			- Well defined clinically relevant change.	- Tester required to administer.
PASAT	Processing speed, working memory, sustained attention	MACFIMS, BRB-N	- Moderately sensitive. - Widely used. - Can be used for patients with poor vision.	- Significant practice effects. - Poorly tolerated. - Low specificity. - Performance can be affected by maths ability. - Ceiling effects. - Tester required to administer. - Specialized equipment required.
CVLT-II	Verbal memory	MACFIMS, BICAMS	- High sensitivity. - Good normative data. - Validated alternate form.	- Only one alternate form, limiting serial testing. - Ceiling effects. - Tester required to administer.
RAVLT	Verbal memory	BICAMS (accepted alternate to CVLT-II)	- High sensitivity. - Good normative data. - Validated alternate form.	- Only one alternate form, limiting serial testing. - Ceiling effects. - Tester required to administer.
Selective Reminding Test	Verbal memory	BRB-N	- High sensitivity. - Alternate forms (yet to be validated).	- Limited normative data. - Tester required to administer.

BVMT-R	Visuospatial memory	MACFIMS, BICAMS	- Excellent sensitivity. - Good reliability. - Well tolerated. - Validated alternate forms.	- Performance can be affected by motor impairment. - Tester required to administer.
10/36 SPART	Visuospatial memory	BRB-N	-Fine motor skills not required (ie. no drawing involved)	- Less sensitive than BVMT-R. - Lack of reliability data. - Lack of normative data. - Tester required to administer. - Specialized equipment required.
Abbreviations **SDMT – Symbol Digit Modalities Test; PASAT – Paced Auditory Serial Addition Test; CVLT-II – California Verbal Learning Test: Second edition; RAVLT – Rey Auditory Verbal Learning Test; BVMT-R – Brief Visuospatial Memory Test Revised;; 10/36 SPART – 10/36 Spatial Recall Test; MACFIMS – Minimal Assessment of Cognitive Functioning in Multiple Sclerosis; BRB-N – Brief Repeatable Battery of Neuropsychological tests; BICAMS – Brief International Cognitive Assessment in Multiple Sclerosis; MSFC – Multiple Sclerosis Functional Composite**				

Digit/Symbol substitution tests.

The SDMT is the most commonly used test of information processing speed in MS (266) and has been recommended as the assessment tool of choice if time is limited (267). First developed and commercialized in the early 1980's, the SDMT is a symbol/digit substitution task where the subject is presented with a page prefaced with a matrix of nine symbols matched to the digits one through nine. Below this, the page contains rows with only symbols and the object is to write or orally report the digit which correctly matches the given symbol (**Figure 2**). The subject completes the first ten matches to familiarize themselves with the task and is then timed to complete as many correct matches as possible in 90 seconds. The SDMT can be administered

in five minutes by a suitably trained non-neuropsychologist and is included in many MS cognitive batteries as the primary measure of cognitive processing speed.

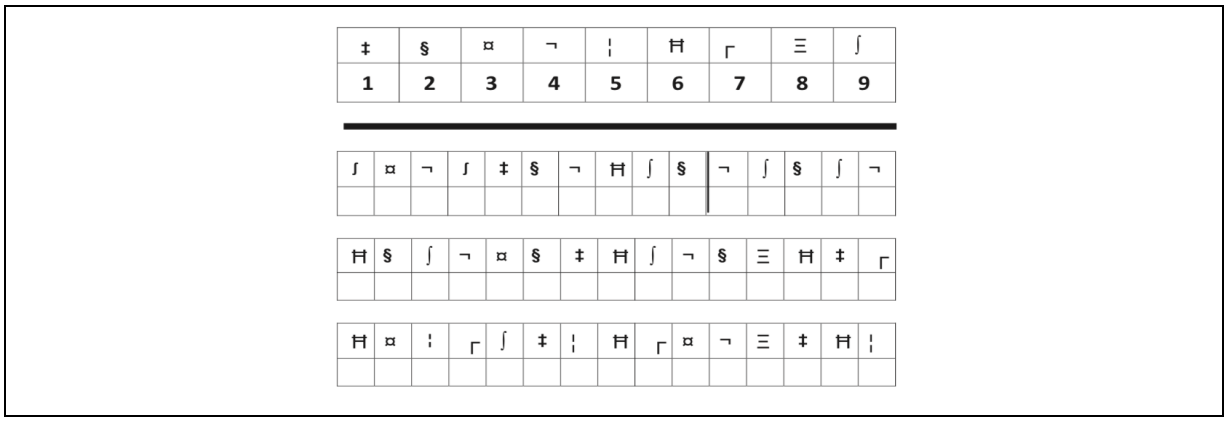

Figure 2: An example of SDMT stimuli. Adapted from Langdon et al. (2012) (267)

Psychometric properties of the Symbol Digit Modalities Test

The SDMT has good psychometric validity. In a study by Benedict et al. that reviewed the validity of the SDMT as an outcome measure of cognitive performance in MS, the SDMT was the most sensitive cognitive task across 15 studies of commonly used neuropsychological tests standard batteries (mean effect size d = 1.11) (268). The SDMT has good to excellent test-retest reliability (results of one test compared to results of the preceding test), depending on the population studied and intertest interval. In 34 MS patients tested over two weeks, reliability was excellent with a test-retest coefficient of 0.97. At longer intervals, the test-retest coefficients were between 0.82 and 0.95 for a one month intertest interval (269); and 0.74 for a two year intertest interval (270). Although the SDMT primarily loads on information processing speed in RRMS patients, in SPMS patients loading on memory factors is also seen (68).

Recently, incidental visual learning of the symbol/digit combinations has been shown to contribute to performance (271) and it has been suggested that this multimodal aspect of the SDMT may account for its very high sensitivity to CI in MS (268).

The SDMT also has good criterion validity. In studies utilizing the MACFIMS battery, the SDMT accounted for most variation in GM volume (205), lesion burden (272) and diffusion abnormalities (273). In another study, central atrophy was able to predict SDMT score (r = -0.71) (172), and SDMT scores correlated with cerebral atrophy (274). The SDMT was also

sensitive to changes in disability progression and has been recommended as the tool of choice for monitoring cognition in MS clinical trials (275). Large amounts of normative data exists for the SDMT (270, 276), allowing for interpretation of age and demographically adjusted scores. As previously highlighted in the methodological considerations sections (page 8), the historical normative SDMT data is limited in that it may not accurately represent a contemporary cohort due to the lack of stratification on sex and crude stratification of education level. Recent work by Strober and colleagues has provided updated norms which include sex and a greater number of educational attainment levels (71).

Limitations of the Symbol Digit Modalities Test

Despite these advantages of the SDMT, it's use in MS clinics as a regular screening tool remains limited. Although brief, the SDMT still requires dedicated personnel to administer and score the test which, in an ever budget-conscious health system poses significant limitation for its (and indeed any test considered superfluous to routine clinical care) integration into busy tertiary clinics. To avoid practice effects, alternate forms of the SDMT have been developed that are reliable and equivalent to the original forms (70). However improvement of SDMT scores was still seen in a longitudinal study of natalizumab treated patients over two years, suggesting significant practice effects which may limit the use of SDMT for detecting treatment response associated cognitive change (277). The SDMT involves the substitution of digits for a symbol and Scherer et al. noted for this reason that it is only suitable for cultures that use Arabic numerals (278).

Alternate Digit /Symbol substitution tests

The Digit Symbol Substitution Test (279), like the SDMT, relies on the digit/symbol substitution paradigm. Here, subjects are presented with a similar matrix of digit/symbol combinations and instead of recording the numeral matching the given symbol, they are required to draw the symbol matching the given digit. Scherer et al. again noted the unsuitability of this test for cultures that do not use arabic numerals.

In response to the cultural limitations with existing symbol/digit substitution tests in, Scherer et al. developed the Faces Symbol Test (FST) (278) using the same underlying principle of stimulus/response substitution. In this test, subjects match symbols to faces instead of numerals and are required to draw each symbol for the corresponding face. The FST was found to be acceptable by patients, was specific (85%), sensitive (84%) and culturally agnostic. Unlike a

test that uses numerals, the FST responses must be drawn by the subject and so is unsuitable for patients with hand or visual dysfunction (which is measured before each testing session). In this paper, the authors propose the FST as an initial screening tool for MS-related cognitive decline.

Like the SDMT, each of these alternatives require dedicated resources for administering and scoring of tests and with limited or no validated alternate versions of the tests are likely susceptible to practice effects with longitudinal repeat testing. More recently, several groups have begun to utilize digital platforms to develop computerised alternates to the SDMT and these will be discussed later in this review.

Paced Auditory Serial Addition Test

Developed in the late 1970's, the PASAT (280) is a test used to assess information processing speed, working memory and sustained attention. Subjects are required to listen to a recording of successive single digit numbers presented at a fixed rate (every two or three seconds for the PASAT2 and PASAT3 respectively) and orally respond with the sum of each consecutive pair of numbers as quickly as possible up to a maximum of 60 correct responses.

Psychometric properties of the Paced Auditory Serial Addition Test

In a meta-analysis of 15 studies, the PASAT was found to be only moderately sensitive in discriminating multiple sclerosis patients from healthy controls (mean effect size d = 0.63) (268). To assess the construct validity of the PASAT and the SDMT, Sonder et al. (281) compared the longitudinal results of each test to the summary cognitive score of a commonly used neuropsychological battery, the BRB-N (of which both the PASAT and SDMT are subtests). The BRB-n will be discussed in more detail later in this review. In this study, the authors found that the SDMT correlated more strongly with the neuropsychological battery score than the PASAT at baseline and after repeat testing at three years. In this same study, the authors noted good reliability for both the SDMT and PASAT, however the SDMT was more reliable with test-retest coefficients consistently over 0.80. Other studies however have noted substantial practice effects associated with the PASAT, limiting its reliability in repeated administrations (282, 283).

Limitations of the Paced Auditory Serial Addition Test

The PASAT is a complex task requiring language function, number visualization and mathematic ability and this may account for its low specificity (284). Subjects frequently report that the PASAT is unpleasant to take (283, 285) and refusal to repeat the test has occurred (286). The PASAT is also susceptible to statistical limitations such as the ceiling effects seen by Sonder et al. (281) and like the SDMT, it is only suitable for cultures that use Arabic numerals.

These limitations have led some in the field of MS cognition to push for the replacement of the PASAT in some neuropsychological batteries with the SDMT (270), however this is not ubiquitous with Williams et al. finding that symbol-digit tasks are not a reliable proxy to replace the PASAT (287).

California Verbal Learning Test: Second Edition (CVLT-II)

The CVLT-II is an auditory/verbal memory test that measures aspects of retrieval of information from memory. In MS, multiple aspects of memory can be impaired including attention and executive related skills such as encoding and retrieval, and consolidation and recognition (204, 288). The primary outcome measures of the CVLT-II are episodic verbal learning and memory, assessing memory encoding, recall (delayed and immediate) and recognition as well as many supplementary measures including learning styles such as clustering and consistency (289, 290). In a principal components analysis, the CVLT-II total learning and delayed recall tasks loaded entirely on the memory component (68) in both RRMS and SPMS. To complete the CVLT-II, the tester reads aloud a list of 16 nouns, drawn from four different semantic categories, at one second intervals (**Figure 3**). The subject is then asked to recall as many words as they can in any order. This is repeated in the same order across five learning trials, with the subject recalling the words after each trial. Following the five learning trials, another list of 16 words, that shares two categories as the initial list, is read aloud and the subjects recalls as many words as they are able. Subjects are then immediately asked to recall words from the initial list once more, by themselves and with cues from the tester. After a 20-minute delay the subject is asked again to recall the words from the initial list. They are then presented with a list of 44 words for which they must indicate whether each is a target word (ie. YES if it was on the initial list) or a distractor (NO it was not on the initial list) (291). Administration time of the standard or alternate version of the CVLT-II is around 30 minutes plus an extra 30 minutes for delays.

Psychometric properties of the California Verbal Learning Test: Second Edition

In a study assessing the validity of the CVLT-II in MS, Stegen et al. found that it was well tolerated by pwMS, even with severe CI, however the authors acknowledge that the test is longer than other word list learning tasks (290). In this study, the authors found that most of the 23 measures assessed from the CVLT-II were able to discriminate pwMS from matched controls with measures of new learning (total from recall trials one to five) and delayed recall being the most sensitive CVLT-II measures. Indeed, many studies utilize just the total/new learning and delayed recall indices of the CVLT-II. Scarrabelotti and Carroll (292) found a moderate effect size (d=0.5) for the total learning measure in a study of 50 pwMS and Thornton et al. (293) reported a similar effect size (d = 0.6) on the delayed recall measure. In data derived from 15 studies, Benedict et al. (268) found the sensitivity of the CVLT-II (mean d=0.89) to be on par with another commonly used test of verbal learning, the Selective Reminding Test (mean d = 0.86).

Limitations of the California Verbal Learning Test: Second Edition

The performance of the CVLT-II test in longitudinal neuropsychological testing can be impacted by both practice effects and reliability between consecutive testing sessions, which can limit the power to detect reliable change. The CVLT-II supports standard and alternate forms to mitigate these limitations. In a study investigating the practice effects and reliability of standard and alternate forms of the CVLT-II, Benedict (2005) found that the practice effects of using the CVLT-II standard form across repeat administrations were often large and compromised test validity whereas use of alternate forms produced no practice effects. Reliability of the alternate forms across consecutive tests were either higher or equivalent to the standard forms, a finding the author attributed to ceiling effects and reduced variance of the standard form at retest (294).

Alternate verbal learning tests

In another study comparing alternate versions of a test of verbal learning, the Rey Auditory Verbal Learning Test, subjects randomly assigned to the alternate-form group displayed no practice effects where the same was not true for the same form group (295). The CVLT-II is a proprietary test, and its use may be financially limiting in a cognitive monitoring environment where many patients need to be serially tested over many years. The Rey Auditory Learning

Test (296) is a reliable, valid and non-proprietary potential alternative that can be used across the lifespan (to include pediatric patients for example). Beier et al. compared the initial learning trials of the Rey Auditory Verbal Learning Test and CVLT-II and found fair to good agreement (kappa = 0.21-0.41) with fair sensitivity and specificity between the tests (297).

Another verbal memory test commonly used in neuropsychological batteries is the Selective Reminding Test. The Selective Reminding Test specifically emphasizes retrieval of words from long term storage, is highly sensitive (mean d=0.86) (268) and has alternate versions (which need further validation for reliability (90)). There is no single authoritative set of normative data for the Selective Reminding Test, although published data in different populations exist (298, 299).

Brief Visuospatial Memory Test-Revised (BVMT-R)

The BVMT-R (300) is a visuospatial memory test using a similar format to the CVLT-II where subjects are exposed to visual stimulus and then immediately recall the stimulus. This is repeated as learning trials, which are followed by a delayed recall and yes/no recognition tasks. For the BVMT-R, the stimulus is a matrix of six visual designs, displayed to the subject for ten seconds (**Figure 4**). Subjects are then asked to reproduce the designs using pencil and paper. Each design is scored a zero, one or two based on accuracy of replication and spatial positioning of designs. There are three learning trials and the total score across the learning trials is the 'Total Learning' score. The learning trials are followed by a 25-minute delay after which the subjects attempt to replicate the stimulus again. This is followed by a YES/NO recognition task (301). In a principal components analysis of RRMS and SPMS subjects, the BVMT-R loaded heavily on the memory component however some loading was seen on the processing speed/working memory component in the RRMS cohort (68). This was confirmed by Tam et al. (302), suggesting that when interpreting BVMT-R scores, the impact of slowed processing speed on performance should be considered.

Psychometric properties on the Brief Visuospatial Memory Test-Revised

The BVMT-R is a sensitive test able to discriminate pwMS from healthy adults (172, 303). In a study that analysed the sensitivity of common neuropsychological tests across up to 15 studies, the BVMT-R had the second highest effect size (mean d=1.03).

Limitations of the Brief Visuospatial Memory Test-Revised

As with other neuropsychological tests that are proposed to be used in repeat administrations to measure cognitive change, alternate forms of the stimulus is important for the BVMT-R. Practice effects and lower reliability are evident when the standard form is used for repeat administrations, however with the use of an alternate form practice effects are removed and reliability is good to excellent in a MS cohort (test-retest for alternate form r = 0.91 for total learning and r= 0.73 for delayed recall) (294).

In another study, Benedict et al (301) found that BVMT-R correlated with a test of verbal memory, suggesting the BVMT-R involves both verbal and visual memory. The authors noted the limitations in the range of scores, resulting in skewed normative values of the recognition task. Subtle practice effects were associated with the learning trials of the BVMT-R, however this was in a non-MS sample and the authors later 2005 paper found no practice effects in a MS cohort.

Alternate visuospatial memory tests.

Another commonly used test of visuospatial memory is the 10/36 Spatial Recall Test (10/36 SPART) (304). The 10/36 SPART outcome measures are total learning and delayed recall. The SPART requires subjects to reproduce the pattern of ten checkers on a checkerboard after a ten second exposure to the stimulus. Unlike the BVMT-R, it doesn't require the drawing of shapes (although still requires placement of checkers) and so may be more suitable to patients with motor deficits (90).

Although the SPART is part of a neuropsychological battery, the BRB-N, and has been used in clinical trials of MS treatments (62, 238, 305), the SPART lacks reliable and demographically corrected normative data (90, 306). Recently, Gerstenecker et al. introduced demographic corrections for the SPART, however the population providing the corrections in this study were limited to those over 50 years of age (307). The SPART has a lower sensitivity than other memory tests (mean effect size d= 0.48) (90) and other tests have been recommended over the SPART for inclusion in brief cognitive assessment of pwMS (267).

Apple
Bear
Piano
Hammer
Banana
Chisel
Trumpet
Orange
Lion
Wrench
Peach
Saw
Drum
Tiger
Violin
Giraffe

Figure 3: Example of verbal stimuli of the CVLT-II. Adapted from Langdon et al. (2012) (267)

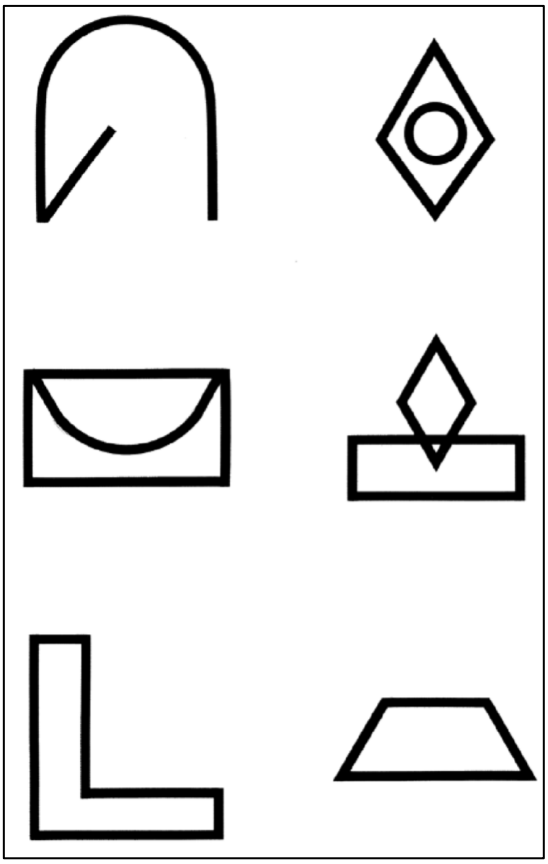

Figure 4: Example of visual stimuli of the BVMT-R. Adapted from Langdon et al. (2012) (267)

Neuropsychological batteries

Regular neuropsychological screening in pwMS is uncommon, in part due to the inaccessibility to neuropsychological services as well as the time and costs associated with comprehensive testing. In response, several groups have designed cognitive batteries comprising of individual neuropsychological tests to facilitate standardized and cost-effective routine testing. Although comprised of mostly validated individual tests, MS neuropsychological batteries should be independently validated as a whole and normative data is required to derive standardized scores when making any meaningful interpretation of CI. The longitudinal performance of the battery should be considered to enable assessment of cognitive change.

The Brief Repeatable Battery of Neuropsychological tests

The **Brief Repeatable Battery of Neuropsychological tests** (304) is one of the most widely used early cognitive batteries in MS. It consists of five tests, the Selective Reminding Test, SDMT, 10/36 spatial recall, the PASAT and word list generation tests. The BRB-N is able to detect cognitively impaired from cognitively intact pwMS with a sensitivity of 71% and specificity of 94% (308); and is able to detect CI as early as CIS (42). To reduce the reliability and practice effect limitations associated with retest, an alternate version of the BRB-N exists however it's equivalence with the primary version of the battery is unclear and has not yet been ascertained (306, 309). Practice effects and compromised reliability of the battery over repeat administrations still exist despite the alternate version (306, 310) and must be considered when contemplating use of the BRB-N for longitudinal administration.

Normative values are also particularly important for the use of the BRB-N as performance on the battery is strongly associated with age and education (306). Whilst few studies have collected data from the BRB-N in healthy control subjects in order to provide raw scores for the demographic corrections required (306), some are small (62) and several collect normative values for non-English speaking populations (309, 311-313). The BRB-N can be administered in around 45 mins (304) by suitably trained non-expert staff and is largely well accepted by pwMS (314) with the exception of the PASAT as previously discussed.

In an effort to develop a sensitive and rapid tool to detect MS-associated CI, Portaccio et al. assessed a shortened version of the BRB-N in 116 RRMS participants. They found that by

administering just three of the tests (Selective Reminding Test, the PASAT3 and the SDMT) in five to fifteen minutes, the short version of the BRB-N could detect CI with an accuracy of 89%, sensitivity of 94% and a specificity of 89% (315). Recently however, another group compared the short version of the BRB-N to the gold standard, a comprehensive neuropsychological examination, and found a sensitivity of 78% and specificity of 65% (316).

Alternate neuropsychological batteries.

In 2002 Aupperle et al. (286) compared three brief cognitive screening batteries, the **Neuropsychological Screening Battery for Multiple Sclerosis (NPSBMS)** (308), the **Screening Examination for Cognitive Impairment (SEFCI)** (317), and the **Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)** (318).

The NPSBMS which is closely related to the BRB-N takes approximately 30 minutes to administer by a suitably trained non-expert and comprises a verbal learning task, a spatial learning task (7/24 spatial learning task), the PASAT and a letter fluency task. The SEFCI also takes approximately 30 minutes to administer and is comprised of a vocabulary test, a verbal reasoning test, a verbal memory test, and the oral version of the SDMT. The RBANS takes approximately 30 minutes to administer and measures immediate and delayed memory, language, attention and visuospatial function. In this study, both the NPSBMS and SEFCI were sensitive to cognitive impairment in MS (~80% for one failed test) however the sensitivity of the RBANS was approximately the same as the Mini-Mental State Exam, a commonly used test that is insensitive to CI in MS. This makes the NPSBMS and SEFCI batteries approximately as sensitive as the BRB-N however the lack of published data on reliability, practice effects and limited normative data is limiting.

The Minimal Assessment of Cognitive Function in MS

In 2001, a consortium of expert neuropsychologists convened with the purpose of reaching a consensus on and defining 'a minimal neuropsychological examination for clinical monitoring of MS patients and research, with the additional aim of developing strategies to improve assessment of MS patients in the future (319). The panel reviewed relevant literature on cognitive dysfunction in MS, defined the purpose and optimal characteristics of a cognitive assessment in MS and examined the psychometric and practical properties of candidate cognitive batteries and tests based on available literature. The ultimate result was the **MACFIMS**.

The MACFIMS is comprised of seven individual neuropsychological tests to measure information processing speed and working memory, learning and memory, executive function, visual-spatial processing, and word retrieval. A measure of premorbid CR is recommended to supplement the MACFIMS as is assessment of confounding factors that may impact interpretation test scores such as depression, fatigue and visual or motor impairment. The seven tasks recommended by the panel are the PASAT 2 and 3 second, the oral SDMT, the CVLT-II, the BVMT-R, the Judgement of Line Orientation (a test of spatial processing) (320), the D-KEFS sorting test (a validated measure of executive function) (321) and the Controlled Oral Word Association Test (a measure of language) (322).

Psychometric properties and validation

The authors then went on to validate the MACFIMS battery as a whole (68) and hypothesized that in their study, effect sizes in discriminating pwMS from healthy subjects would be comparable to those published in the literature for individual tests. Effect sizes ranged from medium to very large with tests measuring processing speed and memory being the most sensitive, approximating the effect sizes seen in studies of individual tests. The authors also carried out a principal components analysis, a statistical analysis to group potentially correlated variables into uncorrelated variables, or principal components. Interestingly, they found that SPMS group into less components than did RRMS patients, concluding that as disease progresses there may be less variability in the presentation of cognitive deficits in MS. They also found, as previously discussed, that the SDMT loads primarily on the processing speed component but some split loading on the memory component was seen in SPMS and almost in the RRMS cohorts. A finding potentially attributed to the incidental learning associated with the SDMT. Additionally, the authors assessed the relationship between the MACFIMS tests and self or informant-reported educational status and found the verbal memory and reasoning or executive function tasks were the strongest independent predictors of employment after controlling for demographics, depression and disease course. The MACFIMS battery has been validated cross culturally in languages including Italian (323), Czech (324) and Persian (325), and has so far been shown to be psychometrically equivalent to the English language version.

Limitations of the Minimal Assessment of Cognitive Function in MS

In addition to the limitations associated with the individual tests chosen for the MACFIMS battery (ie. PASAT), the highly standardized method of administration may limit the

generalizability of the results obtained with the battery. The entire battery takes 90 minutes to administer in full and must be interpreted by a trained professional, reducing its utility in clinics that do not have access to these resources or expertise.

The Brief International Cognitive Assessment for Multiple Sclerosis

In 2012, Langdon and colleagues (267) recognized the need for efficient psychometric assessment of cognitive status without the need for expert neuropsychologists and again convened international experts in the field to reach a consensus to develop a battery of neuropsychological tests that was brief and did not require specialist equipment or personnel. The cognitive literature was reviewed and rated based on psychometric and pragmatic standards including international applicability and acceptability to patients. Tests of cognitive domains in information processing speed, verbal memory and visual memory were to be included, with tests of executive function concluded to be too long and challenging to be included. Acknowledging the heterogenous presentation of cognitive dysfunction, the authors felt addressing the domains selected would capture the majority proportion of CI. The resulting battery of tests was the **Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)**, comprising of the oral SDMT, the CVLT-II and the BVMT-R. The SDMT was chosen over the PASAT primarily based on its superior acceptability and brevity and was considered psychometrically similar (270). The CVLT-II was selected over the Selective Reminding Test, with just the first five recall trials having enough psychometric rigour to be sensitive to MS CI (290, 326). Finally, the BVMT-R was chosen over the 10/36 SPART, with just the three recall trials of the BVMT-R included in the BICAMS. Although the SPART was considered to have higher pragmatic standards, the greater reliability and lack of ceiling effects or need for specialized equipment for the BVMT-R saw it judged as being the superior test.

Psychometric properties and validation

To facilitate the international acceptance, the committee soon published international standards for validation of the BICAMS battery including test standardization across languages, standardized instructions for administration and interpretation, sample sizes required to generate normative data, reliability in repeat testing, and criterion validity established by comparing MS participants and healthy controls (69). This has led to the validation of the BICAMS battery in 11 languages and 14 individual cultures including Portuguese (327), Czech (324), German (328), Turkish (329), Japanese (330), Lithuanian (331), Canadian (332), Irish (333), Brazilian (334), Hungarian (335) and Italian (336). A recent systematic review and

meta-analysis was conducted by Corfield and Langdon (2018) (337) to synthesize evidence from across 14 of these validation studies. The authors identified significant cognitive dysfunction in pwMS compared to healthy subjects when the BICAMS battery was used. Information processing speed, measured by the SDMT, was lower in pwMS than healthy controls with the largest effect size of the three BICAMS tests (hedges g = 0.943). There was no evidence of outliers, heterogeneity or publication bias across the included studies for the SDMT. Verbal memory (CVLT-II) had the second highest effect size between pwMS and controls (hedges g = 0.688), although a moderate amount of heterogeneity was detected across the included studies which may result in imprecision of the effect size estimate. The heterogeneity within the verbal memory task is likely a result of different linguistic demands across cultures and highlights the necessity for cross cultural validation of neuropsychological tasks when establishing international norms for the BICAMS (338). Visual memory (BVMT-R) had a medium effect size between pwMS and healthy controls (hedges g= 0.635), and no outliers, heterogeneity or bias was detected across the included studies. Just one included paper compared the BICAMS to a longer neuropsychological battery (MACFIMS), and the BICAMS battery (with the criteria of one or more abnormal tests) identified 58% of pwMS as cognitively impaired where the MACFIMS (with its criteria of two or more abnormal tests) identified 55% of pwMS as cognitively impaired (339).

Although the BICAMS battery was largely administered by a trained neuropsychologist in the validation studies, it is aimed to be useful in small centres that may not have access to this expertise. To facilitate this, cut-scores that best balance between sensitivity and specificity have been proposed to improve the efficiency of screening and to simplify interpretation. The cut scores (or thresholds that define impairment) for the SDMT were 44 and 38, 39 and 35 for the CVLT-II and 17 and 16 for the BVMT-R, for 1.5SD and 2SD below the means respectively (340). Administration time of the BICAMS battery was reported as between around 12 minutes and 20 minutes, although very few of the validation studies reported this. Widely described as taking 15 minutes to administer, the time to administer the BICAMS may be variable due to the BVMT-R task where the subject has no time limit to reproduce the stimulus from memory. A recent study (341) has examined the relative sensitivity and specificity of a shortened version of the BICAMS when compared to the total battery. The authors found that whilst the full battery was psychometrically optimal, the SDMT and BVMT-R may be a suitable shorter alternative. The authors found that the single tests alone were not sufficiently sensitive. Overall, the BICAMS is a well validated and widely used battery of neuropsychological tests.

Limitations of the Brief International Cognitive Assessment for Multiple Sclerosis

There are some limitations in the tests used, such as reliability and equivalence as previously discussed, and the necessity for additional resources however these may be overcome with a computerised version of the BICAMS which is undergoing validation (ClinicalTrials.gov Identifier: NCT02391064).

Other Neuropsychological batteries - Audio Recorded Cognitive Screen

The batteries discussed here represent the most commonly used and there are, of course, many adaptations and combinations of these tests that have been developed at a local level with specific needs in mind. One example of this is the **Auditory Recorded Cognitive Screen (ARCS)** (342), which was developed at the University of Newcastle in Australia as a hybrid, unsupervised approach to cognitive testing. The ARCS test measures executive function, memory, visuospatial construction, verbal fluency and language using a recorded test and subjects record their responses in a provided booklet. The ARCS takes around 35 minutes for the subject to complete, however requires just five minutes of clinician or technician time (343).

Psychometric properties and validation

Validated for use in an MS population, the ARCS was more tolerable, had better sensitivity (86% vs 68%) and specificity of 71% than the PASAT for detection of impairment in any domain (343). In another study, the ARCS was significantly more sensitive to CI in MS than the Mini-Mental State Examination and was shown to be construct valid in a factor analysis where the ARCS scores could explain 72.4% of the variance of a comprehensive neuropsychological evaluation of the same cognitive domains (342). Compared to the BICAMS battery, the ARCS has comparable sensitivity for cognitive impairment and the memory test (from both batteries) was the strongest predictor of employment status (344). The ARCS has an alternate form for retest, and in this study reliability between repeat assessments was good (all reliability coefficients above 0.70). In a later study however, the authors found practice effects associated with the alternate form that persisted over several months (345). The ARCS has a sound normative base for interpretation of age and demographic adjusted scores (342).

Limitations of the Audio Recorded Cognitive Screen

The ARCS is a proprietary test however the cost is once off and low. Although the administration of the ARCS is unsupervised, it takes approximately 35 minutes to complete and then must be scored by an appropriately trained non-expert.

Computerised cognitive tests and batteries

Advances in computing devices and voice recognition technologies present an exciting opportunity to address some limitations with traditional pen and paper versions of cognitive tests. Computerised cognitive batteries are commonly used in other areas of neurology (346) where they are used to efficiently screen broad cognitive functions such as information processing speed, visual attention and working memory (347). A recent systematic review identified several computerised cognitive batteries and individual tests that display adequate reliability and validity to be useful screening tools in MS clinical practice. However the authors highlight the need for more validation of these tools, especially how they relate to ecological measures and 'patient-relevant' outcomes (348).

Where some computerised cognitive tests have aimed to replicate traditional pen and paper neuropsychological tests, others have used technology to interrogate paradigms such as the N-back paradigm (349) and the basic speed of a response and the speed vs accuracy trade off – one of the only non-introspective measures available (350). The inclusion of reaction time (RT) tests in clinical assessment of information processing speed can provide a rapid and valid method of detecting cognitive impairment, even potentially when no impairment can be found by traditional neuropsychological testing (351, 352). Reaction time tasks (353) have long been used in psychology and are often used as tests of vigilance or pure information processing speed (Simple Reaction Time (SiRT)) (354) and greater perceptual and attentional demands can be introduced (Choice Reaction Time (ChRT)) to robustly measure other cognitive functions such as attention (355). The n-back paradigm (eg. the One-back test) requires information to be stored for a short period of time in working memory and then recalled (356). These measures, amongst others, provide measures of continuous performance. A continuous performance test (357) can measure information processing speed in addition to characteristics of attention including focused, sustained and divided attention. Continuous performance tests can take various forms including visual, auditory or verbal and measures including RT, accuracy of response, preemptive response and missed responses are common performance

measures (358). Another measure derived from continuous performance tests that has shown to be valid as a marker of neurologic and cognitive dysfunction is IIV. IIV as a measure of response consistency across the repeated trials of continuous performance tests of processing speed and attention could be particularly sensitive to cognitive dysfunction and cognitive fatigue in MS (87, 88, 359-362).

A summary of computerised neuropsychological tools available and in various stages of development and validation are provided in **Table 3** and discussed in more detail below.

Table 3: A summary of computerised neuropsychological tools available and in various stages of development and validation

Test	**Cognitive domain measured**	**Tests included**	**Advantages**	**Disadvantages**
c-SDMT	Processing speed	Individual test	- Slightly more sensitive than traditional SDMT - Good reliability	- Less specific than traditional SDMT - Performance can be affected by incidental learning and impairments in visual acuity and speech. - Tester required to administer. - Lack of longitudinal data.
Auto-SDMT	Processing speed	Individual test	- Equivalent sensitivity and specificity with traditional SDMT. - Excellent convergent	- Specialized equipment required. - Lack of validation. - Lack of longitudinal data.

			validity with traditional SDMT. - No tester required to administer.	
PST	Processing speed	Individual test	- Brief - Excellent reliability. - Excellent convergent validity with traditional SDMT. - Slightly more sensitive than traditional SDMT. - No tester required to administer.	- Specialized software required. -Persistence of practice effects not assessed. - Lack of longitudinal data.
PVSAT	Processing speed, working memory, sustained attention	Individual test	- Correlates highly with traditional PASAT. - Tolerated better than traditional PASAT	- Potentially similar to traditional PASAT but no studies available. - Tester required to administer. - Specialized equipment required. - Lack of longitudinal data.
Computerised Cognitive batteries				

ANAM	Processing speed, memory, cognitive flexibility.	Digit substitution tests, reaction time tests.	- Sensitive to MS. - Performance correlates with brain atrophy.	- Proprietary. - Only one study in MS. - Takes 30 minutes to complete. - Specialized equipment required. - Lack of longitudinal data.
Cognitive Drug Research Assessment System	Processing speed, attention, episodic and working memory.	Digit substitution tests, reaction time tests.	- Large effect sizes compared to norms. - Excellent reliability. - Correlates with traditional cognitive measures (PASAT, Digit/substitution)	- 20-30 minutes to administer. - Specialized equipment required. - Lack of longitudinal data.
MCCB	Memory, verbal fluency, executive function, visuospatial function, attention, processing speed.	Arithmetic, reaction time/accuracy, others.	- High sensitivity. - Good specificity. - Good normative data. - Can be installed on patients home computer.	- Proprietary. - Information on reliability and practice effects missing from literature. - Takes 50 minutes to complete. - Lack of longitudinal data.
CANTAB	Processing speed, working memory,	Reaction time, motor screening,	-Sensitive to impairment in MS.	- Limited data in MS.

	executive function, attention, memory, social cognition.	emotion recognition, pattern recognition, many others.		- Many included tests. - Lack of longitudinal data.
CTIP	Processing speed, attention.	Reaction time (Simple reaction time, Choice reaction time, semantic reaction time)	- 15 minutes to complete. - Sensitive to MS. - Equivalent sensitivity as PASAT. - Preferred by patients over PASAT and SDMT. - Associated with pathophysiology changes.	- Practice effects inadequately assessed. - Reliability not reported. - Perceived by patients as being less appropriate in measuring cognitive dysfunction than PASAT and SDMT.
CBB	Processing speed, attention, working memory, visual learning, executive function.	Reaction time (Simple Reaction time, choice reaction time, One back).	-Valid in other conditions. - Minimal practice effects and good reliability. - Preferred over the PASAT. - Sensitive to impairment in MS. - Sensitive to cognitive change in MS.	- Proprietary (for clinical use). - No studies of unsupervised testing.

			- Equivalent to better sensitivity than the BICAMS.	
Abbreviations **SDMT – Symbol Digit Modalities Test; c-SDMT – computerised Symbol Digit Modalities Test; Auto-SDMT – Auto Symbol Digit Modalities Test; PST – Processing Speed Test; PVSAT – Paced Visual Serial Addition Test; PASAT – Paced Auditory Serial Addition Test; ANAM - Automated Neuropsychological Assessment Metrics; MCCB - Mindstreams Computerized Cognitive Battery; CANTAB - Cambridge Neuropsychological Test Automated Battery; CTIP - Computerized Test of Information Processing; CBB – Cogstate Brief Battery; BICAMS – Brief International Cognitive Assessment in Multiple Sclerosis.**				

Computerised variants of the SDMT

c-SDMT

Several groups have developed computerised variants of the SDMT. In 2011, Akbar and colleagues (363) first developed and validated a novel computerised version of the SDMT (**c-SDMT**). For the c-SDMT, subjects respond orally to match numbers one to nine to the corresponding symbol given in the key. Subjects are presented with nine symbols at a time on the lower half of the screen of a desktop computer whilst the key of matching symbols and numbers remains on the upper half of the screen.

In their study, they compared the c-SDMT to the BRB-N battery (including the traditional oral paper SDMT) and found that the computerised version was slightly more sensitive (71% vs 67%) and less specific (84% vs 95%) than the paper version of the SDMT. As a result, the c-SDMT was able to detect more cognitively impaired pwMS than the paper version (37% vs 29%). The authors reported good test-retest reliability (Intraclass correlation coefficient = 0.94) although significant practice effects were evident over repeated trials of the c-SDMT, with improvements in the speed of response over at least eight trials (the same was seen for the paper SDMT). Like the oral paper SDMT, computerised variants of the SDMT may be affected by impairments in visual acuity and speech.

Several modified versions of the c-SDMT have been used subsequently. In 2015, Denney et al. (364) administered the c-SDMT in conjunction with a computerised test of incidental

learning in pwMS and healthy subjects and concluded that it was the cognitive burden of poorer incidental learning in pwMS that affects performance in tasks of information processing speed. In corroboration of this, Patel and colleagues (2017) (271) employed modified c-SDMT versions with fixed and variable symbol-digit keys and found that memory, specifically incidental visual memory, contributes to test performance on the c-SDMT with a fixed key. In the same year this group also developed another modified version of the c-SDMT containing built-in distractors, a telephone ringing and a car horn, repeated three times over the course of the test. They compared the c-SDMT with distractors to a version without distractors and found the inclusion of distractors increased the cognitive burden and improved the sensitivity of the c-SDMT over the traditional SDMT (365).

auto-SDMT

One limitation hampering the widespread use of regular cognitive testing is the need for resources, whether it be personnel or time, which presents a problem for many busy outpatient clinics. In response to this, Patel et al have recently used advances in voice recognition technologies to develop a version of the SDMT (**auto-SDMT**) that requires no tester and is entirely computer administered (366). In the authors feasibility study, they found the auto-SDMT had excellent convergent validity with and equivalent sensitivity and specificity for detecting cognitive impairment as the SDMT. The auto-SDMT was preferred over the tester-administered SDMT and is a promising tool that requires further validation.

Processing Speed Test

Another computerised adaptation of the SDMT that does not require a tester is the **Processing Speed Test (PST)** (367) which forms part of the Multiple Sclerosis Performance Test (MSPT) (368), a modern adaptation of the Multiple Sclerosis Functional Composite. The MSPT has been developed as part of MSPATHS, a large prospective initiative to integrate technological health solutions into real-world clinical practice. With approximately 15,000 participants, this multi-center study collects large volumes of data for which the PST is often a reported outcome (369, 370). The PST is a tablet (Apple iPad) based task, that requires subjects to press the number that corresponds to the matching symbol, as presented in the randomly generated key that resides in the upper half of the screen (**Figure 5**). The subjects are presented with 15 symbols at a time and the score is the number of correct responses obtained over 120 seconds, with the extra time (over the standard oral SDMT) given to account for the slower entry of manual versus oral responses.

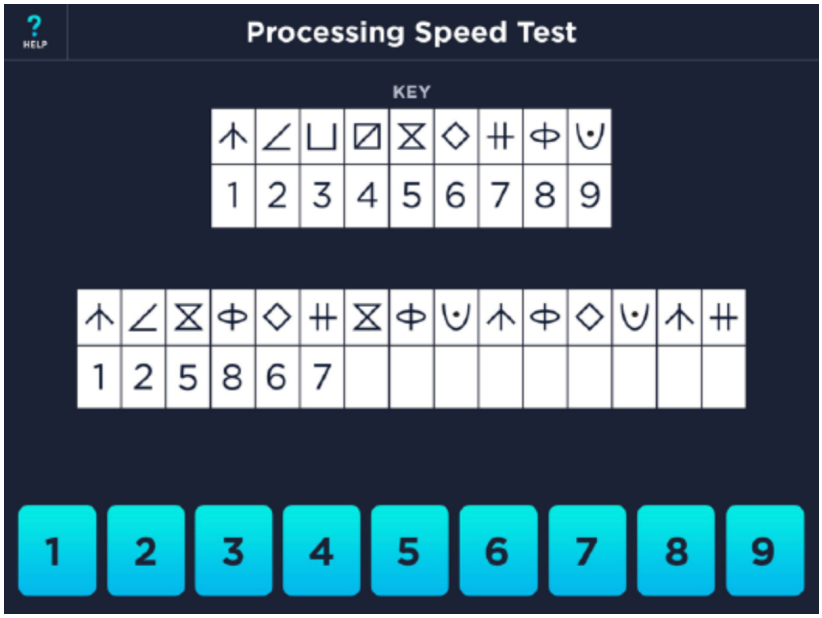

Figure 5: Example of the stimuli of the Processing Speed Test (PST). Adapted from Rao et al. (2017) (367)

In a validation study comparing the PST to the standard oral SDMT, the PST had excellent test-retest reliability in pwMS (concordance correlation coefficient (CCC) = 0.88), although practice effects were evident. The persistence of these practice effects was not assessed. The PST was highly correlated with the SDMT, was slightly more sensitive in discriminating pwMS and healthy subjects and correlated better with T2 lesion load than the SDMT. The authors also investigated whether the presence of a technician or tester impacted the PST results and they found that test scores were equivalent in the presence or absence of a tester. A recent study further supported this, finding that reliable and valid test data was obtained from two computerised cognitive batteries (including the PST) in the absence of a technician/tester (371).

Computerised variants of the Paced Auditory Serial Addition Test

The **Paced Visual Serial Addition Test (PVSAT)** (372) is a visual analogue of the PASAT in which single digit numbers are displayed on a screen. Presentation rate of the stimulus is the same rate as the PASAT. PVSAT (2 and 3 second) scores correlated highly with respective PASAT scores, although participants consistently scored better on the PVSAT than the PASAT (373, 374). Importantly, the PVSAT is better tolerated by patients than the PASAT.

Other computerised neuropsychological batteries

Automated Neuropsychological Assessment Metrics

The **Automated Neuropsychological Assessment Metrics (ANAM)** (375) is a proprietary test that measures information processing speed and memory via a number of tests including digit substitution tests and RT tasks and takes 30 minutes to complete. One study in MS has used the ANAM and found pwMS scored lower in the tests global score than healthy subjects and abnormal scores on three of the included tests of memory, processing speed and cognitive flexibility were associated with reduced normal appearing white matter and normal appearing grey matter volumes (148). No further validation has been published for this battery in a MS cohort.

The Cognitive Drug Research Assessment System

The **Cognitive Drug Research Assessment System** (376) measures processing speed, attention, episodic and working memory using a similar array of tasks as the ANAM in approximately 20 minutes. A single study in pwMS compared the battery to the PASAT and a digit substitution test and found that some of the tasks had excellent test-retest reliability and the battery correlated with the other measures of cognition. Using this battery, large impairments in processing speed and attention were found (effect size d >1) when compared to normative data from a different dataset (377).

Mindstreams Computerized Cognitive Battery by Neurotrax

The proprietary **Mindstreams Computerized Cognitive Battery (MCCB)** by **Neurotrax** (378) assesses memory, verbal fluency, executive function, visuospatial function, attention and information processing speed in a 50 minute battery that is installed on the patient's home computer. Achiron et al. (2007) (379) compared the MCCB to a neuropsychological testing battery (NPSBMS) and demonstrated the computerised battery had good construct validity in the memory, executive function, attention and information processing domains. The MCCB also had good discriminant validity between pwMS and matched normative data, particularly in the areas of executive function and attention.

A recent validation study reported the battery had sensitivity of 85% and specificity of 70% to detect cognitive impairment and found those classified as impaired with the computerised battery were more likely to be unemployed than those who were cognitively intact (380). The

MCCB has been used in studies of MS to investigate the role of cognition in sleep (381), disease duration (382), subjective fatigue and depression (383), falls (384), cognition pathophysiology (385), as well as monitoring cognition during trials of MS therapies (386). The MCCB is installed on a patients local computer, facilitating the possibility of remote self-testing (although this has not been explored). The limitations of the MCCB are the lack of data for longitudinal testing such as reliability and practice effects, as these are important considerations for regular cognitive monitoring. The length and proprietary nature of the battery limit its use in busy outpatients centres as a rapid monitoring tool.

The Cambridge Neuropsychological Test Automated Battery

The **Cambridge Neuropsychological Test Automated Battery (CANTAB)** (387) consists of a number of computerised tests that can be administered via touchscreen platforms to assess discrete cognitive subdomains including working memory, executive function, processing speed, attention and episodic memory. Early studies utilizing the CANTAB in MS studies used single desktop computer cognitive tasks that assessed visual learning, memory and attention (388, 389). A recent study to assess a new, 15 minute, fully-digital touchscreen administered version of the CANTAB found it was able to detect CI (in one or more domains) in 44% of the MS subjects, with executive function being the most commonly impaired cognitive function. Performance on the cognitive tasks was associated with disease duration, severity and depression. Interestingly, nine (9%) of the participants were unable to complete the computerised testing although no reasons were given for this (390). In another recent study comparing CANTAB to the MACFIMS battery, the CANTAB displayed comparable sensitivity in discriminating cognitively impaired MS patients from cognitively intact patients (391). The CANTAB offers a promising cognitive battery which utilizes ubiquitous touchscreen devices, however further validation and longitudinal data from MS cohorts is required.

Computerized Test of Information Processing

The **Computerized Test of Information Processing (CTIP)** (353) consists of three RT based tests: SiRT, ChRT is the time taken for the subject to press one of two keys on a keyboard depending on the stimulus presented, and semantic reaction time is the time it takes the subject to decide which semantic category the presented stimulus belongs. Administration time is approximately 15 minutes. Motor dysfunction can potentially impede assessment of cognition

in any test that requires use of the limbs, and in this study the authors controlled for this by normalizing each result to the 'baseline' SiRT, assuming motor (dys)function was consistent across tasks. In contrast, Luce (1986) (355) suggest that increased motor function in ChRT tasks in fact increases the cognitive burden. In this study, the CTIP was able to discriminate between pwMS and healthy subjects at varying percentile cut-offs (50th, 10th, 5th) and the differences between each group at each level remained significant. To assess learning effects, participants in this study completed 30 trials of the CTIP each preceded by a practice trial. The authors then divided these into three ten trial blocks and found no significant mean difference in reaction time across the three blocks, concluding the test was free from learning effects. Unfortunately, this analysis does not inform of any improvements in test scores that may be present during the early trials, say over the first three to four trials if the learning curve is steep, and indeed a more granular approach is needed. In addition, the authors did not report test-retest reliability over repeat trials in the MS cohort, a key psychometric property.

In a similar study Tombaugh et al. (392) compared the CTIP to the PASAT3 in pwMS and healthy subjects, finding similar results and concluding the CTIP may be a viable alternative to the PASAT in the MSFC. The CTIP has also been used in studies of IIV over serial cognitive testing in pwMS. Wojtowicz et al. (88) hypothesized that this may provide a more precise measure of processing speed than mean level outcomes. They assessed IIV over 30 test trials in pwMS and healthy subjects and found pwMS demonstrated greater within-subject variability than controls even after controlling for mean level group differences and learning effects, suggesting this may provide unique insights into cognitive functions in MS. In another study from the same group, mean CTIP performance and within-subject variability was sensitive to changes in lesion burden, global brain atrophy and integrity of WM tracts. Increased IIV on the CTIP was more strongly associated with reduced WM integrity than the SDMT or the SiRT test of the CTIP, suggesting it may be a stronger marker of neurologic degeneration than traditional processing speed tests (89).

An interesting study by Walker et al. (393) assessed subjective acceptability, difficulty and appropriateness of three information processing speed tests: the PASAT, the SDMT and the CTIP in pwMS. Perhaps unsurprisingly, the PASAT was the least tolerable of the tests although the SDMT and PASAT were perceived by patients as being more appropriate for measuring cognitive dysfunction. Both pwMS and controls found the CTIP to be easier than the SDMT and PASAT.

The Cogstate Brief Battery

The **Cogstate Brief Battery (CBB)** (347) is a self-administered, computerised cognitive assessment battery which measures processing speed, attention, working memory, visual learning, spatial problem solving and executive function. Designed specifically to be sensitive to cognitive changes, the CBB uses testing paradigms including SiRT, ChRT and n-back (One-back) to efficiently assess broad cognitive domains (**Figure 6**). To limit practice effects with repeat testing, alternate forms of the CBB stimuli are automatically generated with randomly variable pre- and post-stimulus intervals. The Cogstate battery has been shown to be sensitive to subtle CI in a wide range of conditions including fatigue (394), concussion (395), post-operative (396) and HIV (397).

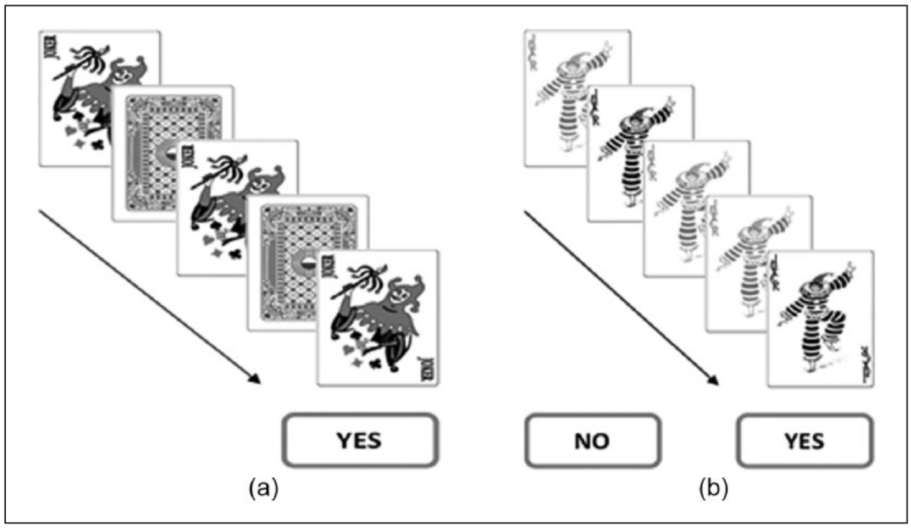

Figure 6: An example of stimuli used in the Cogstate Brief Battery. (a) Simple Reaction Time task and (b) Choice Reaction Time task.

It's validity and reliability has been assessed across a range of ages (398, 399) showing moderate to high correlations with other tests of psychomotor speed/information processing speed, and moderate to high reliability (intra-class correlation 0.15-0.90). The CBB has been shown to have good construct and criterion validity in mild traumatic brain injury, Schizophrenia and AIDS dementia complex (347) and is stable and reliable in unsupervised self-testing in community dwelling older people (400, 401). In a study of remote self-testing over 12 months, the CBB was acceptable to participants performing remote self-testing although attrition was relatively high with nearly 25% of participants discontinuing testing,

despite reminder emails and phone calls (402). In one MS study (371), the performance on the CBB tasks were compared when completed with a technician providing guidance to the performance on the tasks when a technician was absent. The results did not differ when the CBB was self-administered. However, technical problems such as accidently closing a window or failure to understand the instructions were more common in the self-administered group and attributed to the instructions of the CBB being solely visual. The CBB has been shown to have minimal practice effects that stabilize rapidly with serial longitudinal testing (403). The CBB has been used in relatively few studies in a MS setting. In one study, Charvet et al. (404) compared the CBB to the BICAMS battery in a pediatric-onset cohort and found that although both batteries were approximately equivalent in sensitivity, the SiRT and CHRT tasks of the CBB were the most sensitive tests to cognitive impairment. A recent study by my supervisors compared the sensitivity and acceptability of the CBB tasks and the PASAT. They found that both the CBB and PASAT were able to discriminate between pwMS and healthy subjects at baseline however, the SiRT and ChRT tasks of the CBB were sensitive to changes in cognitive function over 12 months whereas the PASAT was not. The CBB was more tolerable than the PASAT (153). The CBB has an extensive normative database consisting of over 50000 representative participants for cross-sectional and longitudinal comparison across the life span (ages 10 to 99 years)(404, 405).

The CBB has also been used in trials of MS therapeutics. One study used the CBB and SDMT to monitor cognitive impairment evolution during 24 months of natalizumab therapy and found no decline in cognitive performance was detected with either tool (406). Another study used the CBB and BICAMS battery in a trial of cognitive rehabilitation in conjunction with transcranial stimulation and found that the CBB battery was able to detect improvements in cognition in the treated group relative to controls where the BICAMS could not (407).

Development of a new computerised cognitive battery.

With the advantages and limitations of computerised cognitive testing in mind, my supervisors developed a web-based battery by adapting digital tests provided by uBrain (www.ubrain.com.br). The new battery, MSReactor, consists of a SiRT, a ChRT and a One-back RT task, assessing psychomotor processing speed, information processing speed, attention and working memory **(Figure 7)**. The cognitive function tasks included in the

MSReactor battery are specifically chosen to optimize longitudinal monitoring of cognitive function based on our preliminary data from using the Cogstate Brief Battery (153). The MSReactor battery is accessible from any internet-connected device and can be administered in the outpatient clinic setting, with the option to complete remote home-based self-testing.

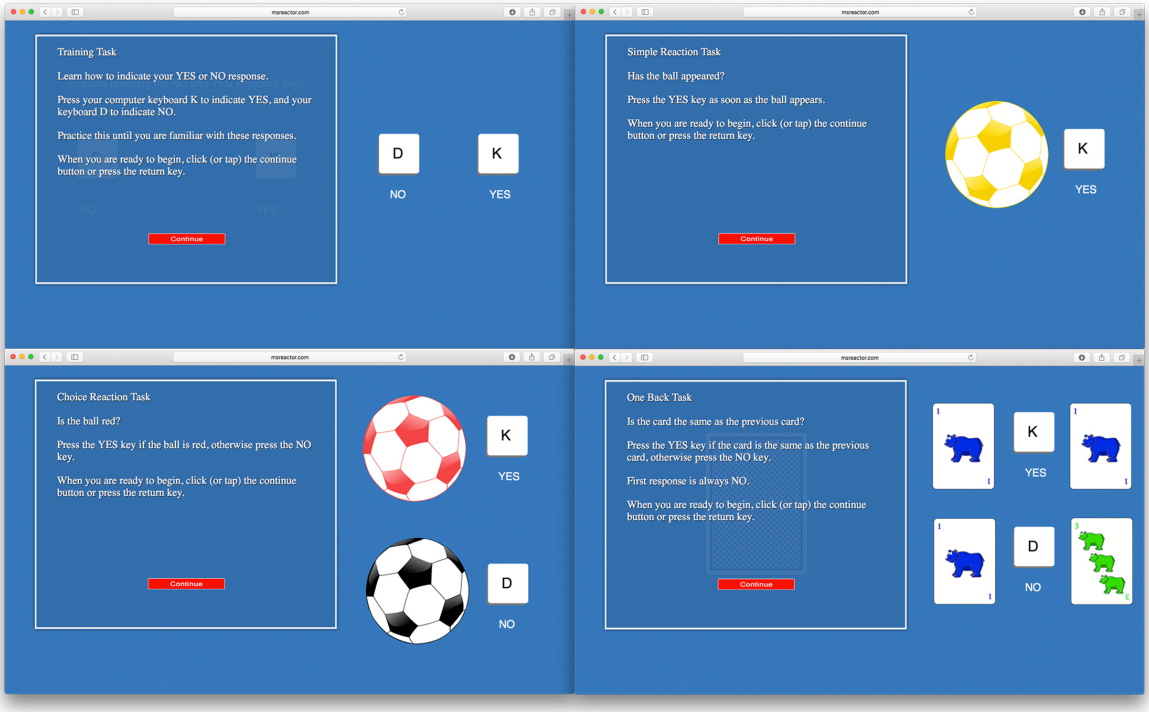

Figure 7: MSReactor reaction time battery. Clockwise from top left – Instructional screen, Simple Reaction Task, One Back Task and Choice Reaction Task.

MSReactor presents subjects with randomly generated stimuli to minimize learning effects and is designed with no range or distribution restrictions. Following initial instructions, subjects are able to independently complete the testing in clinic and at home. At the completion of each test, results are automatically collated with their previous results and graphically presented. Following each test done in the clinic, subjects can complete electronic acceptability, subjective performance, depression, anxiety and quality of life surveys within the testing portal. Safety alerts are built into the system to alert investigators to any adverse score on the psychological surveys. In addition, a mirror testing website has been developed to independently collect normative data from people without MS.

As MSReactor is a new test, an important first step in defining its use is to determine its feasibility, usability and acceptability in pwMS. The psychometric properties of the battery should be assessed whilst acknowledging that the aim of a cognitive screening tool is not to

detect cognitive impairment but change in cognitive performance from some previous level. The ability to perform reliable and sensitive serial testing with the MSReactor battery allows the examination of subtle changes in task performance and its relationship to changes in demographic, clinical and paraclinical measures, resulting in identification of clinically relevant changes in MSReactor outcomes and potential biomarkers of cognitive change. This will ultimately allow the modelling of individual cognitive trajectories and change, accounting for potentially modifying factors, providing patient and clinician with another tool with which to inform clinical management.

Summary of neuropsychological assessment in MS

Many tests and batteries have been used and validated for the assessment of CI in MS. Although usually highly specific and sensitive to cognitive impairment, many neuropsychological tests may be insensitive to cognitive change over time due to practice effects associated with repeat testing making them unsuitable for the serial assessment of cognition required for clinical management. In addition, many batteries require additional resources such as trained personnel or extended periods of time for administration making them impractical for use in MS clinical practice.

Computerised cognitive tests and batteries, whilst still in their relative infancy, present an innovative and promising solution to monitor for cognitive changes in a MS clinic population. Computerised batteries are, in general, practical for use in clinical practice and can offer significant benefits and address many of the limitations of traditional neuropsychological testing in MS clinical practice. Advantages of computerised tests include the ability to randomly generate many alternate equivalent versions of tests to minimize practice effects, no ceiling or floor effects, no range restrictions of scores, standardization of presentation and scoring thus reducing human error (408), use of everyday equipment and ease of integration with electronic medical records and research databases such as MSBase (409).

The published computerised tests are not without their limitations. Whilst generally designed to interrogate only a limited number of cognitive domains, the brevity of the screening tests can result in a loss of specificity (347). In addition, many of the tests lack the level of validation needed for clinical acceptance and most have poorly defined clinically relevant changes that can be used to inform clinical practice. In addition, the reliability and persistence of practice

effects associated with these tools across repeat administrations are only assessed over short retest intervals and do not reflect the testing frequency in the clinic environment. Lastly, some computerised batteries still require a tester to be present and may require the purchase of specialist or proprietary equipment. Although the use of computerized testing opens up the possibility of remote testing, performed in the patients home or unsupervised testing in the outpatient clinic, these may introduce many risks to the validity of the testing. Unsupervised testing increases the risk of distractions during testing, difficulty in maintaining motivation to perform optimally or even variability associated with the time of day the tests are performed. In addition to issues of validity, these uncontrollable variables may introduce variability to the data which hampers the ability to measure longitudinal changes in outcomes. The challenges of testing in an uncontrolled environment should always be considered in design of research studies and interpretation of data, and efforts should be made to minimize these sources of variability and standardize the testing environment. This is a relatively new field however and we can expect that the coming years will bring great advances in technological monitoring of diseases and integration with electronic health records and databases.

Summary

Cognitive impairment in MS is common, and leads to lower rates of employment, social isolation and affected activities of daily living. Cognitive changes are difficult to detect with existing tests which are resource intensive and impractical to use in clinical practice. Brief, computerised cognitive batteries that can be self-administered may be sensitive to preclinical cognitive changes, for example, when monitoring for early signs to a treatment response. This is important, as intervention with DMT's have the greatest impact on physical disability when used early in the disease and the same beneficial effects potentially apply to cognition (235) where the long-term effects of DMT use are still unknown (253).

The potential benefits of computerised cognitive screening in research and clinical practice are large, however the accessibility of reliable and valid tests remain a major hurdle to widespread use. New tests should of course be psychometrically sound, but also designed in a way that provides the greatest accessibility to all pwMS, their clinicians and the research community. The increased sensitivity of computerised testing to cognitive change is an important characteristic. In a recent article discussing the current state of cognitive testing in MS clinical practice and priorities for the future, Sumowski (90) advocates for routine cognitive screening

of all MS patients upon their entry into the clinic to allow changes from their baseline to be assessed regularly. This highlights the complementary need for both computerised cognitive screening and comprehensive neuropsychological assessment in MS clinical practice. Over half of pwMS will experience cognitive dysfunction and as cognition is rarely measured during routine clinical visits, many of those that require neuropsychological services remain unidentified. With computerised screening in place, patients whose performance on these tasks have persistently worsened over time can be referred to neuropsychologists for assessment.

Thesis Overview

This thesis follows a cohesive and logical journey from initial implementation of MSReactor computerised cognitive monitoring into busy MS outpatient clinics. I determine the feasibility, acceptability, usability and some psychometric properties of MSReactor in chapters one and two. I explore the relationship between objective changes on the MSReactor tasks and the patients perception of their performance. Finally, I identify longitudinal trajectories of reaction time changes and the clinical and demographic factors that are associated with the change trajectories such as disability, disability progression, disease modifying therapy use, age and disease duration in chapters three and four.

In chapter one, I enrolled mostly RRMS patients from two tertiary MS outpatient clinics in Melbourne, Australia. I report information important to the implementation of a new tool into a busy clinic including acceptability of the computerised tasks, compliance and factors that are associated with the persistence to home-based testing. In addition, I explore some psychometric measures of the MSReactor tasks including practice effects, test-retest reliability, concurrent validity and discriminative validity. Chapter two is a further study on the validity of the MSReactor tasks. In this study, RRMS patients with 'early' MS were enrolled from six tertiary outpatient clinics across Australia. Study participants completed the MSReactor tests, manual dexterity testing and the PST (see page 45). I explore the relationship between the MSReactor tasks and upper limb motor function, as well as further investigate concurrent and predictive correlations between the MSReactor tasks and PST.

Chapter three of this thesis investigates the relationship between the subjects perceived performance on the MSReactor tasks and objective changes in reaction speed and accuracy on

the same tasks. In addition, I look at the relationship between the patient reported outcomes of depression, anxiety and quality of life and subjective performance, and control for these potential confounders using partial correlations where necessary. In chapter four, I use advanced statistical methods to model the heterogenous, longitudinal RT outcome for each task. This approach simplifies the heterogenous longitudinal data into distinct groups or 'classes' of individual trajectories sharing common underlying, or latent, characteristics. I validate the optimal model for each task and determine the minimum number of tests required by each participant to predict the assigned class of each optimal model. I then explored the inter-class differences of baseline clinic and demographic measures including disability, disease duration, DMT use, age and age at diagnosis. Finally, I performed survival analysis to determine the inter-class differences in the probability of reaction time slowing and confirmed disability progression.

Hypotheses

Chapter 1

The feasibility, reliability and concurrent validity of the MSReactor computerised cognitive screening tool in multiple sclerosis.

i. Brief self-administered computerised cognitive testing is acceptable and feasible when administered in the MS patient setting.

ii. The majority of participants will opt to perform remote testing and compliance will be high. Factors that affect remote testing adherence will be identified.

iii. The MSReactor computerised cognitive battery is sensitive to MS, reliable over repeat testing and correlates with another validated instrument measuring comparative cognitive domains, the SDMT.

Chapter 2

The MSReactor computerised cognitive battery correlates with the processing speed test in relapsing-remitting multiple sclerosis.

i. The MSReactor tasks correlate concurrently with an electronic version of the SDMT, the Processing Speed Test, independent of manual dexterity.

ii. The MSReactor tasks predict a future PST test, independent of manual dexterity.

Chapter 3

Subjective versus objective performance in people with multiple sclerosis using the MSReactor computerised cognitive tests.

i. Patient reported subjective cognitive performance will not predict the subtle objective changes detectable by the MSReactor computerised cognitive battery.

Chapter 4

Computerised cognitive measures can detect reaction time slowing and predict disability progression in relapsing remitting multiple sclerosis.

i. Discrete trajectories of reaction time changes are identifiable from the longitudinal MSReactor task performances.

ii. Baseline factors such as age and disability will predict longitudinal reaction time changes trajectories.

iii. MSReactor reaction time change trajectories will identify a group of patients with worsening cognitive function and predict disease progression.

Chapter 1

The feasibility, reliability and concurrent validity of the MSReactor computerized cognitive screening tool in multiple sclerosis

This chapter is a reproduction of the peer-reviewed article published in Therapeutic Advances in Neurological Disorders in July 2019.

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Paper highlights

- Computeried cognitive monitoring is feasible to implement in the MS outpatient setting and acceptable to patients.
- Most participants opted to complete remote testing and compliance was high. I identified factors that may inhibit remote testing persistence.
- The MSReactor computerised cognitive tasks could discriminate people with MS from controls without MS, and all tasks correlated moderately with the SDMT.

Abstract

Background

Multiple sclerosis cognitive tests are resource intensive and limited by practice effects that prevent frequent retesting. Brief, reliable, and valid monitoring tools are urgently needed to detect subtle, subclinical cognitive changes in people with multiple sclerosis. Cognitive monitoring over time could contribute to a new definition of 'No Evidence of Disease Activity', supplementing routine clinical monitoring.

Methods

MSReactor is a web-based battery that measures psychomotor (processing) speed, visual attention and working memory using simple reaction time tasks. Clinic-based tasks were completed at baseline and 6 monthly, and home-testing 1 to 3 monthly. Acceptability, quality of life, depression and anxiety surveys were completed. We studied its correlation with the Symbol Digit Modalities Test, practice effects, test-retest reliability and the discriminative ability of MSReactor.

Results

450 people with MS were recruited over 18 months with 81% opting to complete home-based testing. Most participants (96%) would be happy (or neutral) to repeat the tasks again and just 4 reported the tasks made them 'very anxious'. Persistence of home testing was high and practice effects stabilised within 3 tests. MSReactor tasks correlated with Symbol Digit Modalities Test scores, and participants with MS performed slower than healthy controls.

Conclusion

MSReactor is a scalable and reliable cognitive screening tool that can be used in the clinic and remotely. MSReactor task performance correlated with another highly validated cognitive test, was sensitive to MS and baseline predictors of cognitive performance were identified.

Introduction

Cognitive impairment affects 40-65% of people with MS, leading to lower rates of employment, social isolation and affected activities of daily living (113). Cognitive impairment occurs throughout the MS disease course (410), most commonly impacting information processing speed, attention, working memory, and executive function (68). In its early stages, cognitive change is, however, difficult to detect, both by clinicians (91) and by standard neuropsychological tests (92), because individuals with cognitive decline will remain in the normal range of standard tests at this time. Complex cognitive batteries and even simpler, adapted tests such as the Brief International Cognitive Assessment for MS (267) require dedicated resources to administer and score, making it impractical to use in under-resourced outpatient clinics. The Symbol Digit Modalities Tests (SDMT) is recommended for use as a brief and valid cognitive screening measure where time is limited (268). Despite the availability of alternate versions of these test, learning effects still occur and this limits their use in situations where frequent and repeated cognitive screening is required, for example when monitoring for early signs of a treatment response (277). Other commonly used cognitive screening tools also lack sensitivity to preclinical cognitive change in MS (411). This is important, as intervention with disease modifying treatments have the greatest impact on physical disability accumulation if used early in the disease course (412). The same beneficial effects potentially applies to cognition (235, 413), but conclusive evidence regarding long-term effects of current therapies on cognition is lacking (253). The ability to perform regular cognitive monitoring in the outpatient clinic is currently an unmet need in MS (90) and requires the development of a screening test that can be repeated frequently, with minimal learning effects. An ideal screening test needs to be brief, interesting and self-administered in addition to being valid, reliable and sensitive to subtle cognitive changes.

Computerized cognitive batteries have gained traction in other fields of neurology (346) and efficiently screen broad cognitive functions such as information processing speed, attention and working memory (347). Where early computerized cognitive tests aimed to replicate existing ‘pen and paper’ tests, recent studies have investigated the basic speed of a response, a

measure of information processing speed. This is a key foundational cognitive domain that can be responsible for impairments in higher cognitive abilities including working memory and executive function (414). Computerized cognitive batteries are highly useable (415), stable and reliable across a range of ages in healthy and impaired populations (400), can be self-administered and have a relative lack of practice effects due to the ability to generate many alternate versions. In our previous work investigating the use of a computerized battery in MS, the detection (Simple reaction time), identification (Choice reaction time) and One-Back tasks of the Cogstate brief battery were able to discriminate between 70 MS and 37 healthy controls, with the detection and identification tasks more sensitive to cognitive change over 12 months than the Paced Auditory Serial Addition Test (PASAT) (153). 'MSReactor', adapted from tests made available by uBrain (http://ubrain.com.br), is a web-based battery to monitor cognitive abilities in three commonly affected cognitive domains. In this study, we explored the usability, test-retest reliability and practice effects of the MSReactor battery. In addition, we determined the correlation with SDMT score and compared performance on the cognitive tasks between MS and healthy controls (HC).

Materials and methods

Participants and recruitment

Adult MS participants were recruited between March 2016 to September 2017 from two tertiary MS clinics in Melbourne, Australia. Inclusion criteria included: 1) diagnosis of relapsing-remitting or secondary-progressive MS; 2) no upper limb, visual or cognitive deficits that preclude performance on a touch-screen device in the clinic; and 3) willing to use their own computer or tablet device with internet access for home-based testing. HC participants were recruited via community notices, self-enrolled and completed testing via the testing website. The study was approved by the relevant Ethics Committees, and all participants provided written informed consent.

Study design

A prospective convenience sample of participants were enrolled during their outpatient visit and provided with a unique password to access the testing website. Clinic-based testing was completed at baseline and each subsequent clinic visit (approximately 6-monthly). Optional home-based testing was offered to all participants and performed 1-3 monthly. HC participants completed home-based testing only. All participants completed at least one (maximum of two) brief practice tests prior to their baseline test and were encouraged to perform a practice test

prior to the home-based test. Immediately following completion of the tasks, electronic surveys assessing acceptability, quality of life (QoL), anxiety and depression were presented. Total clinic-based testing time was 12-15 minutes. Surveys were omitted from home tests, resulting in a testing time of about 5 minutes. Persistence was encouraged by two automated email reminders (sent 1 week apart) if no scored test (clinic or home) had been recorded for 3 months.

Computerized cognitive battery (MSReactor)

MSReactor is accessible via any modern internet browser. The battery consisted of three tasks using a visual game-like interface, including a psychomotor (processing) speed (Simple Reaction Time, SiRT) test, a visual attention (Choice Reaction Time, ChRT) test and a working memory (One Back, OBK) test, where participants reacted to soccer balls or custom playing cards appearing on the screen. Participants were required to become familiar with the 'yes' and 'no' buttons, and each task displayed a textual instruction screen. For the SRT task, participants pressed the 'Yes' button when they detected a yellow ball appear on the screen. For the ChRT task, participants indicated 'yes' if the ball was red and 'no' if the ball was not red. For the OBK task, participants responded 'yes' if the face-up card was identical to the immediately previous card and 'no' if the card was different to the previous card. On completion of the tasks, results were uploaded to a central database, automatically analysed and collated with prior results for the same participant.

Acceptability, Quality of Life, Depression and Anxiety Surveys

Participants completed an acceptability questionnaire to assess the enjoyability, level of anxiety, engagement, duration and repeatability of the tasks (**supplementary file a**). Depression was assessed using the Patient Health Questionnaire (PHQ-9) (416); Anxiety using the Penn State Worry Questionnaire (PSWQ) (417); and QoL assessed using the Multiple Sclerosis Quality-of-Life Score (MusiQoL) (418).

Concurrent validity and discriminative ability.

A subset (n=30) of MS participants completed the pen and paper version of the SDMT in addition to MSReactor in the same testing session. To determine the ability of the MSReactor tasks to discriminate between MS patients and controls without MS, the baseline task performance of this subset of participants was compared to the baseline task performance of HC participants, and controlled for education attainment.

Data Analysis

Descriptive data are presented as mean and standard deviation (SD), median and interquartile range (IQR) where appropriate, and frequency data as proportions. Acceptability was recorded on Likert scales, ranging from a negative response (0) to a positive response (10), and recoded to 5-point ordinal dummy variables for analysis. For each task, the speed of performance was the average reaction time (milliseconds, ms) for the first 30 correct responses. Individual performance speeds were log-transformed and mean reaction times calculated. Accuracy was defined as the proportion of correct responses made for each task, normalised with an arcsine square root transformation.

The probability of discontinuing home testing was assessed using a Cox proportional hazards model, with covariates of age and quartiles of baseline task performance. Correlation between baseline task performance and QoL, depression and anxiety were assessed using a Spearman rank coefficient. To assess baseline associations between task performance and disease and demographic factors, multivariable linear regression was performed with task performance as dependent variable and age, EDSS and disease duration as independent variables. The effect of time between repeat testing and the number of completed tests on practice effects was assessed in separate linear mixed effects models and then together using a multivariate analysis with task performance as the dependent variable. Test-retest reliability was assessed by calculating the Concordance Correlation Coefficient (CCC) between each consecutive pair of tests. To visualise the mean distribution of reaction time over the first 10 repeat tests, a curve was interpolated through each timepoint using non-parametric bootstrap for 10,000 resamples and bias-adjusted confidence intervals calculated from the bootstrapped distributions. The mean first derivative, or slope of a line tangent to the interpolated curve, was calculated for each timepoint and bias adjusted confidence intervals calculated. One-sample t-test was used to compare the first derivative at each timepoint (n= 10,000) to a hypothesized first derivative mean of zero (*mu*=0). Performance at the second clinic test (approximately 6 months from baseline) was compared to the preceding home test using a linear-mixed effect model. Devices used to perform home-tests were summarised. A general linear model was used to compare baseline performance between MS and controls, with all models controlled for years of education. Raw correlations between MSReactor and SDMT scores were calculated using Pearson correlation coefficient. Disattenuated correlation coefficients, between the latent test scores, were then calculated by adjusting for reliability of MSReactor (following stabilisation of learning effect) and previously published reliability data for the SDMT (269) for the equivalent testing epoch.

Results

Participant characteristics – MS

Characteristics of the 450 MS participants who completed baseline clinic tests are shown in **table 1**. Of these, 364 (81%) opted to complete additional home testing, with most participants (80%) completing a home test within 3 months of baseline. Most participants completing home testing used the Windows operating system (42%), followed by iOS (38%), Macintosh operating system (13%) and 'Other' platform (7%). Seventeen participants (3.8%) withdrew from the study.

Table 1: MS Participant characteristics

	Participants	**Withdrawers**
	n (%)	**n (%)**
Total - RRMS - SPMS	**450** 435 (97%) 15 (3%)	**17** 17 (100%) 0
Female	338 *(75%)*	12 *(70.5%)*
Age (*std dev*)	43.1 years (*11.09*)	44.7 years *(9)*
EDSS; median (IQR)	2 (*1-3.5*)	2 *(1-4)*
Disease duration (std dev)	13.52 years *(8.14)*	14.07 *(7.56)*
Opted to complete home-testing - Repeated testing within 3 months of enrolment.	364 (81%) 289 (80%)	
Withdrawn from study	17 (3.8%)	

Home testing persistence

Home-based testing was discontinued by 40 participants (11%) who reverted to clinic only testing. In multivariate survival analysis, lower quartile (or slower reaction time) performance on all tasks (SRT (HR 1.48 (95% Confidence Interval (CI) 1.10-1.99), ChRT (HR 1.44 (CI 1.08-1.93), and OBK (HR 1.35 (CI 1.01-1.80)) was significantly associated with greater rates of home-testing discontinuation (**Figure 1a-c).** In addition, older participants were more likely to persist with home-testing.

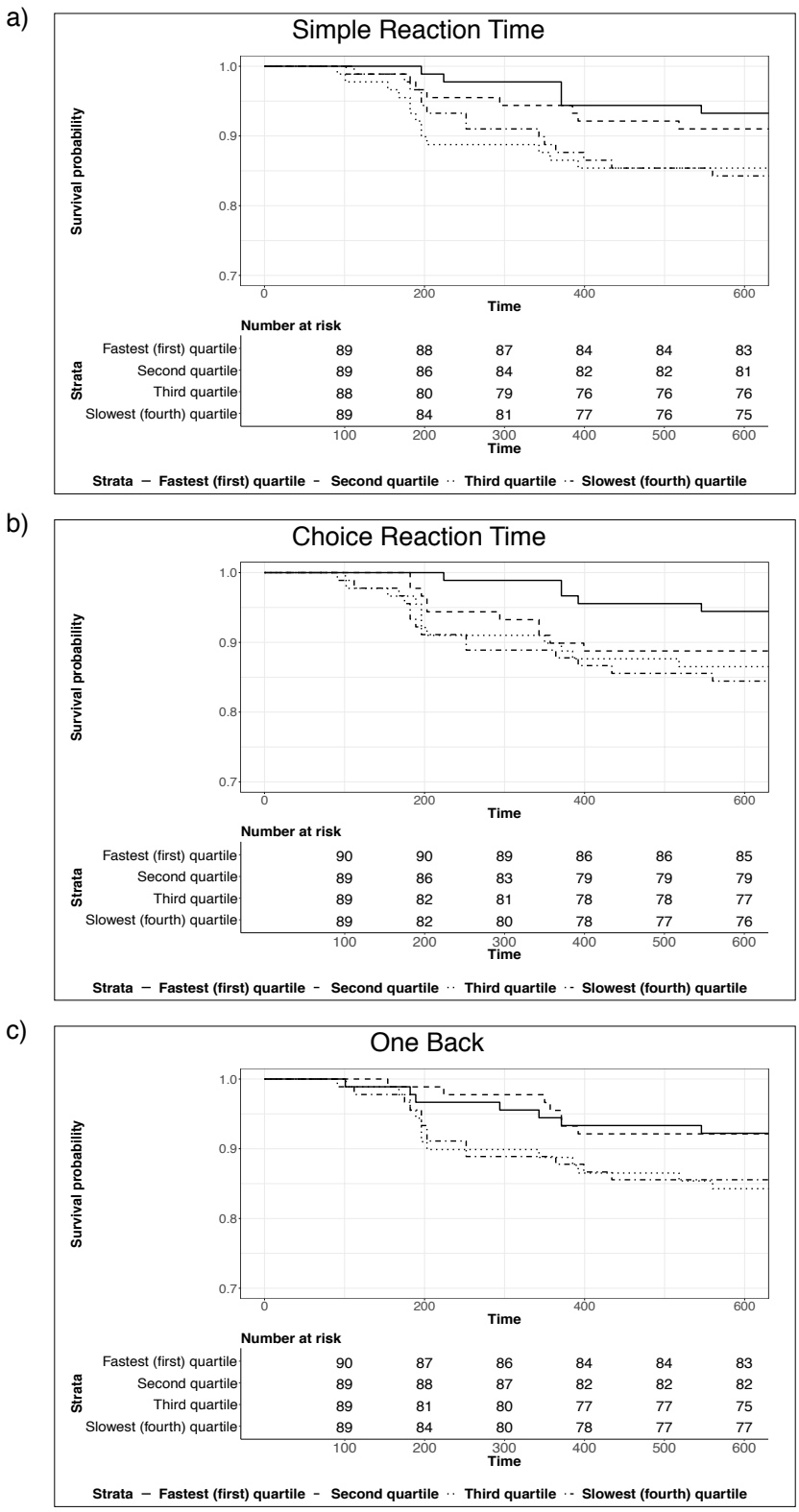

Figure 1: Probability of home testing persistence based on quartiles of baseline task performance. (a) Home testing persistence based on Simple Reaction Time task performance; (b) Home testing persistence based on Choice Reaction Time task performance; (c) Home testing persistence based on One Back task performance.

Acceptability

Acceptability surveys were completed by 438 (97.3%) participants at baseline. Participant rated acceptability of the cognitive tasks was high and is summarized in **table 2.**

Table 2: Baseline acceptability of the MSReactor tasks

	Not anxious at all	**Not anxious**	**Neutral**	**Slightly anxious**	**Very anxious**	**Total**
Did the test make you anxious?	227 (52%)	63 (14.5%)	120 (27%)	24 (5.5%)	4 (1%)	438
	Very much	**A little bit**	**Neutral**	**Not really**	**Not at all**	**Total**
Did you enjoy the test?	79 (18%)	126 (28.8%)	222 (51%)	10 (2%)	1 (0.2%)	438
	Very interesting	**A little bit interesting**	**Neutral**	**Not that interesting**	**Very boring**	**Total**
Did you find the test interesting?	22 (5%)	39 (9%)	317 (72%)	48 (11%)	12 (3%)	438
	Very happy	**Happy**	**Neutral**	**Unhappy**	**Very unhappy**	**Total**
Would you be happy to repeat the test?	197 (45%)	111 (25%)	116 (26%)	7 (2%)	7 (2%)	438
	Too short	**Slightly too short**	**About right**	**Slightly too long**	**Too long**	**Total**
What did you think about the duration of the test?	3 (0.5%)	15 (3.5%)	409 (93%)	7 (2%)	4 (1%)	438

Quality of Life, Depression and Anxiety

Most participants completed baseline QoL (95.5%), depression (94.9%) and anxiety surveys (94.9%). QoL scores correlated weakly with reaction time on the SRT ($r=-0.26$, $p<0.001$), ChRT ($r=-0.29$,$p<0.001$)and OBK ($r=-0.26$,$p<0.001$)). PHQ-9 scores correlated weakly with reaction time on the SRT ($r=0.24$,$p<0.001$), ChRT ($r=0.26$, $p<0.001$)and OBK ($r=0.26$, $p<0.001$). PSWQ scores did not significantly correlate with performance on any of the speed measures ($p>0.05$).

Cognitive performance and baseline predictors

Baseline task performance was independently associated with EDSS and age, but not disease duration **(table 3).** For the SRT, ChRT and OBK tasks, each 1 step increase in EDSS resulted in slowing of the transformed reaction times by between 0.015 and 0.02 log milliseconds, translating to a prolonging of between 13 and 25ms in reaction time per step of increase in EDSS. For each year increase in age, reaction times slowed between 0.001 and 0.002 log milliseconds (or 1 and 3.2ms). Sex was associated with faster reaction times on the OBK task only, with males performing 0.029 log milliseconds (or approximately 44ms) faster than females.

Table 3: Multivariable linear regression estimates of the association between baseline patient characteristics and the performance on the MSReactor tasks

MSReactor task	**Independent variable**	**ß**	**95% Confidence Interval**	**p-value**
Simple Reaction Time	Intercept	2.4963151		
	EDSS	0.018	0.013 - 0.024	<0.0001*
	Age	0.0014	0.0004 - 0.0024	0.006*
	Sex (male)	-0.138	-0.14 – 0.01	0.51
	Disease duration	0.0005	-0.0008 - 0.002	0.46
	Intercept	2.6872189		
	EDSS	0.017	0.012 - 0.022	<0.0001*

Choice Reaction Time	Age	0.001	0.0002 - 0.002	0.018*
	Sex (male)	-0.01	-0.03 – 0.005	0.16
	Disease duration	0.0003	-0.0008 - 0.001	0.54
One Back	Intercept	2.8354256		
	EDSS	0.016	0.01 - 0.02	<0.0001*
	Age	0.002	0.0008 - 0.003	<0.001*
	Sex (male)	-0.029	-0.05 - -0.009	0.005*
	Disease duration	0.0003	-0.0009 - 0.0016	0.61

Learning effects and test-retest reliability

To assess learning effects and test-retest reliability, task performance was examined in MS participants who had performed up to 10 successful testing sessions. In this home-testing cohort, the median time interval between tests was 82 days between the first and second test, reducing to 31 days between the second and third test, 29 between the third and fourth test and then stabilising around 27 days between subsequent tests. In the nonparametric bootstrap fitted data, mean reaction time performance on all tests improved after baseline as evidenced by the slope of the curve being significantly different to the hypothesized mean of zero at baseline ($p<0.001$). The slope of the fitted curve stabilized rapidly, and no more learning effect was evident from the second test for the SRT task, and from the third test for the ChRT and OBK tasks respectively **(figure 2)** (One sample t-test provided in Appendix 1). The reliability of the tasks improved over time following stabilization of learning effect and the CCC for test 4 to 5 was 0.77, 0.71 and 0.83; and for tests 8 to 9 was 0.83, 0.81 and 0.86 for the SRT, ChRT and OBK, respectively **(figure 3)** (all CCC provided in Appendix 2). Mean reaction time performance on all tasks at the second clinic testing session was not significantly different than the preceding home test ($p>0.05$).

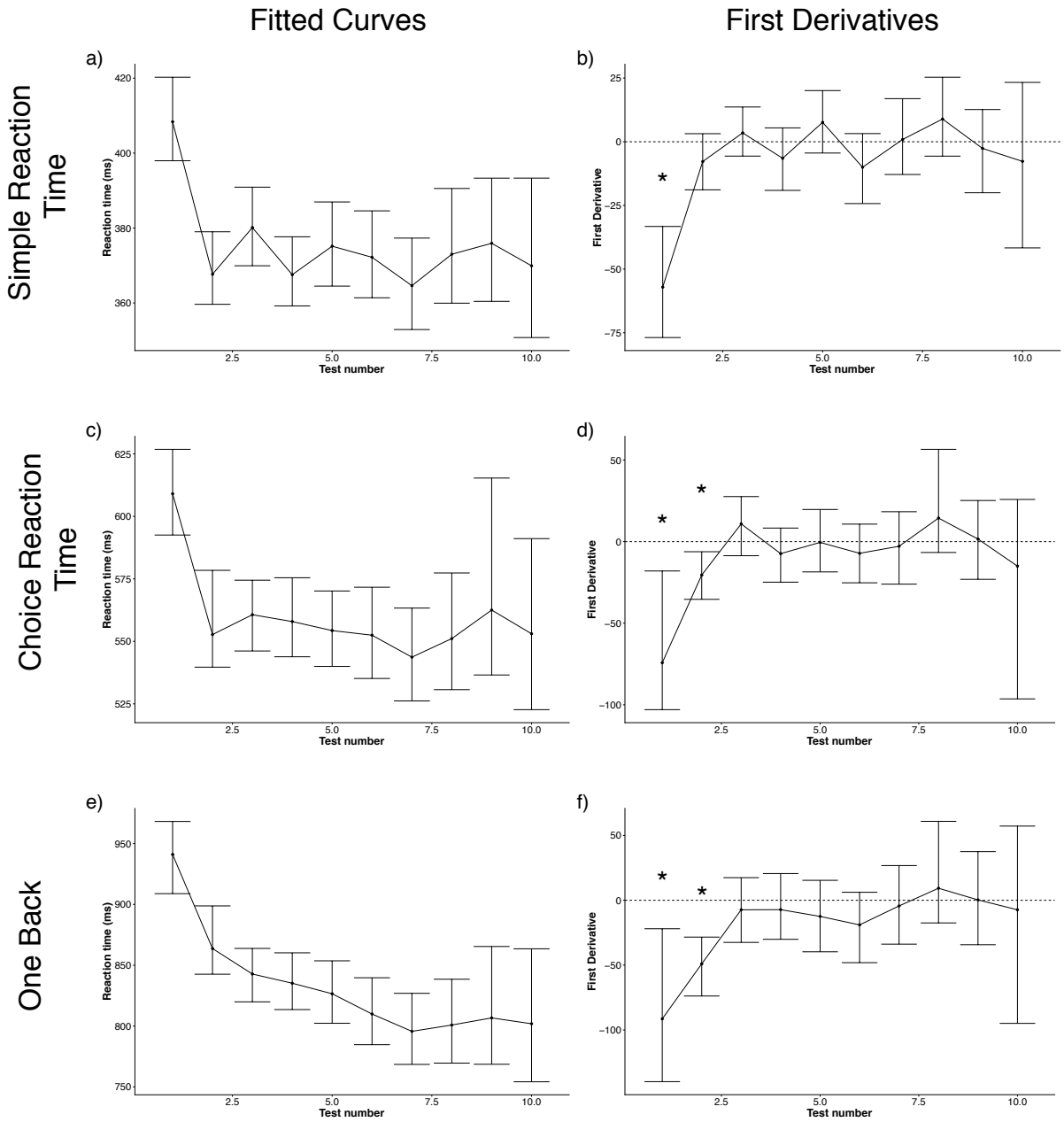

*Figure 2: Learning effects on the MSReactor tasks. Cubic splines were fitted to the distribution of the first 10 tests for each task using non-parametric bootstrap and bias-corrected confidence intervals calculated (a, c, e). The mean first derivative was calculated for each timepoint and bias-adjusted confidence intervals calculated for each timepoint (b, d, f). * indicates timepoints where H_0 is rejected ($p<0.05$) in one-sample t-test ($\mu = 0$).*

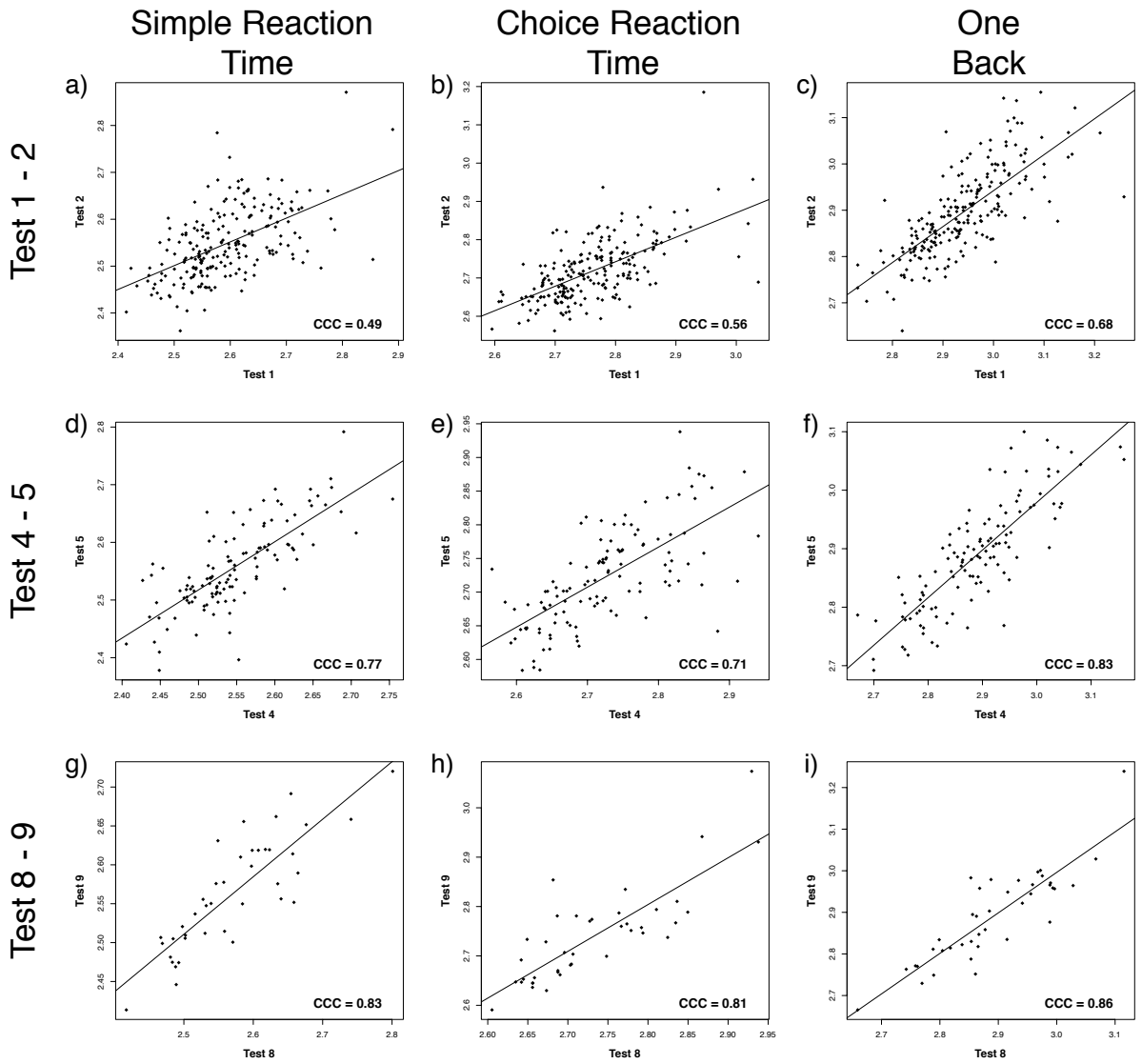

Figure 3: Test-retest reliability. The Concordance Correlation Coefficient (CCC) was calculated for performance between consecutive pairs of tests for the Simple Reaction Time, Choice Reaction Time and One Back tasks. The CCC improves over time from between test and 2 (a, b, c); to tests 4 and 5 (d, e, f) and tests 8 and 9 (g, h, i).

Concurrent validity and discriminative ability

SDMT scores correlated moderately with SRT performance (Pearson's r= -0.51, p=0.004), ChRT performance (r= -0.59, p<0.001) and OBK performance (r= -0.43, p=0.015) (**figure 4).** Disattenuated correlation coefficients were r_{dis} = -0.68, r_{dis} = -0.73 and r_{dis} = -0.50, respectively.

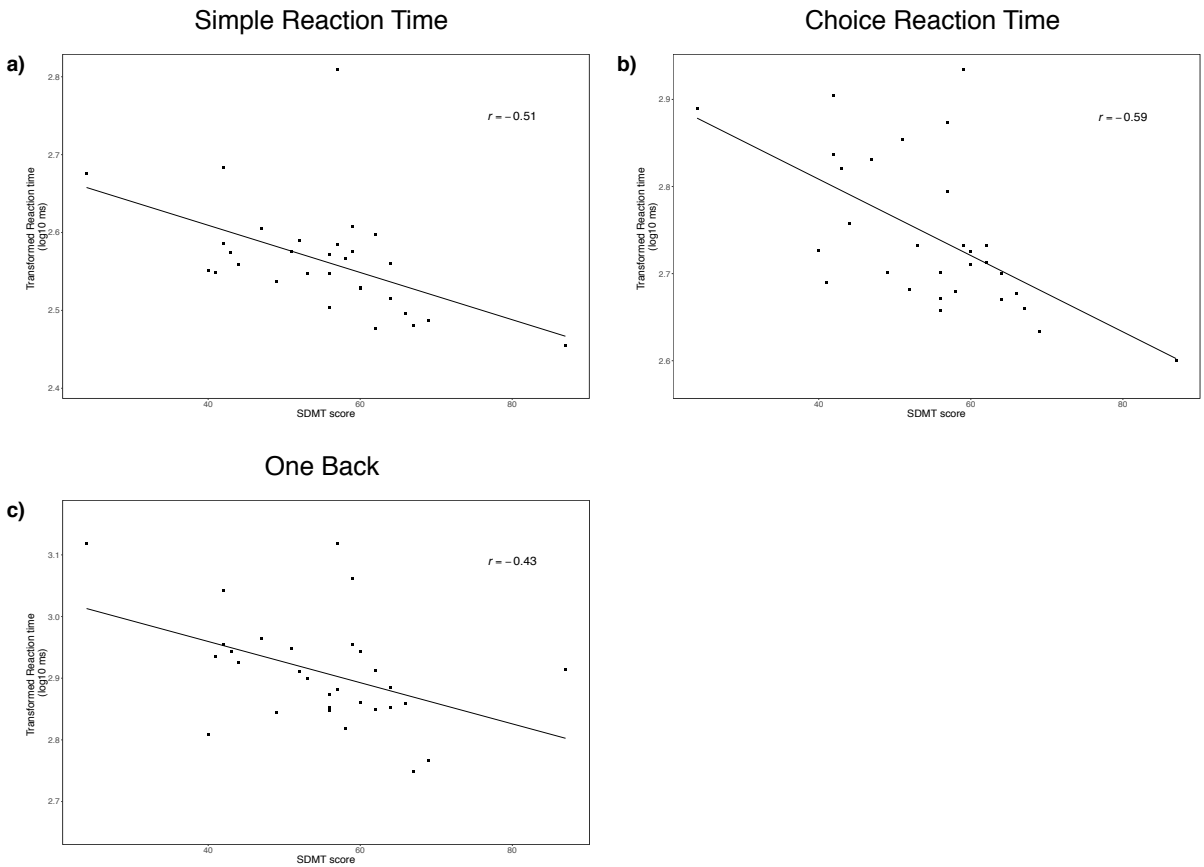

Figure 4: Correlations between SDMT and MSReactor tasks. Pearson product-moment correlation coefficient was calculated for a subset of participants who completed the MSReactor battery and the Symbol Digit Modalities Test in the same testing session. Pearsons r for the Simple Reaction Time (a), Choice Reaction Time (b) and One-back (c) tasks are shown.

MS and HC participants were well balanced with regards to age (MS mean 41.5 years (sd 11.13) and HC mean 38 years (sd 14.25)), gender (77% (23/30) female and 72% (13/18) female) and years of education (MS mean 15 years (sd 2.72) and HC mean 16.4 years (sd 2.53)) respectively. The mean baseline difference between MS and HC participants for the SRT, ChRT and OBK tasks was -59.5ms (95% CI 28 - 94ms, $p<0.001$), -89ms (95% CI 23 - 162ms, $p=0.01$) and -127ms (95% CI 21 - 249ms, $p=0.02$) respectively, independent of years of education.

Discussion

This study investigated the usability (acceptability, efficiency, stability (415)) and validity of a computerized cognitive screening platform, MSReactor. Assessing the usability of the battery is an important first step in defining its utility in the clinic setting. Any test that uses an individual's previous test scores to detect subtle change in cognition needs to be administered regularly. Factors that maintain a patient's motivation for testing are therefore critical and the task needs to be brief, non-anxiety-provoking, and reasonably interesting to perform. Participant response to MSReactor tasks were favourable, with most being happy to repeat the testing and the majority indicating that they thought the duration of the tasks was 'about right'. Only a small fraction of participants found that the tasks made them feel anxious, in contrast to prior studies with tests such as the PASAT, which is frequently reported to be aversive and stressful (283).

Implementation of MSReactor is uncomplicated and allows rapid recruitment of large groups of participants. In this study, it allowed 450 participants to be enrolled by a single, non-expert, member of the research team over 18-months at just 2 clinic sessions per week. The brief testing time of 5-15 minutes and self-administration of the battery means most participants were able to complete the testing, on their own, whilst waiting for their clinical consultation with no extra time required. This ease of use and lack of requiring a technical support person (371) is a major practical advantage which makes MSReactor suitable for use in a busy tertiary MS clinic.

The majority of participants chose to enrol and also persisted with home-testing over time. Benefits of home testing include testing in a familiar or remote environment and allows frequent testing. This can increase fidelity of serial assessments and should enable earlier detection of change. Home-testing performance over time was equivalent to repeat outpatient

clinic testing. The ability to complete testing on a range of everyday electronic screen devices reduced the barrier to remote-testing and did not affect the overall performance measures. On the other hand, disadvantages of home testing could include testing in a variable environment, technical support challenges and the possibility of tester-substitution.

Although compliance for home-testing was high during the follow up period, 40 participants (11%) chose to revert to clinic only testing. Interestingly, younger participants were less likely to persist with home testing than older participants, a difference possibly attributable to age-related lifestyle and social differences. Poorer baseline performance on MSReactor tasks was also associated with lower home testing persistence and possibly reflects lack of motivation, frustration and/or apathy (419). Identification of patients who are non-compliant with remote testing could prompt more detailed cognitive evaluation in addition to offering tailored support to improve testing persistence including increased email reminders or mobile phone optimized platforms.

Practice effects can be evident in cognitive measurement tools where regular use leads to improvements in test scores in the absence of neurological change. Although practice effects were not eliminated completely with the MSReactor computerized battery, the learning curve is steep and task performance stabilized within 2-3 retests with subsequent high test-retest reliability demonstrated. Task performance correlated only weakly with depression and quality of life scores, but not with anxiety. The ability to perform regular testing to identify and quantify the practice effects using a computerised battery is an advantage to standard tools where limited number of alternate versions restrict retest frequency. In a recent study of a computerized version of the SDMT, the Processing Speed Test (PST), Rao et al. found significant practice effects in both MS patients and healthy controls when administered across two sessions (2-3 hours apart), however the persistence of these practice effects in subsequent testing was not explored (367). Like the PST, the MSReactor tasks demonstrated excellent test-retest reliability following the second administration of the tasks, coinciding with a shorter intertest interval.

MSReactor task performance and SDMT scores were moderately correlated. The SDMT is a commonly used valid and reliable tool which correlates with lesion burden and brain atrophy (26, 199) yet despite these advantages, the SDMT remains impractical to administer in a busy outpatient clinic. Self-administered computerized cognitive batteries such as MSReactor and

the PST may be able to address this limitation. The CogState brief battery, a computerised battery employing a similar testing paradigm to MSReactor, was shown to be construct valid, with the strongest associations between the Identification task (processing speed) and the SDMT (347). Although the MSReactor cognitive tasks described here do not interrogate just a single neuropsychological construct (psychomotor (processing) speed, visual attention), the good concurrent correlations with the SDMT provide preliminary evidence of measuring comparative neuropsychological functions. Further work is planned to comprehensively validate the MSReactor battery.

The MSReactor tasks were able to discriminate between MS participants and participants without MS. Performance on any cognitive task can be influenced by demographics such as educational attainment, age and sex; thus, any meaningful interpretation of cognitive impairment from a test battery must be derived from standardised scores based on normative values. Although the ultimate aim of a screening tool such as MSReactor is to monitor for cognitive change within an individual, where demographics do not change, collection of normative data from people without MS remains a focus of current work.

This study had some limitations. Participation in the study was limited to (predominantly) participants with relapsing-remitting MS. We are now broadening the population to include Clinically Isolated Syndrome (CIS), as cognitive impairment is present in up to 30% of patients with CIS. As early intervention with disease modifying therapies have the greatest impact on disability trajectories, we predict that detection of cognitive change in periods of pre-treatment observation or during early therapy in CIS and early RRMS is most likely to improve long-term outcome.

The MSReactor cognitive battery is highly scalable, well accepted, reliable and valid, suggesting it should be evaluated further as a cognitive screening tool in MS. It is important to note that computerized cognitive batteries are not intended to replace neuropsychological testing but to act as sensitive screening tools that can prompt further clinical testing (420). Having a brief self-administered monitoring tool could also provide the treating team and the patient with an earlier indication of subtle changes or cognitive relapses. If confirmed using neuropsychological testing, this could lead to early intervention with education on coping strategies and positive efforts to maintain employability. The results from this study forms the basis of future research to define cognitive trajectories across the MS disease course, and impact of treatment change on these trajectories.

Article Information

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Author Contribution

DM, DD, HB, AVW conceived and designed the study. DM was responsible for the statistical analysis. DM, TK, DD, HB, AVW interpreted the data. DM drafted the manuscript. DM, TK, DD, HB, AVW contributed to data acquisition and edited the manuscript.

Chapter 2

The MSReactor computerized cognitive battery correlates with the processing speed test in relapsing-remitting multiple sclerosis

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Paper highlights

- All MSReactor computerised cognitive tests exhibited moderate concurrent correlations with another computerised test of information processing speed, the PST, independent of manual dexterity.
- All MSReactor computerised cognitive tests moderately correlated with future (6-month) PST scores.
- MSReactor and the PST were both moderately correlated with manual dexterity and exhibited acceptable test-retest reliability over 6 months.

Abstract

Background:

Monitoring and screening of cognitive function in the ambulatory setting requires simple, brief cognitive tests that are reproducible. MSReactor (MSR) is a web-based platform that screens psychomotor (processing) speed, attention and working memory using a game-like interface. The Processing Speed Test (PST) is a validated computerized version of the Symbol Digit Modalities test (SDMT) and component of the Multiple Sclerosis Performance Test (MSPT).

Objective:

To determine the baseline and 6-month predictive correlations between the MSReactor computerised cognitive battery and the PST.

Methods:

Prospectively enrolled relapsing-remitting multiple sclerosis (RRMS) patients completed the MSR and the PST during 6-monthly clinic visits. Pearson's product-moment coefficients with partial correlation adjustment were calculated between the PST and MSR reaction times for Simple reaction test (SRT), Choice reaction test (CRT) and One- back test (OBK).

Results:

379 RRMS patients from six tertiary MS centres in Australia were enrolled. The mean age was 40.4 years (SD 10.3) and median Expanded Disability Status Scale (EDSS) score was 1.5 (IQR 1.0 – 2.0). Most (66%) were on high efficacy disease-modifying treatment. Baseline PST

scores correlated with the MSR reaction times: SRT (R=-0.40), CRT (R= -0.44) and OBK (R= -0.47), $p < 0.05$. There was a moderate correlation between the first visit MSR and 6-month PST test for SRT (R= -0.37, $p<0.001$), CRT (R=-0.44, $p<0.001$) and OBK (R= -0.43, $p<0.001$) speed.

Conclusions:

MSR-measured psychomotor speed, attention and working memory at baseline moderately correlates with baseline and 6-month PST; suggesting overlapping cognitive processes are being tested. Six-month test-retest reliability was acceptable for both tests.

Introduction

Over the last two decades, disease-modifying therapies (DMT) have significantly impacted on disability (421) and quality of life in patients living with MS (pwMS). However, a significant gap in the monitoring and treatment of insidious cognitive decline persists that can have vast consequences and affect social interactions, quality of life and employment (422, 423). Cognitive processing speed and working memory are most commonly affected (308) with processing speed being of particular interest. Processing speed may reflect decreased neuronal conduction speed and is a basic cognitive function influencing downstream processes (424, 425).

A challenge in constructing a cognitive monitoring battery is to balance brevity with accuracy, whilst providing testing across a range of cognitive domains (414). Moreover, an ideal cognitive battery should also have a short administration time, without the need for expert administration, have pan-cultural applicability, automated scoring and be sensitive to subtle cognitive changes (153). Computerized, web-based, cognitive tests may be able to efficiently monitor for cognitive changes (348) in select domains and have the potential advantage of facilitating remote self-testing but require validation.

Sumowski and colleagues reviewed currently available cognitive tests used in MS and identified the Symbol Digit Modalities Test (SDMT) (90), as the monitoring test of choice in the clinical setting (267). The SDMT is a sensitive, reliable and well-tolerated test that is easy and quick to administer but with learning effects and visual scanning requirements (268). A

computerized iPad®-based version of the SDMT, the Processing speed test (PST) is available with the possible advantages of increased discriminative sensitivity (367) and excellent test-retest reliability over a short retest interval.

MSReactor (MSR), adapted from software developed by uBrain (http://ubrain.com.br), is a web-based cognitive battery that uses three brief tests of reaction speed and accuracy, with automated analysis and immediate availability of results. It can be used remotely (at home) and in the MS clinic and is well accepted by patients with high home-testing persistence, thus broadening its applicability (133). Furthermore, it correlates moderately with the SDMT, has excellent test-retest reliability and minimal practice effects with repeated use (133). In this study, we aimed to evaluate the correlations at baseline and 6-months between two computerized cognitive screening tools: the MSR and the PST.

Materials and Methods

Participants and recruitment

Relapsing- remitting multiple sclerosis (RRMS) patients were prospectively recruited between December 2017 until June 2019 from six tertiary MS clinics across Australia. All participants were enrolled into the Australian arm of the IMPROVE-MS study and the MSBase Registry. We included patients with a Clinically Isolated syndrome or RRMS, Expanded Disability Severity Scale (EDSS) < 4, disease duration of less than 15 years, aged >18 years with internet access and a valid email address. Patients with significant visual or upper limb impairment that could affect ability to effectively perform the computerized tests or participate in the manual dexterity test (MDT) were excluded. Known cognitive impairment due to MS or another condition, or a neurologist-confirmed MS relapse within 30 days of the testing date were other exclusions. Written informed consent was obtained from all participants.

Study design

All participants completed both the MSR and the Multiple Sclerosis Performance test (MSPT) (368) during their routine clinic attendance with repeat testing occurring at approximately 6 monthly intervals. Participants were allowed to do the MSR test at home between clinic visits, but only the supervised clinic visit tests were included in this study. Anxiety and depression were assessed using the Penn State Worry Questionnaire (PSWQ) and the Patient Health Questionnaire (PHQ-9) respectively (416, 417). Quality of life was assessed using the Multiple

Sclerosis Quality-of-Life Score (MusiQoL) (418). All evaluations were administered on an iPad® with headphones to limit ambient noise.

MSReactor testing

The MSR consists of three tests: Simple reaction test (SRT), Choice reaction time (CRT) and One Back Test (OBK) that has been previously described (133). In brief, cognitive domains assessed by MSReactor include psychomotor (processing) speed (SRT), visual attention (CRT) and working memory respectively (OBK). All participants performed one or two practice tests prior to their recorded baseline and repeat test. In the SRT, participants were required to press a 'Yes' button as soon as they detected a yellow soccer ball appearing on the screen. In the CRT, participants pressed 'Yes' for a red ball and 'No' for a black ball appearing. The OBK tested working memory by asking participants to press 'Yes' if the face-up card shown was identical to the one shown immediately prior and 'no' if not. Outcome measures were the mean reaction times for each test measured in milliseconds. Results were uploaded to the msreactor.com web database where graphed and tabular results were immediately available to the treating physician and patient.

Multiple Sclerosis Performance Test (MSPT)

The MSPT is an iPad®-based disability assessment tool that includes the PST, a 25ft walking speed test and the manual dexterity test (MDT) using dominant and non-dominant hands (368). In the PST, the participant is shown a symbol key with matching symbols and numbers. After a practice test, they were presented with a series of rows of 15 symbols and instructed to select numbers which matched the symbols based on the key shown by lightly touching the keyboard at the bottom of the screen containing the digits 1-9. Once a row was completed a new row of symbols was presented and the test continued for 2 minutes, after which the total number of correct responses was tallied. The key was regenerated for each test to reduce the effects of visual memory. In the MDT, participants transferred 9 pegs from the starting row into a grid of 9 holes as quickly as possible and then without pausing removed the pegs one at a time and returned them to the starting row using their dominant hand before touching a tablet screen upon task completion. This was repeated for the non-dominant hand. A test of visual acuity using Sloan LCLA charts was not included in the version of the MSPT used in this study.

Data analysis

Descriptive data is presented as mean values and standard deviation (SD). Baseline tests are defined as the first MSR testing the patient had ever undertaken, some of which were undertaken prior to enrollment in this study. MSR performance was measured and analysed using a base 10 logarithmic transformation of the reaction time (in milliseconds) for correct responses in each of the three tests, in order to transform the data to fit a normal distribution to allow for analysis with parametric methods. PST performance was measured as the total number of correct symbol/digit matches in 2 minutes. Correlation between performance in the MSR and PST was assessed using Pearson's correlation coefficient. To account for any differences in measurement error between the two tests, the latent correlations were examined by calculating the disattenuated correlation coefficient (426) using the formula $r_{xy}/\sqrt{r_{xx}r_{yy}}$ (where r_{xy} represents correlation between MSR and PST and r_{xx} and r_{yy} represent the concordance correlation coefficient (CCC) for the MSR and PST respectively). The CCC for each of the MSR tests and PST were calculated for the first and second test of each test (at 6-months) (427). Six-month correlations were assessed using correlation analyses between the baseline MSreactor test and the 2nd visit test (ie. at 6 months) PST. The effect of manual dexterity on the performance over 6 months for each test was assessed by comparing the linear regression coefficients of a model including MDT change as an explanatory variable to one excluding MDT change (428). Correlation between the batteries and depression, anxiety and Quality of Life (QoL) scores, MDT, EDSS and disease duration were assessed using Pearsons *r*. Linear mixed models were fitted using the R package "lmerTest" to examine changes in MSR reaction times and PST correct responses over time, with individual ID treated as a random effect (429).

Results

Demographics

379 MS patients were enrolled in the study. Seven participants were excluded due to baseline tests within 30 days of a MS relapse **(Figure 1).** Patient characteristics are summarized in **Table 1**. The median EDSS score was 1.5 (IQR 1.0 – 2.0) with the majority on higher efficacy DMT (66%). The mean disease duration for the cohort was 7.3 years (SD 5.4 years). There was a moderate correlation between EDSS and SRT (R= 0.33, p<0.001), CRT (R=0.30, p=0.09) and OBK (R= 0.25, p<0.001) speed. Similarly, the EDSS correlated moderately with the PST (R=-0.32, p<0.001). There was a moderate correlation between the PST and disease duration

(R= -0.23, p<0.001). There was no significant correlation between disease duration and SRT (R=0.063, p= 0.23), CRT (R= 0.096, p= 0.59) and OBK (R=0.099, p=0.06) speed.

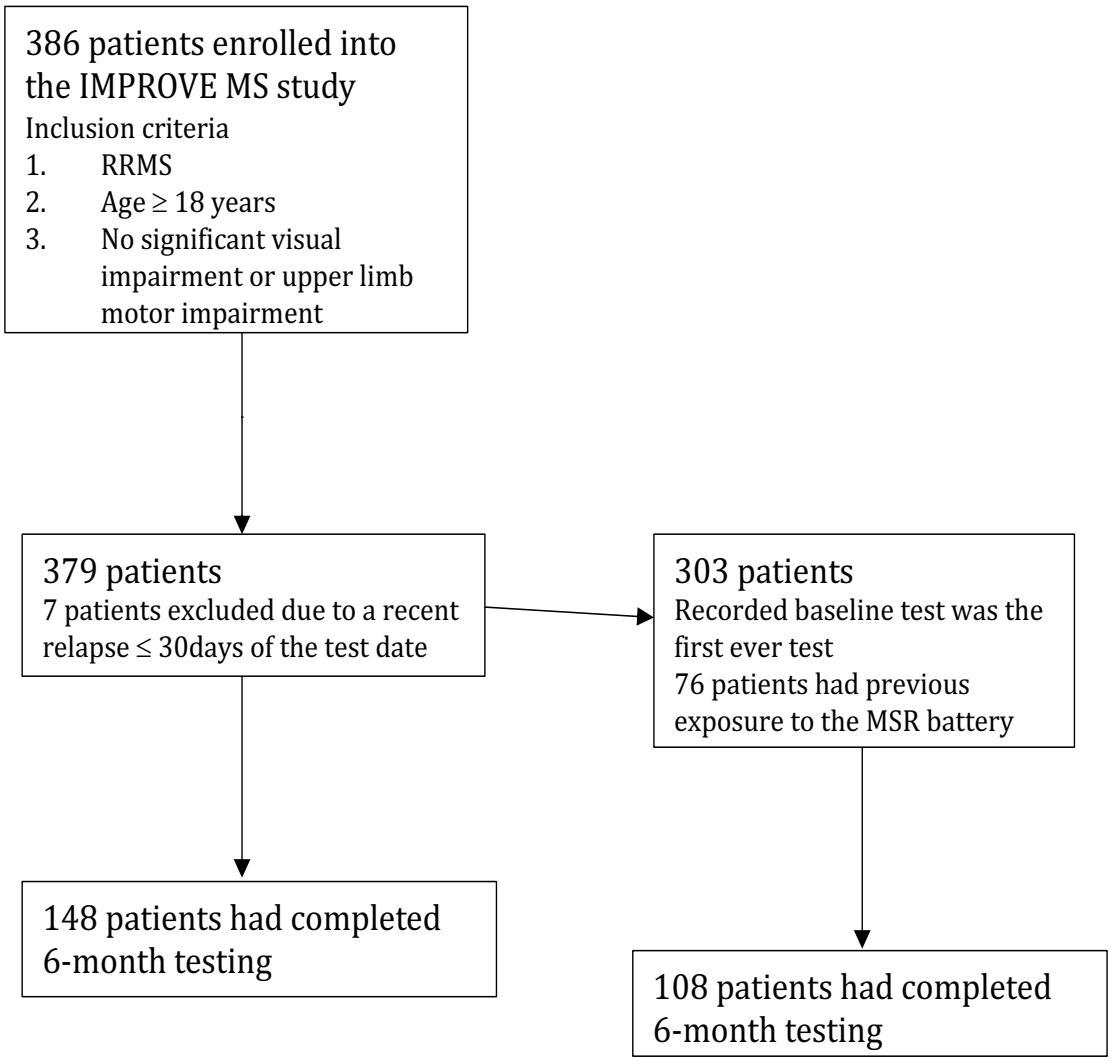

Figure 1: Flowchart showing patient cohort after inclusion and exclusion criteria.

Table 1: Demographics.

Variable	**n=379**
Age- mean years (SD)	40.4 (10.3)
Gender- females n (%)	287 (76.0)
Disease duration- mean years (SD)	7.3 (5.4)
EDSS score- median (IQR)	1.5 (1.0 – 2.0)
Disease-modifying treatment-n (%)	
Lower-efficacy DMT (%):	59 (15.5)
-Interferon beta	9 (2.35)
- Teriflunomide	14 (3.7)
- Dimethyl Fumarate	20 (5.25)
- Glatiramer acetate	16 (4.2)
Higher-efficacy DMT (%):	250 (66.0)
-Natalizumab	82 (21.6)
-Ocrelizumab	69 (18.2)
-Fingolimod	90 (23.7)
-Alemtuzumab	6 (1.6)
-Cladribine	2 (0.5)
Other DMT (%):	
-Rituximab	1 (0.26)
-No treatment or NA	70 (18.5)

Baseline correlations

Seventy-six patients out of the cohort of 379 patients had been exposed to the MSR tests prior to entering the study and 22 of these patients had also done home-testing in between clinic visits. An analysis of the complete dataset demonstrated moderate correlations between the PST and SRT (R= -0.40), CRT (R=-0.44) and OBK (R=-0.47), which were statistically significant ($p<0.001$) for tests completed in the same testing session **(Figure 2).** Test-retest reliability between the baseline and 6-month tests (mean 197.5days, IQR 175-217 days, SD 52 days) were calculated (CCC = 0.67, 0.61 and 0.67 for SRT, CRT and OBK respectively, and 0.88 for PST) and used to determine the disattenuated correlation coefficient. The disattenuated correlation coefficients R_{dis} were -0.52 for SRT, -0.60 for CRT and -0.61 for OBK.

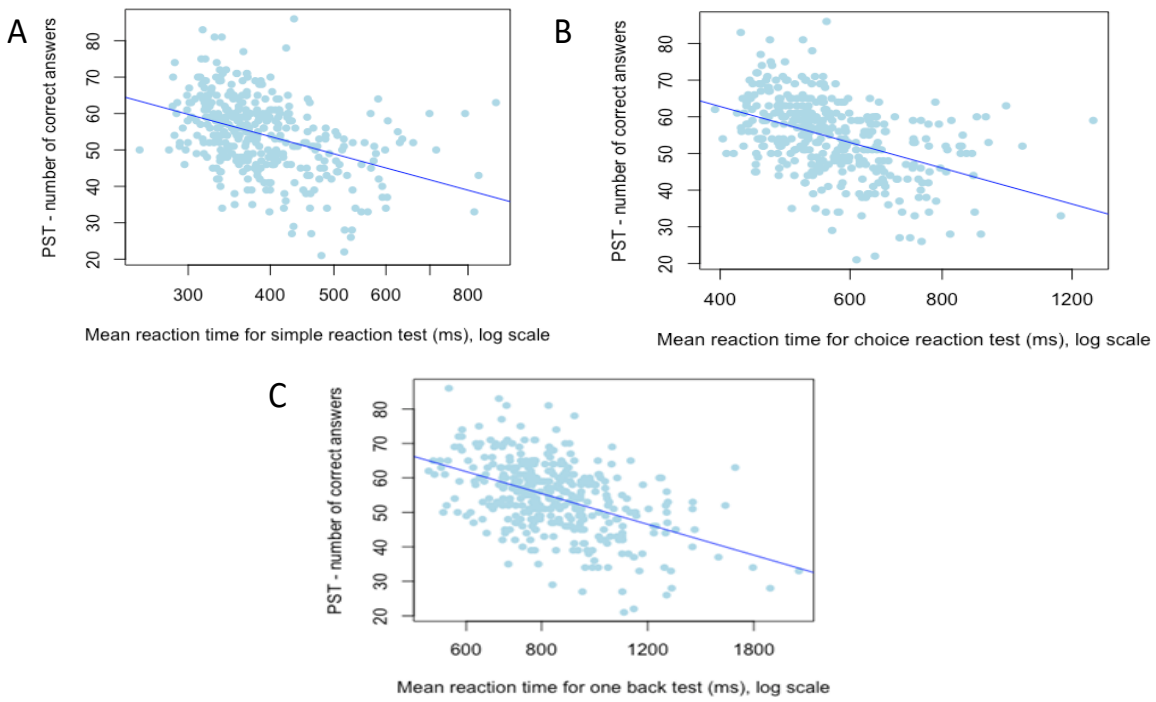

Figure 2: Plots showing the baseline correlation between MSR task performance and the PST score.

To examine the influence of increased exposure to the MSReactor tasks, a subgroup analysis of n=281 participants excluding the 98 participants who entered the study with prior trials of the MSR and 22 participants who had done home testing in-between clinics was performed. The correlation between the baseline PST and MSR tests were similar to those of the complete cohort: SRT (R=-0.43), CRT (R=-0.46), OBK (R=0.47), p<0.001.

Manual dexterity

There was a moderate correlation between the MDT and the SRT (R= 0.30, p<0.001), CRT (R=0.36, p<0.001) and OBK (R= 0.30, p<0.001). The MDT also correlated moderately with the PST (R= -0.34, p<0.001). The effect of manual dexterity on the baseline correlations between MSR and the PST was negligible, with correlations only changing by 0.02 (**Table 2**). The MDT speed declined over the first 6 months of testing, with a mean change of -0.68 seconds (95% CI -2.13 to 1.19 secs). The models of change for each MSR and PST test over 6 months were corrected using the MDT change with no effect found (β-coefficients before and

after correction: SRT 0.053 vs 0.052, CRT 0.0073 vs 0.0081, OBK 0.79 vs 0.79, PST 0.79 vs 0.79).

Table 2: Pearson's correlation for baseline MSR vs PST corrected for manual dexterity.

Concurrent validity at baseline	**Unadjusted Pearson's**	**Adjusted Pearson's for MDT (partial correlation)**
SRT vs PST	-0.40	-0.38
CRT vs PST	-0.44	-0.42
OBK vs PST	-0.47	-0.45

Six-month correlations between MSR and PST

Six-month correlations were determined between first MSR tests and the second visit (approximately 6 months) PST tests in 148 patients. The median time interval between the baseline and second visit test was 193 days (interquartile range (IQR) of 175- 217 days). There was a moderate correlation between the first visit MSR and second visit PST test for SRT (R= -0.37, p<0.001), CRT (R=-0.44, p<0.001) and OBK (R= -0.43, p<0.001) speed **(Figure 3**). There was no significant change in these correlations after correcting for days between the first and second test **(Table 3).** A subgroup analysis for 6-month correlations excluding the patients with prior MSR testing or home testing in-between clinics was performed in 88 patients with repeat testing available. Results were similar to that of the complete cohort (SRT -0.39, CRT -0.46, OBK -0.42, p< 0.001).

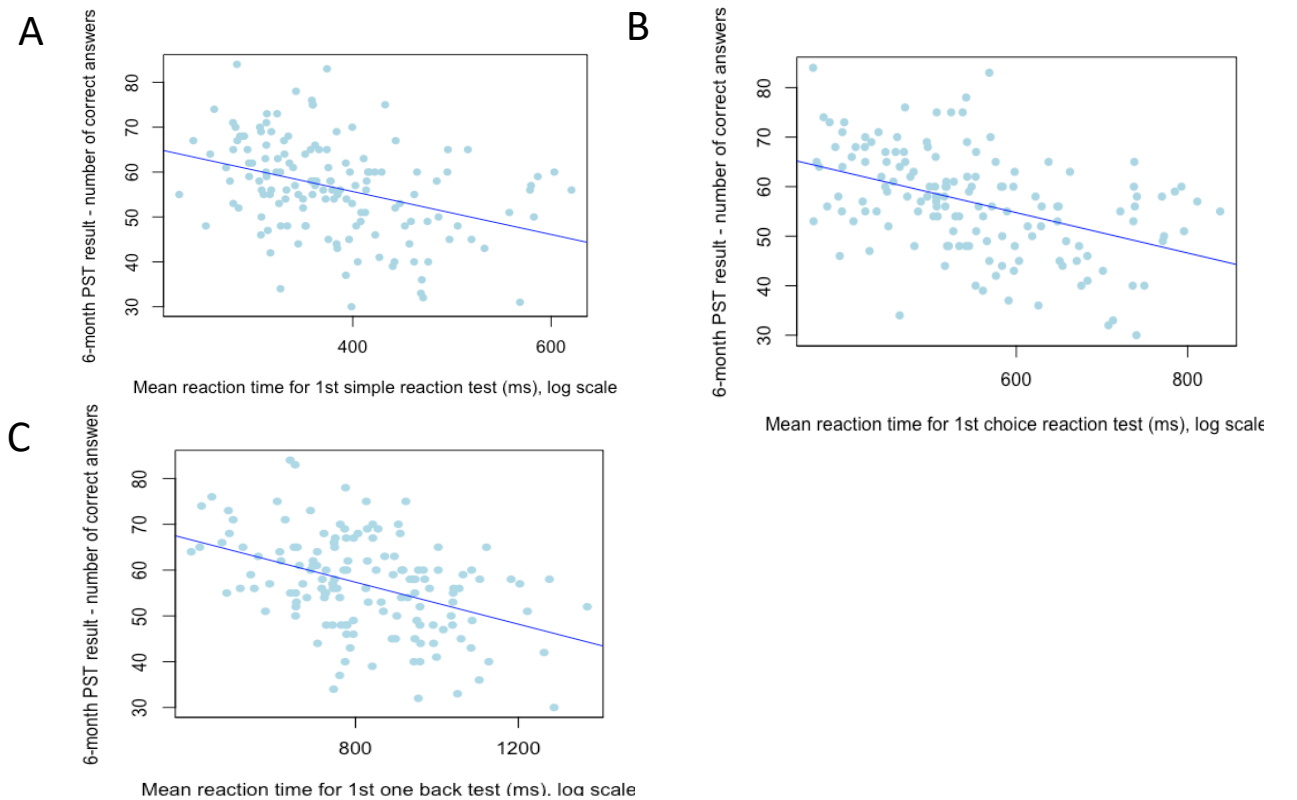

Figure 3: Plots showing the correlation between the first MSR test and the second (6-month) PST test.

Table 3: Pearson's correlation for baseline MSR vs 6-month PST corrected for manual dexterity.

Six-month correlation	**Unadjusted Pearson's**	**Adjusted Pearson's (partial correlation) for days between tests**
SRT vs 6-month PST	-0.37	-0.35
CRT vs 6-month PST	-0.44	-0.45
OBK vs 6-month PST	-0.43	-0.43

Correlation with Depression, Anxiety and Quality of Life Scores

The majority of patients completed depression (99.7%), anxiety (99.2%) and QoL scores (99.2%). Overall the depression scores were low (median score 5, IQR 2-10) with high QOL

scores (median score 78.4, IQR 70.3- 86.5). The majority of patients had low to moderate anxiety scores (median 41, IQR 27-52.5).

Depression scores correlated weakly with SRT (R=0.20, p<0.001), CRT (R=0.19, p< 0.001) and OBK (R= 0.11, p=0.04). Anxiety scores correlated weakly with SRT (R=0.13, p =0.013), CRT (R=0.14, p= 0.0086) and did not significantly correlate with OBK (R= 0.076, p= 0.15). QoL scores also correlated weakly with SRT (R= -0.20, p<0.001), CRT (R= -0.22, p<0.001) and OBK (R= -0.17, p=0.0018). The PST correlated weakly with QoL scores (R= 0.15, p= 0.0043) and did not significantly correlate with depression scores (R= -0.066, p= 0.21) or anxiety scores (R= -0.053, p= 0.32).

Sensitivity to longitudinal change

For the SRT and CRT tests, a small non-significant improvement in the rate of reaction times per year was observed (2.3% and 2.7% respectively) **(Table 4).** However, the rate of reaction time improvement for the OBK was 9.7% per year, p <0.001, consistent with a practice effect in the more difficult task. A small improvement in the number of correct answers in the PST over time was also observed but this was also not significant (p=0.31).

Table 4: Linear mixed models for MSR and PST reflecting test performance changes over time.

	SRT	CRT	OBK	PST
Slope of graph (change/year)	-2.3%	-2.7%	-9.7%	0.60 answers
p- value	0.16	0.29	<0.001	0.31
95% CI (change/year)	-5.4 to +0.9%	-7.4 to +2.0%	-13.6 to -5.5%	-0.58 to 1.75 answers

Discussion

This study compared the speed measures (reaction time) of the MSR battery and the number of correct responses given of the PST. We demonstrated a moderate correlation between MSR

speed measures and the PST number of correct responses at baseline assessments. This being consistent with correlations found in previous studies of reaction time tasks and traditional SDMT (348). The test-retest reliability was moderate for the MSR tests and high for the PST, similar to previously reported correlations of the PST (367). The relationship between the baseline MSR results and performance on the 6-month PST was moderate. Our results suggest that there is a moderate overlap in the cognitive domains tested by the MSR and PST. The PST is a single test incorporating reaction time and visual working memory, whereas in MSR, testing of these cognitive functions are separated into three different paradigms with likely different diagnostic properties.

For the SRT and CRT there is only a slight reduction in reaction times over 12 months likely reflecting normal test-retest variability. However, there was significant improvement in reaction times for the working memory, OBK task, which reflects the known prominent effects of training on working-memory tasks and thus accentuated practice effects (430, 431). We have previously shown that MSR reaches stabilization after the third test for OBK compared to the second test for SRT. In that study, the period between tests was shorter, varying between a median of 27 to 82 days (133). The long-term practice effects of the PST have not been reported to our knowledge for periods out to 6 and 12 months and our results help clarify the fact that there are no significant practice effects for this test over this timeframe. These observations are important as these batteries carry multiple test formats in an attempt to ameliorate these practice effects (271).

The effects of manual dexterity on the performance in MSR and PST were explored since both tests required sufficient dexterity skills to tap with a finger on a tablet screen and upper limb weakness or incoordination could potentially affect task performance. However, our results showed that the effect of the MDT performance was negligible both on tests completed on the same day and on the evaluation of test-retest reliability at baseline and 6 months suggesting that the variability in the coefficient is not attributed to variability in the MDT test result over time, thereby removing this potential confounder. Furthermore, MDT (or the change in MDT scores) had no effect when included in models of change over 6 months for both the MSR and PST.

Psychiatric factors are potential confounders of cognition which can be difficult to discern even with detailed neuropsychological testing. The MSR and PST both demonstrated weak or no

correlation with depression and anxiety scores. However, unexpectedly, the QOL scores only correlated weakly with performance on both MSR and PST. This is in contrast to previous claims that cognitive impairment is associated with lower patient perceived mental QOL, more so than the EDSS (432). This may be partly explained by the overall high QOL and low EDSS scores in our cohort.

There were several limitations to this study. Firstly, the follow-up period of 6 months was relatively short. This study is continuing which will allow re-visiting of these preliminary results with a longer follow-up period. Secondly, performance on both computerized batteries may have been affected by visual factors including scanning but this parameter was not explored in our study in part due to the contrast sensitivity component of the MSPT not being available. Only clinically evident visual and physical disabilities that might affect ability to do these tests were included in the exclusion criteria however more subtle deficits were not evaluated. In addition, the impact of fatigue on test performance was also not explored, although previous studies have suggested that there is no significant relationship between perceived physical or mental fatigue on cognitive performance (433, 434). Thirdly, our study was limited to patients with RRMS, low EDSS scores and relatively short disease duration. Thus, the results were not reflective of patients with more advanced disease which may be associated with more significant cognitive deficits. Patients with higher EDSS scores may also suffer more significant motor impairments and thus perform poorer on the MDT, thus affecting MSR test performance. Furthermore, the number of patients in the cohort who have cognitive impairment is unknown as there is currently no threshold for the PST or MSR to indicate this, nor is there comparative formal neuropsychology testing available to differentiate the two groups in our study.

To summarise, both the MSR and the PST are practical cognitive screening tools which warrant further validation for use in the clinical setting. MSR and PST were moderately correlated at baseline, and MSR was moderately associated with PST test scores at 6 months. Further evaluation would require longer follow-up to determine efficacy in detecting cognitive change, correlations with other clinical measures, quality of life, productivity and treatment effects.

Article information

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Author Contribution

DM, CY, AVW conceived and designed the study. DM, CY, JS was responsible for the statistical analysis. DM, CY, JS, AVW interpreted the data. DM, CY drafted the manuscript. DM, MG, TK, TJK, JLS, BT, MB, HB, AVW contributed to data acquisition and DM, CY, JS, DD, MG, TK, TJK, JLS, BT, MB, HB, AVW edited the manuscript.

Chapter 3

Subjective versus objective performance in people with multiple sclerosis using the MSReactor computerised cognitive tests.

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Paper highlights

- Subjective performance on the MSReactor tasks weakly correlates with depression but not anxiety or quality of life.
- Subjective response speed only weakly correlates with objective changes in psychomotor processing speed; and subjective accuracy weakly correlates with objective accuracy changes on the attention and working memory task.
- People with RRMS do not reliably perceive changes in function as measured by the MSReactor computerised cognitive tests.

ABSTRACT

Background

Perceived cognitive impairment in MS is associated with adverse changes in employment capacity and aspects of daily living. Subjective cognitive performance in people with MS has not previously been compared to their objective performance on a computerised cognitive battery.

Objective

To compare the perceived and objective cognitive performance of people with MS on computerised cognitive tests.

Methods

Participants completed at least 6-monthly testing on the MSReactor computerised cognitive testing platform consisting of 3 reaction time tasks. These measure psychomotor processing speed, attention and working memory. In addition, we collected subjective cognitive performance and patient reports of depression, anxiety and quality of life. The relationship between subjective and objective performance was examined using Kendalls rank coefficient. We calculated partial correlations where subjective performance was associated with patient reported outcomes.

Results

Subjective overall performance correlated weakly with the working memory task (Tau -0.10). Subjective performance correlated weakly with depression but not anxiety or quality of life. Subjective reaction speed correlated weakly with psychomotor processing speed (Tau -0.10); and subjective accuracy correlated weakly with the attention (Tau 0.12) and working memory (Tau 0.15) tasks, respectively.

Conclusion

Participants' perception of their cognitive performance is only weakly associated with cognitive changes detected using MSReactor.

Introduction

People with MS (pwMS) commonly have cognitive impairment. Though many cognitive domains can be impacted, the most frequently impaired ones include information processing speed, executive function, working memory, and attention (308). Cognitive impairment is only moderately correlated with physical disability or disease duration (435), and often not well appreciated by the treating neurologist (91). Cognitive function is not routinely monitored in the management of MS and most clinicians rely on self-reported changes in cognition to base clinical decisions. Discrepancies between perceived or subjective cognitive impairment and objectively measured cognitive impairment are relative common in people with MS. This discordance can partially be explained by the relationship between cognition and mental health conditions (95, 96).

However, measuring changes in cognitive functioning from a previous state remains very difficult in the outpatient setting. Conventional neuropsychological testing is time and resource inefficient and cannot detect subtle changes where an individual remains within the 'normal' ranges of the tests (90). The development of brief and reliable cognitive screening tools has been recommended (90) as one of the top priorities for the management of cognitive impairment in the clinic. Computerized cognitive batteries that are reliable and sensitive to changes in broad cognitive domains show great promise in filling this monitoring gap (133). The MSReactor is a self-administered, web-based battery of reaction time tasks (133). MSReactor is easy to administer in busy outpatient clinics and is reliable and sensitive to changes over serial testing. To date, there is no literature regarding the relationship between

the subjective rating of performance and objective performance using a computerised cognitive battery. In this study, we assess the differences between perceived performances and objective performances using the MSReactor battery. In addition, we explore possible predictors of subjective-objective differences in performance including depression, quality of life and anxiety.

Materials and methods

Participants and recruitment

Adult participants were recruited from six tertiary MS clinics in Australia between March 2016 and December 2019. Inclusion criteria included: 1) diagnosis of relapsing-remitting multiple sclerosis (RRMS); and 2) no upper limb, visual or cognitive deficits precluding the use of a touchscreen device.

Approvals and informed consent

The study protocol was approved by relevant Human Research Ethics Committees and all participants provided written informed consent prior to registration on the study website and any data collection. In addition, all participants were previously enrolled in the MSBase longitudinal registry (409).

Study design

Participants were enrolled at their outpatient visit and provided with access to the secure testing website. The initial computerised cognitive battery was completed at the baseline visit and then at approximately 6-monthly intervals during routine outpatient appointments. Patient reported outcomes (PROs) were collected at each testing session immediately following completion of the cognitive tasks. PROs included subjective performance, depression (Patient Health Questionnaire-9 (PHQ9) (416), Quality of Life (QoL) (Multiple Sclerosis Quality of Life 54 (MSQoL54) (418) and anxiety (Penn State Worry Questionnaire – (PSWQ)) (417). All participants could opt to complete the cognitive tasks at home, in addition to tests completed in clinic. PROs were not administered for home-based tests. Participants completed at least one (and no more than two) practice tests prior to all recorded tests.

Disease specific and demographic data were collected by the treating neurologist during routine consultations in accordance with the MSBase minimum dataset requirements. All clinical and demographic data was then sourced via MSBase using its registered substudy function.

Computerised cognitive screening battery

The MSReactor computerised cognitive screening battery has previously been described (133). Briefly, MSReactor is a web-based battery of reaction time tasks to assess psychomotor function (Simple Reaction Time; SRT), attention (Choice Reaction Time; CRT) and working memory (One Back; OBK). For each task, participants react as fast as possible to stimuli on the screen. Reaction time speed and accuracy for each trial are automatically recorded. Clinic based tests were typically completed within 10 minutes, inclusive of PROs.

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) or median and interquartile range (IQR), as applicable. We plotted frequency distributions and contingency tables for ordinal variables. For the outcome of the computerised cognition tasks, the reaction time speed of each task performance was calculated as the mean reaction time in milliseconds (ms) of all correct responses. Accuracy for each task on the computerised battery was calculated as the mean accuracy over all responses. Subjective or perceived performance (reaction speed, accuracy and overall) for each testing session was captured electronically using a Likert scale ranging from 0 ("Much slower than usual/much less accurate than usual/much worse overall than usual") to 10 ("Much faster than usual/much more accurate than usual/much better overall than usual"). A dummy variable was created to collapse the subjective performance variable to 3 ordinal levels for analysis. Depression, anxiety and quality of life data were also captured and scored as per the published literature. Objective changes in reaction time and accuracy was defined as the difference between the result of the current test and a moving average of their previous two test scores.

We correlated the subjective rating of performance and objective changes on the SRT, CRT and OBK tasks with PRO's, using the non-parametric Kendalls Rank coefficient. Confidence intervals (95%) of the coefficient, Tau, were calculated by bootstrap (n=1000). Where subjective performance response and PRO correlated at year 1, we computed partial correlation coefficients with the depression, anxiety or QoL outcome included as covariate. To assess the possibility of recall bias of the subjective outcomes, we next examined Pearson correlation coefficients between the time interval since the previous test (in days) and the subjective measures. Analysis was performed 12 months after the initial test (year 1) to allow for

variability associated with practice effects in the initial testing phase (133). We again performed the analysis at the fifth clinic-based test, 24 months after baseline testing (year 2). All statistical analyses were conducted in R version 4.0.2.

Results

Participants

In total, 1190 relapsing remitting multiple sclerosis (RRMS) participants completed at least baseline testing on the MSReactor computerised cognitive battery. Of these, 464 also completed testing and the perceived cognitive performance survey at year 1. One hundred and seventy-one (171) of these participants then went on to complete the testing and PROs at year 2. The year 1 and 2 timepoints included data from 273 and 121 participants, respectively, who were completing home-based testing in addition to tests performed at the outpatient clinic. Age, disability, disease duration and mood at initial testing did not differ significantly from the participants who completed year 1 and 2 testing. In addition, there were no systematic differences in initial MSReactor task performances between the participants included in this study and those not included due to insufficient follow-up. Participant characteristics are found in Table 1.

Table 1: Participant characteristics at baseline.

	Baseline cohort (n=1190)	Year 1 (n=464)	Year 2 (n=171)
Sex (female n (%))	890 (75%)	351 (76%)	127 (74%)
Age (mean years (SD))	42.1 (11)	41.6 (10.8)	41.4 (10.6)
EDSS (median (IQR))	2 (1-2.5)	2 (1-2.5)	3 (1-3)
Disease duration (mean years (SD))	9.8 (7.3)	10.3 (7.6)	10.5 (7.5)
Depression (mean PHQ9 score (SD))	6 (5)	6 (5)	7 (6)
Anxiety (mean PSWQ score (SD))	39 (18)	39 (18)	39 (19)
Quality of Life (mean MSQoL score (SD))	76 (13)	75 (13)	75 (13)

EDSS, Expanded Disability Status Scale; n, number; SD, standard deviation; IQR, Inter-quartile range; PHQ9, Patient Health Questionnaire 9; PSWQ, Penn State Worry Questionnaire; MSQoL, MS Quality of Life.

Depression, anxiety and quality of life

At year 1, the depression survey score correlated with subjective overall performance, subjective reaction speed and subjective accuracy measures, respectively (Figure 1; table 2). No correlation was found between the subjective outcome measures and anxiety or quality of life at year 1. No correlation between the depression, anxiety or quality of life PROs and any of the subjective rating measures were found at Year 2.

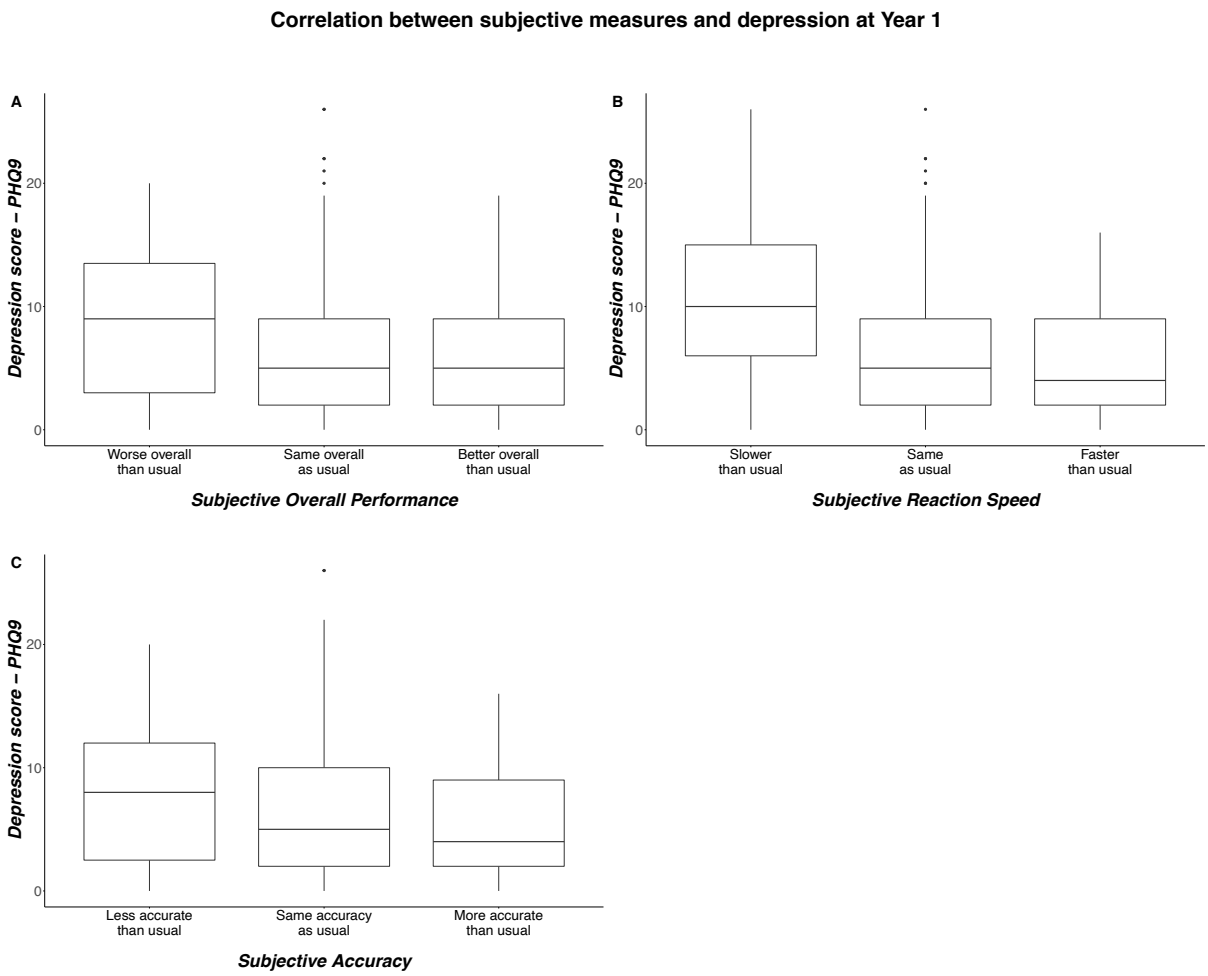

Figure 1: Correlations between subjective measures and depression at Year 1. Between subjective overall performance and depression (A); subjective reaction speed (B); and subjective accuracy and depression (C).

Subjective overall performance

At year 1, objective changes in the OBK task (tau = -0.10, 95% CI -0.17, -0.023) (figure 2C) correlated weakly with the participants subjective rating of their overall performance and this relationship was retained when the variance associated with depression was accounted for ($Tau_{partial}$ = -0.10, 95% CI -0.19, -0.01). At year 2, objective changes in SRT (Tau -0.15, 95% CI -0.26, -0.03), CRT (Tau -0.18, 95% CI -0.28, -0.06) and OBK (Tau -0.17, 95% CI -0.30, -0.06) reaction time correlated with participants subjective rating of their overall performance, respectively. The associations between objective changes in the CRT ($Tau_{partial}$ = -0.17, 95% CI -0.31, -0.03) and OBK ($Tau_{partial}$ = -0.17, 95% CI -0.31, -0.01) tasks and subjective overall performance remained after partial correlations were calculated. Table 2 contains all correlation data for subjective overall performance.

Subjective reaction speed

Participants subjective rating of their reaction speed correlated weakly with objective reaction time changes on the SRT (Tau = -0.10, 95% CI -0.18, -0.025), CRT (Tau = -0.09, 95% CI -0.17, -0.004) and OBK (Tau = -0.07, 95% CI -0.15, -0.001) tasks at year 1, respectively (figure 2D-F). Only weak correlations between the subjective rating of speed and the SRT task remained after adjusting for the effects of depression. Objective reaction time changes on the SRT and CRT tasks correlated with the participants subjective rating of reaction speed at year 2. However, the correlations no longer remained after controlling for the effects of depression. Results from all correlations with subjective reaction speed are in Table 2.

Subjective accuracy

At year 1, objective changes in accuracy correlated weakly with participants subjective rating of their accuracy in the CRT (Tau = 0.12, 95% CI 0.035, 0.20) and OBK (Tau = 0.15, 95% CI 0.07, 0.23) tasks, respectively (figure 2H-I). After adjustment for the effects of depression, evidence of weak associations between subjective and objective accuracy on the CRT and OBK tasks remained. At year 2, objective changes in accuracy for the CRT and OBK tasks again correlated with the participants subjective rating of their accuracy performance and were retained after adjusting for the effects of depression. Correlation results for the subjective accuracy outcome are in Table 2.

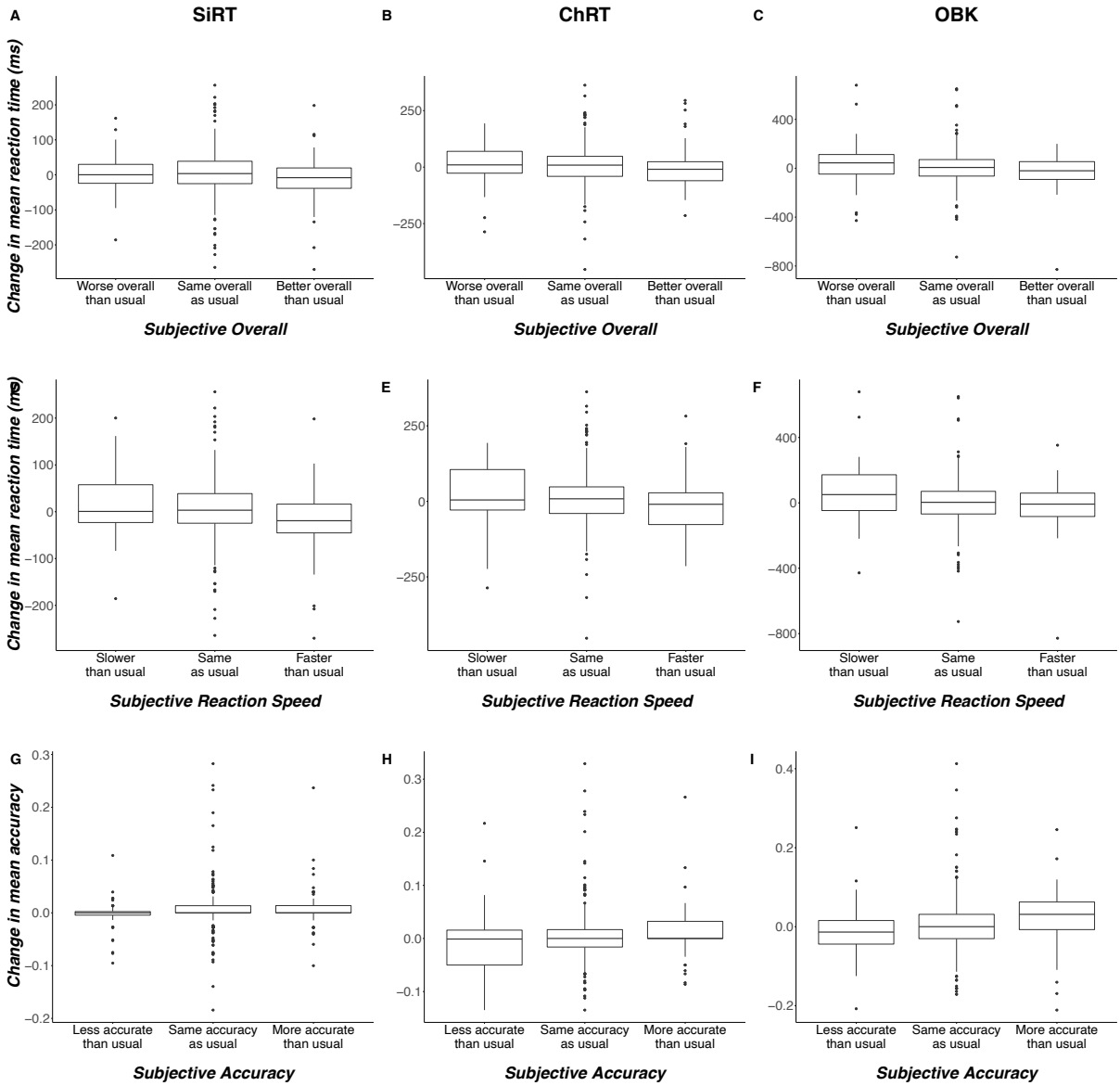

Figure 2: Subjective performance vs Objective changes on MSReactor tasks at the year 1 timepoint. Correlations between subjective overall performance and objective changes in reaction time for the SRT task (A), CRT task (B) and OBK task (C); Correlations between subjective reaction times and objective changes in reaction time for the SRT task (D), CRT task (E) and OBK task (F); Correlations between subjective accuracy and objective changes in accuracy for the SRT task (G), CRT task (H) and OBK task (I).

*Table 2: Kendall correlations between subjectively reported outcomes and objective measures. Tau partial correlations were calculated where PROs correlated with subjective measures. * denotes where confidence intervals for the estimates do not include the null hypothesis estimate.*

		Year 1		**Year 2**	
Subjective Outcome	**Objective/ PRO**	**Tau (95% CI)**	**Partial Tau (95% CI)**	**Tau (95% CI)**	**Partial Tau (95% CI)**
Overall performance	**Depression (PHQ9)**	-0.08* (-0.159,-0.005)	-	-0.03 (-0.16, 0.10)	-
	Anxiety (PSWQ)	-0.02 (-0.098,0.057)	-	0.04 (-0.07, 0.17)	-
	Quality of Life (MusiQoL)	0.002 (-0.064,0.069)	-	0.03 (-0.10, 0.15)	-
	Time interval since last test	0.06 (-0.01, 0.14)	-	-0.07 (-0.19, 0.05)	-
	SRT change	-0.06 (-0.13, 0.024)	-0.06 (-0.15, 0.04)	-0.15* (-0.26, -0.03)	-0.15 (-0.29, 0.01)
	CRT change	-0.07 (-0.145,0.002)	-0.07 (-0.16, 0.02)	-0.19* (-0.30, -0.08)	-0.19 * (-0.31, -0.03)
	OBK change	-0.10 * (-0.17, -0.023)	-0.10 * (-0.19, -0.01)	-0.17 * (-0.30, -0.06)	-0.17 * (-0.31, -0.01)
Speed	**Depression (PHQ9)**	-0.13 * (-0.205, -0.4)	-	-0.08 (-0.20, 0.06)	-
	Anxiety (PSWQ)	-0.01 (-0.09, 0.07)	-	-0.08 (-0.21, 0.05)	-
	Quality of Life (MusiQoL)	0.006 (-0.07, 0.08)	-	0.06 (-0.08, 0.19)	-
	Time interval since last test	0.07 (-0.01, 0.14)	-	-0.08 (-0.18, 0.03)	-
	SRT change	-0.10 * (-0.18, -0.025)	-0.10 * (-0.19, -0.01)	-0.09 (-0.21, 0.03)	-0.08 (-0.23, 0.07)
	CRT change	-0.09 *	-0.09	-0.18 *	-0.15

		(-0.17, -0.004)	(-0.18, 0.01)	(-0.30, -0.04)	(-0.31, 0)
	OBK change	-0.07 * (-0.15, -0.001)	-0.07 (-0.16, 0.03)	-0.13 (-0.26, 0.02)	-0.12 (-0.27, 0.04)
Accuracy	**Depression (PHQ9)**	-0.10 * (-0.174, -0.01)	-	-0.05 (-0.18, 0.08)	-
	Anxiety (PSWQ)	-0.03 (-0.107, 0.04)	-	0.01 (-0.13, 0.15)	-
	Quality of Life (MusiQoL)	0.002 (-0.069, 0.066)	-	0.08 (-0.5, 0.21)	-
	Time interval since last test	0.07 (-0.006, 0.14)	-	-0.08 (-0.20, 0.04)	-
	SRT change	0.06 (-0.02, 0.14)	0.06 (-0.03, 0.15)	0.08 (-0.05, 0.21)	0.08 (-0.07, 0.23)
	CRT change	0.12 * (0.035, 0.20)	0.12 * (0.03, 0.21)	0.13 * (0.002, 0.25)	0.13 * (0.03, 0.21)
	OBK change	0.15 * (0.07, 0.23)	0.15 * (0.05, 0.24)	0.24 * (0.12, 0.35)	0.24 * (0.09, 0.38)

95% CI: 95% Confidence intervals; SRT: Simple Reaction Time task; CRT: Choice Reaction time task; OBK: One Back task. SRT/CRT/OBK change is the correlation between objective change in performance (difference between test result and mean of previous two tests) and the subjective measures.

Time interval since previous test

The time interval since the previous test did not correlate with any of the reported subjective performance measures. In addition, the time interval since the previous test did not correlate with any of the objective changes in reaction time on the MSReactor tasks at either timepoint.

Discussion

In this study, we examined RRMS participants' perceived performance on a computerised reaction-time based set of tasks measuring psychomotor processing speed, attention and working memory. We investigated the relationship between perceived performance changes on the MSReactor tasks and objective changes in reaction time and accuracy on the same tasks. We found that self-reported depression correlated with subjective reporting of cognitive

performance on the computerised tests at approximately one year following testing initiation. Depression did not correlate with subjective measures at the year 2 timepoint. However, given the potential for depression to play a confounding role, we still adjusted for it using partial correlation calculations. We found no clinically meaningful correlations between objective performance measures on the reaction time tasks and participants subjective reporting of their performance. At years 1 and 2, objective changes in the OBK task weakly correlated with the subjective overall performance, independent of the effects of depression. Subjective reaction speed correlated weakly with objective changes on the SRT task at year 1, independent of depression. However, there was no association between subjective and objective SRT speed at year 2, perhaps indicating a lack of power to detect an effect or reflect the weak evidence of an association between these measures. Changes in CRT (year 1 and 2) and OBK performance also correlated weakly with subjective speed. However, the associations were not retained in partial correlation analysis, reflecting confounding by depression. Objective changes in accuracy in the CRT and OBK tasks correlated weakly with the subjective reports of accuracy at years 1 and 2, independent of the effects of depression.

Perceived cognitive changes in pwMS are commonly reported and have been associated with many areas of pwMS' lives, from employment outcomes (436) and work capacity (101), to sexual function (99). In one qualitative study, pwMS reported a range of concerns that they associated with changes in their cognitive functioning including forgetting names, difficulty in staying on task, difficulty in reading and learning, and difficulty in comprehending instructions or in social situations (437). Given that objective changes in cognition are not often measured, and that clinicians may rely on self-reported cognitive worsening, the accuracy of a pwMS' perception of their changing cognitive functioning is of great interest. In the quantitative studies performed to date, objective assessment of cognition using conventional tools determined if a participant was impaired or non-impaired. Diagnosis of cognitive impairment usually requires a significant change in cognitive function so it is not unreasonable that a pwMS would perceive this change, especially in the presence of comorbid depression (95). The measurement of subtle changes in cognition requires tools that can reliably measure changes in functioning from a previous state, even where the person remains within the normal ranges of conventional tests. Computerised tests of reaction speed show great promise in this area. To date, no studies in MS have assessed the relationship between perceived cognitive changes and an objective measure using a computerised test.

Our present study identified that RRMS participants do not accurately perceive their changing performance on a computerised cognitive task. We found evidence that depression may influence a pwMS perception of their changes in cognitive function, particularly in the subjective rating of their reaction speed. The choice of non-parametric method, Kendalls tau, was in part taken for the uncomplicated interpretation of the estimate. The estimate is calculated directly from the count of concordant and discordant pairs of the ranked scores; thus we can provide some clinical relevance to the estimates obtained. The most substantial relationship found was the correlation between changes in OBK accuracy and subjective accuracy on the same task (Tau = 0.24). An estimate of this magnitude requires just 38% of ranked observations to be concordant, leaving the remaining ranked observations to be discordant between the outcome measures. Hence, the relationships found in this study, if any, are weak and not clinically meaningful. Our results suggest that the MSReactor battery may detect changes in cognitive functioning below the threshold of a pwMS awareness of these changes. This observation is similar to findings in other areas of neurology, where computerised reaction time tests could detect changes in cognitive functioning preceding impairment measured with conventional tools (438).

This study had some limitations. Firstly, fewer numbers in the year 2 cohort meant we were likely underpowered to detect an association between depression and subjective outcomes. However, applying partial correlations did indeed detect some confound effects of depression. The larger estimates and wider intervals of the underpowered timepoint created some unexpected discrepancies between the year 1 and year 2 cohorts. Secondly, the lack of endpoint neuropsychological assessment meant we could not determine the extent or presence of cognitive impairment in the cohort. It is also possible that the small proportion of participants whose subjective and objective measures of cognitive functioning were concordant were indeed cognitively impaired. We, therefore, may have detected gross changes in function rather than more subtle changes. We did not include a PRO to measure cognitive fatigue. In other studies, subjective cognitive decline and fatigue are often associated (97). However, in our pilot study of using a computerised reaction time battery in pwMS we found no association with changes over 12 months on the reaction time tasks and participant-reported fatigue (153). Our study was limited to people diagnosed with relapsing-remitting multiple sclerosis. Participants with progressive forms of MS may perceive worsening of their cognitive functioning due to a greater cumulative disease burden (100). Finally, we did not include any

daily functioning measures such as work productivity, which can be associated with subtle cognitive changes and would have provided some external validity to our data.

In serial testing, RRMS participants could not reliably perceive changes in their performance using a computerised reaction time battery. This finding may have clinical significance as clinicians often have no choice but to rely on patient self-reported cognitive changes to make clinical judgement decisions. Computerised cognitive batteries that can detect subtle changes in broad cognitive domains may fill the cognitive monitoring gap in MS outpatient care.

Article information

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Author Contribution

DM conceived and designed the study. DM was responsible for the statistical analysis. DM, AVW interpreted the data. DM drafted the manuscript. DM, TK, MG, JLS, TJK, MB, BT, KB, HB, AVW contributed to data acquisition and DM, TK, CZ, MG, JLS, TJK, TK, MB, BT, DD, HB, AVW edited the manuscript.

Chapter 4

Computerised cognitive measures can detect reaction time slowing and predict disability progression in relapsing remitting multiple sclerosis

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Paper highlights

- Modelling of serial data collected with MSReactor can identify discrete longitudinal RT change trajectories.
- Participants classified into a worsening trajectory were at greater risk of sustained RT slowing.
- Participants classified into a worsening trajectory in the attention and working memory tasks were at greater risk of disability progression.
- Participants could be assigned into predicted trajectories after just 5 tests with between 64% and 89% accuracy.
- Slower baseline reaction time, age and disability predicted assignment into a worsening longitudinal RT trajectory.

ABSTRACT

Objectives

To identify discrete longitudinal reaction time trajectories in relapsing remitting multiple sclerosis using a computerised cognitive battery and assess the association between trajectories of reaction time and disability progression.

Methods

All participants serially completed computerized reaction time tasks measuring psychomotor speed, visual attention and working memory. Participants completed at least three testing sessions over a minimum of 180 days. Longitudinal reaction times were modelled using Latent Class Mixed Models to identify groups of individuals sharing similar latent characteristics. Optimal models were tested for consistency using a cross-validation approach and baseline associations with class membership tested using multinomial logistic regression. Inter-class differences in the probability of reaction time worsening and the probability of 6-month confirmed disability progression were assessed using survival analysis.

Results

A total of 460 relapsing remititng multiple sclerosis patients were included in the analysis. For each task of the MSReactor battery, the optimal model comprised of 3 latent classes. All

MSReactor tasks could identify a group with high probability of reaction time slowing. The visual attention and working memory tasks could identify a group of participants who were 3.7 and 2.6 times more likely to experience a 6-month confirmed disability progression, respectively. Participants could be classified into predicted cognitive trajectories after just 5 tests with between 64% and 89% accuracy.

Conclusion

Latent class modelling of longitudinal cognitive data collected by a computerized battery identified patients with worsening reaction times and increased risk of disability progression. Slower baseline reaction time, age and disability increased assignment into this trajectory.

Keywords

Multiple sclerosis, cognition, computerized testing, processing speed, attention, working memory.

Introduction

Cognitive impairment is common in MS and can affect up to 56% of people with MS (pwMS) within 10 years after diagnosis (439). However, monitoring of longitudinal change in cognitive performance trajectories remains challenging {Damasceno:2019ik}. This is in part due to the lack of tools that detect subtle changes in cognitive performance and can be applied repeatedly during routine clinical follow up. Although highly specific for cognitive impairment, traditional neuropsychological batteries cannot reliably detect MS-associated cognitive change in the "normal" range {Sumowski:2018jk}. Shorter tests, such as the Symbol Digit Modalities Test or Brief International Cognitive Assessment for MS {Langdon:2012id} battery can be used serially. However, these tests require testing and scoring personnel, and are therefore not implemented in routine practice due to resource limits. Sumowski et al. (2018) highlighted the need for 'validated cognitive monitoring tools that can be practically and seamlessly be incorporated into the clinical MS center setting', preferably tablet based. Computerised tests that serially assess reaction times could fill the routine monitoring gap. In addition, early classification of patients into prognostic trajectories of cognitive function could indicate treatment failure, disease progression, or improve early management and treatment initiation or change.

In this study, we used the MSReactor {Merlo:2019fx} reaction time-based tasks to serially assess cognitive performance in relapsing-remitting MS patients. We then used unsupervised latent class mixed modelling to identify discrete latent cognitive trajectories. We evaluated demographic and clinical prognostic factors for classification of cases into each trajectory.

Methods

Participants and recruitment

We recruited a convenience sample of relapsing-remitting multiple sclerosis (RRMS) adult patients from four tertiary MS clinics within Australia between March 2016 and December 2019. Inclusion criteria included: 1) diagnosis of relapsing-remitting multiple sclerosis; 2) no upper limb, visual or cognitive deficits precluding use of touchscreen devices; and 3) access to an internet connected device for home-based testing.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by relevant Human Research Ethics Committees and all participants provided written informed consent prior to registration on the study website and any data collection. In addition, all participants were previously enrolled in the MSBase longitudinal registry {Butzkueven:2006dr}.

Study design

Participants were enrolled during their outpatient visit and given access to the secure testing website. We collected longitudinal cognitive data at baseline and at approximately 6-monthly intervals during routine clinic appointments. All participants could choose to complete the MSReactor tasks at home, at an unlimited testing frequency (minimum monthly testing was encouraged), in addition to the clinic-based tests. Participants completed at least one practice test prior to clinic based tests and were encouraged to also complete practice tests prior to home based testing. Participants who had completed less than three MSReactor tests or had been enrolled for less than 180 days were excluded from this analysis.

Demographic and clinical data including date of disease onset and diagnosis, Expanded Disability Status Scale (EDSS) scores, and disease modifying therapy start and end dates were collected during routine consultation with the treating neurologist in accordance with the

MSBase minimum dataset requirements. All demographic and clinical data was sourced via MSBase as a registered substudy.

Computerised cognitive screening battery

We previously described the MSReactor computerised cognitive screening battery {Merlo:2019fx}. In brief, MSReactor is a web-based, reliable and self-administered battery of reaction time tasks to assess psychomotor function (Simple Reaction Time; SiRT), attention (Choice Reaction Time; ChRT) and working memory (One Back; OBK). In each task, stimuli appear on the screen and participants react as fast as possible. Both speed and accuracy of the responses are automatically recorded. The tasks were typically completed within 10 minutes and performed on a range of electronic devices including tablets and personal computers. We also electronically captured symptoms of depression, anxiety and quality of life using patient-reported outcome measures (PROMs) on the same platform. Home-based tests excluded PROMs and were completed in approximately 5 minutes.

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) and frequency data as proportions. The speed of task performance was calculated as the mean reaction time (milliseconds, ms) for the first 30 correct responses. For this study, a sustained change in reaction time was defined as change in the mean response time between timepoints, usually baseline and a later timepoint, that remains slower than a designated threshold for the remainder of the follow up. To determine a 'baseline' test for each participant whilst minimizing the practice effects shown previously{Merlo:2019fx}, we made a number of assumptions. We first calculated the variability (SD) over each participants first 5 tests. Their baseline test was then defined as the first test within 1.5 SD of the previous test.

<u>Latent Class Mixed Models (LCMM)</u>

Longitudinal reaction times for the SiRT, ChRT and OBK tasks were modelled using latent class mixed models{Proust:2006da}. Latent class analysis is a statistical approach to model the between-individual heterogeneity and organise the study population into more homogenous clusters termed classes. This method offers the potential ability to identify divergent classes of individuals sharing similar within-class characteristics. To derive a 'core' latent class model with correct underlying model structure assumptions, we followed the framework proposed by Lennon et al. {Lennon:2018gi}.

Initially, we explored the relationship between underlying latent processes and the reaction time outcome. We fitted the LCMM of a single class with different linking functions including linear, beta cumulative distribution function or varying number of quadratic I-splines (3, 4 and 5) with either equidistant knots or knots at quantiles, respectively. We selected the most appropriate link function by comparing goodness-of-fit measures including Akaike information criterion (AIC) and Bayesian information criterion (BIC). We next fitted models with varying numbers of latent classes (1-4) and the selected linking function to the data, with the best model selected according to goodness-of-fit criteria. In order to avoid selecting overfitted models based solely on fit criteria we additionally considered model parsimony, clinically plausible trajectories and proportion of individuals assigned to trajectories (inclusion of classes with at least 5% of the study cohort used in this study) {Lennon:2018gi}.

We examined the posterior probability of individuals being accurately classified into a particular trajectory. A posterior probability of over 70% was considered acceptable {Lennon:2018gi} and proportions of individuals classified into each class is reported. All latent class models included only age as a covariate to control for age-related cognitive changes.

Validation of selected models

Cross validation was performed to assess consistency of the modelling. For each task outcome, the dataset was split (50:50) into training and test cohorts without replacement. The selected model was then fitted to each dataset independently and predicted trajectories compared at each day of follow up. We then calculated the mean root mean squared error of the difference between the estimated training and test trajectories, across 100 repetitions. The mean difference in numbers of participants assigned to each class between the training and test sets was calculated and reported with pooled 95% confidence intervals.

Minimum number of tests required to predict latent class membership

To determine the minimum number of tests required to predict class membership, we fitted the selected model to a restricted dataset of 3, 4 or 5 test observations for each individual and each task (SiRT, ChRT and OBK). We determined accuracy of the predicted class membership from the restricted models as a proportion of the final class membership for each patient (derived from the full test trajectory).

Baseline associations of class membership

We assessed baseline demographic and clinical characteristics as predictors of assigned class , using univariate and multivariable multinomial logistic regression with the largest class in each model as the reference class. We included EDSS at baseline, age at baseline, time since disease onset in years at baseline, baseline task performance and therapy use at baseline as independent variables. Disease Modifying Therapy (DMT) use was defined as high (alemtuzumab, autologous stem-cell transplant, cladribine, dimethyl-fumarate, fingolimod, natalizumab, ocrelizumab and rituximab) or low efficacy (interferon beta, glatiramer acetate and teriflunomide) and none.

Survival analyses

Survival analyses were used to assess each model for inter-class differences in probability to reach sustained changes in reaction time thresholds of 5%, 10% and 20% of baseline task performance, respectively. Cox proportional hazards modelling was used where the proportional hazards assumption was maintained. Where proportional hazards assumption was not met, accelerated failure time models with relevant distribution were employed.

Survival analyses were used to assess each model for inter-class differences in the probability to reach a 6-month confirmed disability progression, measured by the EDSS. Disability progression was defined using the 3 strata definition as described by Kalincik *et al* (2015) {Kalincik:2015gq}, with a 6-month confirmation period. Cox proportional hazards modelling was used where the proportional hazards assumption was maintained. Where proportional hazards assumption was not met we again applied accelerated failure time models with relevant distribution. Lastly, we again used survival analyses to assess the probability of reaching sustained reaction time thresholds as well as 6-month confirmed disability progression in participants assigned to class 1 across all three tasks compared to those whose class assignation was discordant between tasks.

All statistical analyses were conducted in RStudio version 1.2.1335 with the 'lcmm' package.

Data availability

Anonymised data, not published in the article, will be shared on reasonable request from a qualified investigator.

Results

Participants

A total of 1238 RRMS participants enrolled on the MSReactor testing website between 2016 – 2019. Of these, 460 completed at least 3 tests over more than 180 days following baseline identification and were included in this analysis. Characteristics of included participants are found in Table 1. In total, 3846 individual tests (observations) were included. The median number of observations per participant was 5 (range, 3 - 332) and mean follow up time was 2.2 years (standard deviation (SD) +/- 0.95 years; range 0.5 – 3.9 years).

Table 1: Participant characteristics

Patient characteristic	**Summary statistic**
Age (years) (mean (SD))	42 (10.9)
Female (n (%))	353 (77%)
Time since disease onset (years) (mean (SD))	10.8 (7.7)
EDSS at beginning of follow up (median (IQR))	2 (1-3)
Therapy (n (%))	
High Efficacy	384 (83%)
o Alemtuzumab	10 (2%)
o Autologous stem-cell transplant	1 (0.2%)
o Cladribine	5 (1%)
o Dimethyl Fumarate	31 (6.8%)
o Fingolimod	179 (39%)
o Natalizumab	127 (27.6%)
o Ocrelizumab	29 (6%)
o Rituximab	2 (0.4%)
Low efficacy	76 (17%)
o Interferon beta (beta1a, 1b, peg)	8 (2%)
o Glatiramer acetate	13 (3%)
o Teriflunomide	12 (3%)
o None	10 (2%)
o Unknown	33 (7%)

Latent class models

Estimating latent class mixed models requires an assumption of the relationship of the outcome and the underlying latent process it measures. The linking function that provided best fit to the longitudinal reaction times for the SiRT, ChRT and the OBK tasks was a nonlinear linking function consisting of 5 quadratic I-splines with nodes spaced equidistantly.

The selected models had the best fit (quantified with size adjusted BIC, AIC and entropy closest to 1), whilst retaining a meaningful proportion of participants in the smallest class (greater than 5% of the cohort).

Simple reaction time (SiRT) model

The optimal SiRT (psychomotor function) model was best described by three distinct latent class trajectories (Figure 1A). The first class, class 1, (Figure 1B) consisted of 112 (25.4%) patients, classified into a slowing cognitive performance trajectory. The majority of participants (229 (51.9%)) included in the psychomotor function latent class model were classified into class 2 (Figure 1C). The remaining 100 (22.7%) participants in the SiRT model were classified into class 3 (Figure 1D). The mean probability of an individual being classified into class 1, 2 or 3 of the SiRT model was high (91%, 92% and 93% respectively), implying most participants are assigned with high confidence. Baseline characteristics for participants included in the SiRT model including age, time since disease onset, EDSS, DMT use and baseline task performance can be found in Table 2.

Choice reaction time (ChRT) model

The optimal ChRT model (visual attention) was again best described by three distinct latent class trajectories (Figure 2A), comprising of 180 (39.4%) in class 1, 237 (51.9%) in class 2 and 40 (8.7%) participants to class 3 (Figure 2B-D). The mean probability of an individual being classified into class 1, 2 and 3 of the ChRT model was high (95%, 93% and 95% respectively), implying most participants are assigned with high confidence. Baseline characteristics for participants included in the ChRT model can be found in Table 2.

One Back (OBK) model

The optimal OBK model (working memory) was also best described by three distinct latent class trajectories (Figure 3A). The three classes described by the OBK model comprised of 173 (37.6%) individuals in class 1, 234 (50.9%) in class 2 and 53 (11.5%) in class 3 (Figure 3B–

D). The mean probability of an individual being classified into class 1, 2 and 3 of the OBK model was again high (96%, 94% and 93% respectively). Baseline characteristics for participants included in the OBK model can also be found in Table 2.

Some participants were consistently assigned to the same class across all three models. Sixty-four participants (14% of cohort) were consistently classified into class 1 by all task models, 102 participants (22%) were classified into class 2 and 20 participants (4.5%) were classified into class 3.

SiRT predicted class trajectories

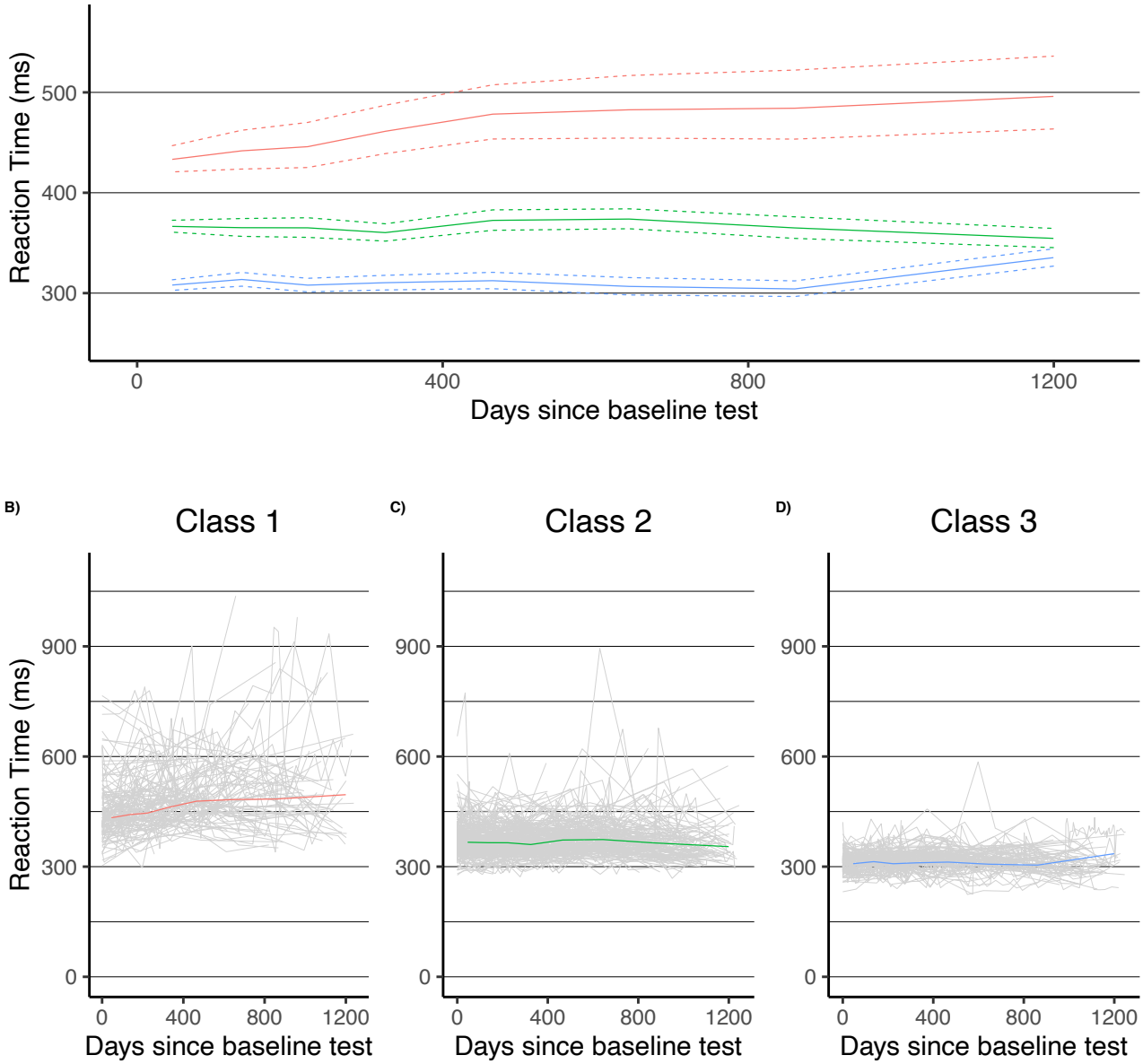


Figure 1: Longitudinal trajectories (A) in psychomotor function task (SiRT) performance (plotted with 95% confidence intervals) as identified by latent class mixed model. The lower panels (B, C, D) show the individual performance trajectories (in grey) with the predicted class trajectory.

ChRT predicted class trajectories

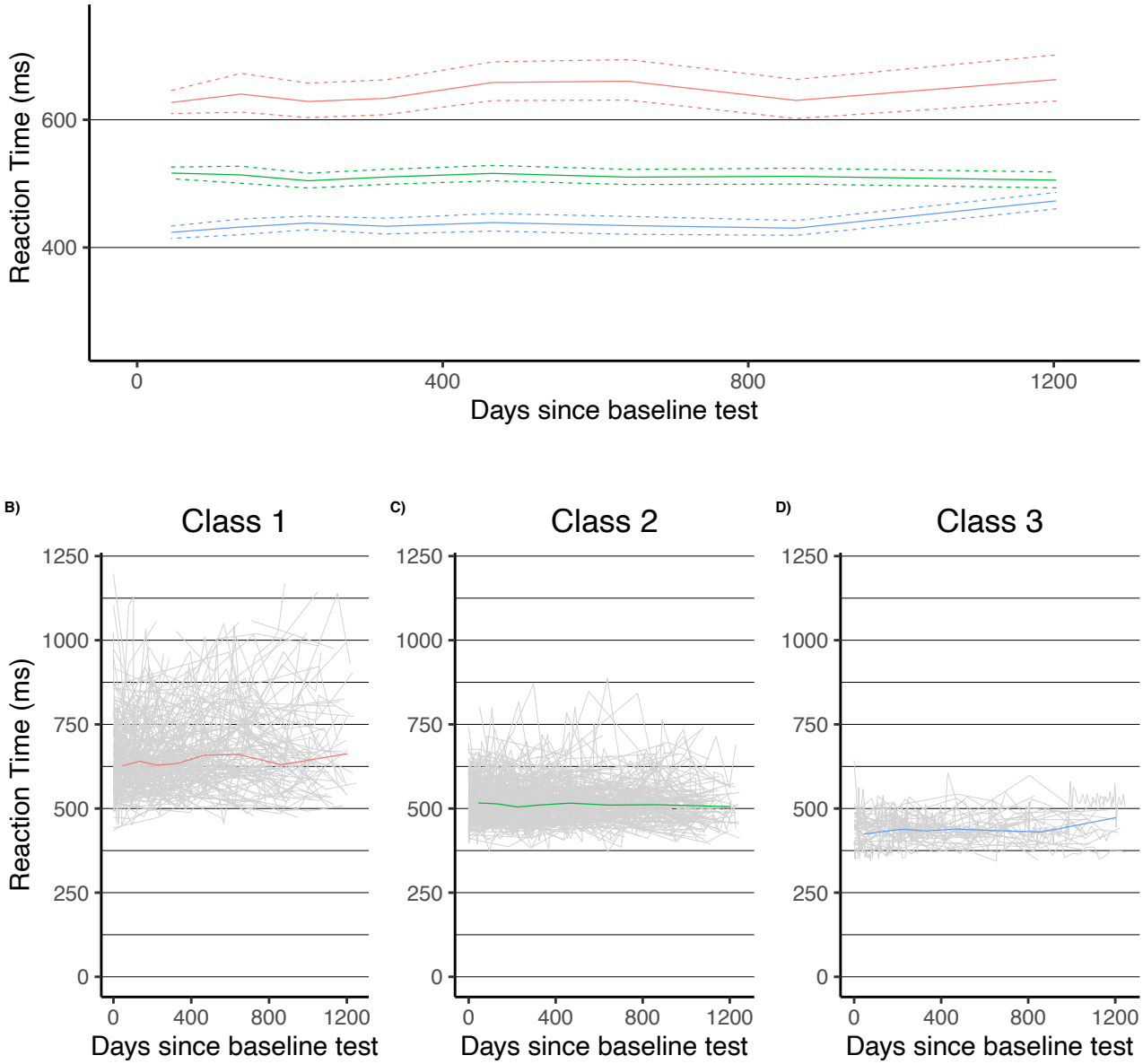


Figure 2: Longitudinal trajectories (A) in visual attention task (ChRT) performance (plotted with 95% confidence intervals) as identified by latent class mixed model. The lower panels (B, C, D) show the individual performance trajectories (in grey) with the predicted class trajectory.

OBK predicted class trajectories

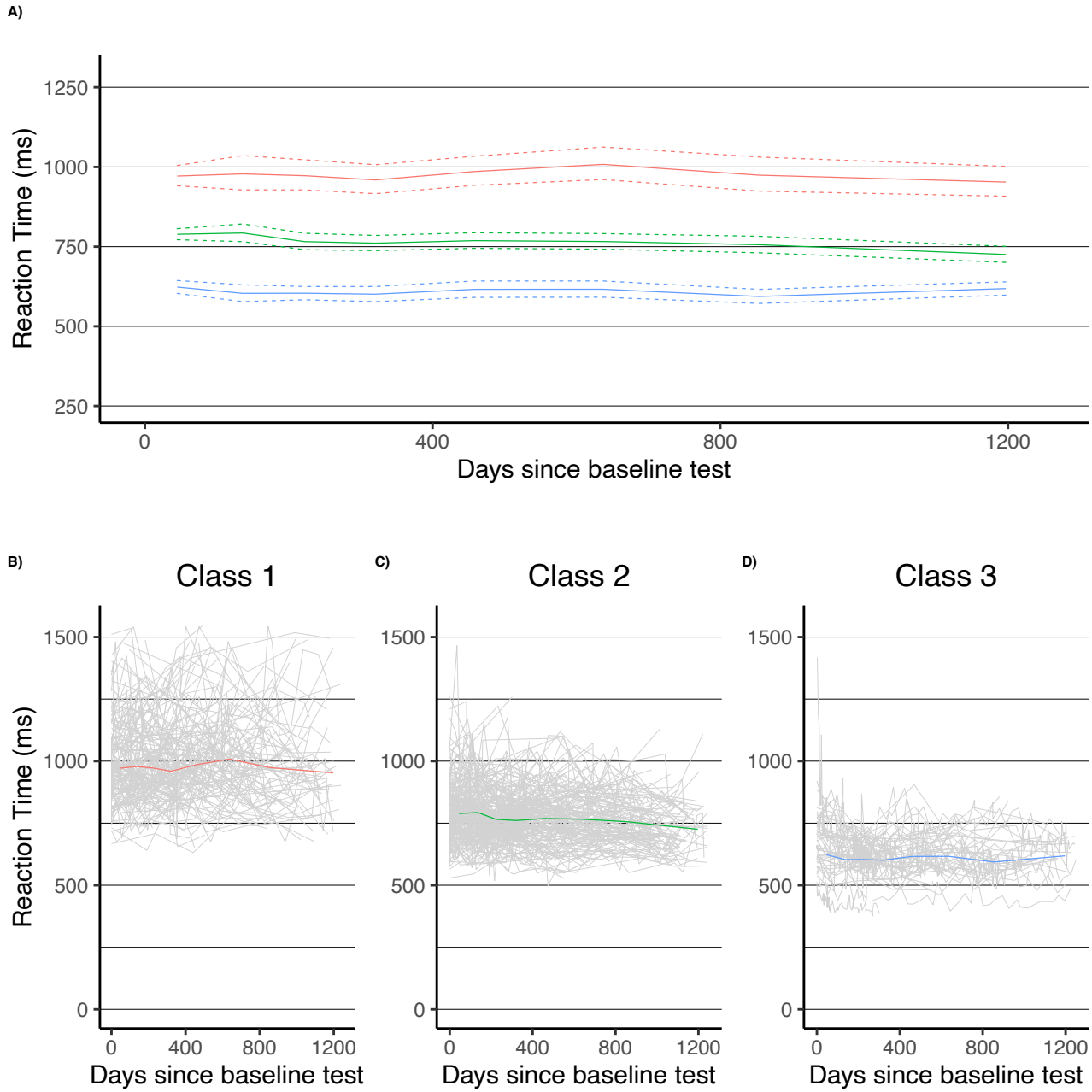


Figure 3: Longitudinal trajectories (A) in working memory task (OBK) performance (plotted with 95% confidence intervals) as identified by latent class mixed model. The lower panels (B, C, D) show the individual performance trajectories (in grey) with the predicted class trajectory.

Validation of selected models

For the SiRT latent class model, the mean root mean squared error of the difference between training and test sets for class 1, class 2 and class 3 were 68ms (95% CI 59 – 77ms), 61ms (95% CI 50 – 72ms) and 16ms (95% CI 14 – 18ms), respectively. For the ChRT model, the mean root mean squared error of the difference between training and tests sets for class 1, class 2 and class 3 were 114ms (95% CI 101 – 126ms), 95ms (95% CI 82 – 108ms) and 29ms (95% CI 27 – 32ms), respectively. For the OBK model, the mean root mean squared error of the difference between training and test sets for class 1, class 2 and class 3 were 137ms (95% CI 119 – 155ms), 138ms (95% CI 118 – 158ms) and 46ms (95% CI 37 – 55ms), respectively. For the SiRT model, the mean difference in numbers of participants assigned between training and test sets in class 1, 2 and 3 was 7 (95% CI –1 – 15), 9 (95% CI 0.5 - 17) and 7 (95% CI 2 - 11), respectively. For the ChRT model, the mean difference was 0.4 (95% CI –8 – 9), 3 (95% CI –4 – 9) and 1 (95% CI –5 – 8) for class 1, 2 and 3 respectively. For the OBK model, the mean difference in numbers assigned between training and test sets was 0.35 (95% CI –5 – 6), 1 (95% CI –4 – 5) and 1 (95% CI –3 – 5) for class 1, 2 and 3 respectively.

Minimum number of tests required to predict latent class membership

The selected models were fitted on test datasets containing either 3, 4 or 5 tests for each participant and then compared to the class assignation of the model encompassing the entire dataset. The proportion of participants in the limited test datasets assigned to the same class for the SiRT model were 81%, 86% and 89% for 3, 4 and 5 tests per participant, respectively. For the ChRT and OBK models they were 61%, 66% and 64%, and 64%, 67% and 67% for 3, 4 and 5 tests per participant, respectively.

Comparison of baseline demographic and clinical features between classes

For baseline characteristics for each class in all models, see Table 2. For all models, the largest class (class 2) was set as the reference group. In multivariable analysis of the SiRT task, slower baseline task performance, higher baseline age and higher baseline EDSS score were all independently associated with membership of class 1 over the reference class 2. In the SiRT model, the odds of being assigned to class 1 over class 2 increased by 9% for every additional year of age at baseline. For every additional 10 year of age at baseline, the odds of being assigned to class 1 over class 2 increased by 136% (OR 1.09^10). Similarly, for each millisecond increase of SiRT task performance at baseline, the odds of being assigned to class 1 over class 2 increased by 3%. For an increase of 50 milliseconds of baseline task

performance, these odds increased to 338%. In multivariable analysis of the ChRT task, only baseline task performance was significantly associated with membership of class 1.

Class membership in the multivariable analysis of the OBK task was significantly associated with baseline age and task performance. Compared to class 2, participants classified into class 1 were younger at baseline and had slower baseline task performance. Conversely, those assigned to class 3 were older and had a faster baseline task performance. Baseline EDSS, DMT efficacy group and sex were not significantly associated with class membership in the multivariable model.

Table 2: Class characteristics and multinomial logistic regression.

	Baseline variable	**Class 1 (n=112)**	**Class 2 (n=229)**	**Class 3 (n=100)**	**MN log regression (Class 2 reference)**	
					Class	**OR (95% CI)**
SiRT	Age at baseline test, mean years (SD)	44.5 (9.9)	41.4 (11.7)	40.7 (9.7)	1	1.09 (1.04 - 1.13)
					3	0.94 (0.91 - 0.98)
	Age at disease onset, mean years (SD)	32 (9.7)	31 (10.8)	30 (7.6)	Not included in multivariable model	
	Time since disease onset at baseline test, mean years (SD)	12.2 (8.9)	11 (7.5)	10.2 (7)	Not included in multivariable model	
	EDSS at baseline test, median (IQR)	3.0 (2.0-4.0)	1.5 (1.0-2.5)	1.0 (1.0-2.0)	1	1.4 (1.1 - 1.6)
					3	0.87 (0.7 - 1.08)
	Disease modifying therapy use at baseline test, % High efficacy group (count)	84% (94)	87% (199)	85% (85)	Not included in multivariable model	
	Mean SiRT performance at baseline test, mean milliseconds (SD)	459 (88.2)	372 (45.7)	318 (30.3)	1	1.03 (1.02 - 1.04)
					3	0.94 (0.92 - 0.96)
	Sex, female % (count)	85% (95)	77% (177)	68% (68)	Not included in multivariable model	

	Baseline variable	**Class 1 (n=180)**	**Class 2 (n=237)**	**Class 3 (n=40)**	**MN log regression (Class 2 reference)**	
					Class	**OR (95% CI)**
ChRT	Age at baseline test, mean years (SD)	41.6 (10.6)	43 (11.1)	41.6 (10.5)	Not included in multivariable model	
	Age at disease onset, mean years (SD)	31 (10.6)	33 (9.6)	33 (7.4)	Not included in multivariable model	
	Time since disease onset at baseline test, years (SD)	10.7 (8.3)	10 (6.9)	7.5 (5.4)	Not included in multivariable model	
	EDSS at baseline test, median (IQR)	2.5 (1.5-3.75)	1.5 (1.0-2.5)	1.5 (0.0-2.0)	1	0.99 (0.8 - 1.2)
					3	0.99 (0.7 - 1.3)
	Disease modifying therapy use at baseline test, % High efficacy group (count)	81% (146)	84% (198)	85% (34)	Not included in multivariable model	
	Mean ChRT performance at baseline test, mean milliseconds (SD)	657 (129)	529 (63)	451 (50)	1	1.02 (1.01 - 1.03)
					3	0.97 (0.96 - 0.98)
	Sex, female % (count)	84% (151)	74% (175)	58% (24)	1	1.8 (0.94 - 3.6)
					3	0.69 (0.3 - 1.5)
	Baseline variable	**Class 1 (n=173)**	**Class 2 (n=234)**	**Class 3 (n=53)**	**MN log regression (Class 2 reference)**	
					Class	**OR (95% CI)**
OBK	Age at baseline test, mean years (SD)	40 (10.4)	43 (11.2)	44 (10.8)	1	0.86 (0.8 - 0.9)
					3	1.08 (1.03 - 1.13)
	Age at disease onset, mean years (SD)	30.6 (9.5)	31 (10)	34.8 (9.7)	Not included in multivariable model	

	Time since disease onset at baseline test, mean years (SD)	10 (7)	10.3 (8)	7.4 (4.5)	Not included in multivariable model	
	EDSS at baseline test, median (IQR)	2.0 (1.0-3.5)	1.5 (1.0-2.5)	1.5 (1.0-2.5)	1	1.01 (0.8 - 1.3)
					3	0.99 (0.8 - 1.3)
	Disease modifying therapy use at baseline test, % High efficacy group (count)	84% (146)	82% (191)	79% (42)	1	0.55 (0.2 - 1.9)
					3	1.66 0.6 - 5.0)
	Mean OBK performance at baseline test, mean milliseconds (SD)	652 (130)	548 (81)	493 (69)	1	1.02 (1.01 - 1.03)
					3	0.98 (0.982 - 0.988)
	Sex, female % (count)	87% (152)	74% (173)	53% (29)	1	2.16 (0.9 - 4.8)
					3	0.7 (0.3 - 1.5)

SiRT, Simple Reaction Time task; ChRT, Choice Reaction Time task; OBK, One Back Task; n, number; SD, standard deviation; MN log regression, multinomial logistic regression; IQR, Interquartile range; OR, Odds ratio; CI, confidence intervals

Time to sustained reaction time slowing thresholds

Survival analyses showed participants assigned to class 1 in all tasks had a higher probability of reaction time slowing and being sustained above each set threshold. Across all tasks, increasing thresholds of reaction time changes resulted in increasing risk of participants in class 1 reaching thresholds of reaction time change. For all tasks, participants assigned to class 1 were between 1.8 (95% CI 1.3 – 2.5) and 2.1 (95% CI 1.3 – 3.5) times more likely to reach a 5% threshold of reaction time slowing, relative to those in class 2. In addition, participants in class 1 were between 5.3 (95% CI 1.9 – 14) and 10.1 (95% CI 2.1 – 46) times more likely to reach a 20% threshold of reaction time slowing, relative to those in class 2. Kaplan-Meier curves are shown for 5% and 20% threshold models are shown in Figure 4. Participants assigned to class 1 in the SiRT, ChRT and OBK models were 1.7 (95% CI 1.2 – 2.5), 2.2 (95% CI 1.3 – 3.9) and 4.4 (95% CI 2.0 – 9.3) times more likely to reach 10% threshold of reaction time slowing, respectively. No significant differences were seen between class 2 and 3 of any model.

For the SiRT task, compared to participants who were discordant for class assignation participants assigned to class 1 over all tasks had higher probability of reaching sustained reaction time slowing of 5% (Hazard Ratio (HR) 2.1; 95% CI 1.24-3.5), 10% (HR 2.6; 95%CI 1.3-5.0) and 20% (HR 7.3; 95%CI 2.2-23.8). For the ChRT task, compared to participants who were discordant for class assignation participants assigned to class 1 over all tasks had a higher probability of reaching sustained reaction time slowing of 5% (HR 2.5; 95%CI 1.5-4.2), 10% (HR 3.5; 95%CI 2.0-6.1) and 20% (HR 9.7; 95%CI 4.1-22.7). For the OBK task, compared to participants who were discordant for class assignation participants assigned to class 1 over all tasks had a higher probability of reaching sustained reaction time slowing of 5% (HR 2.6; 95%CI 1.4-4.6), 10% (HR 3.3; 95%CI 1.7-6.4) and 20% (HR 9.8; 95%CI 3.2-30.0).

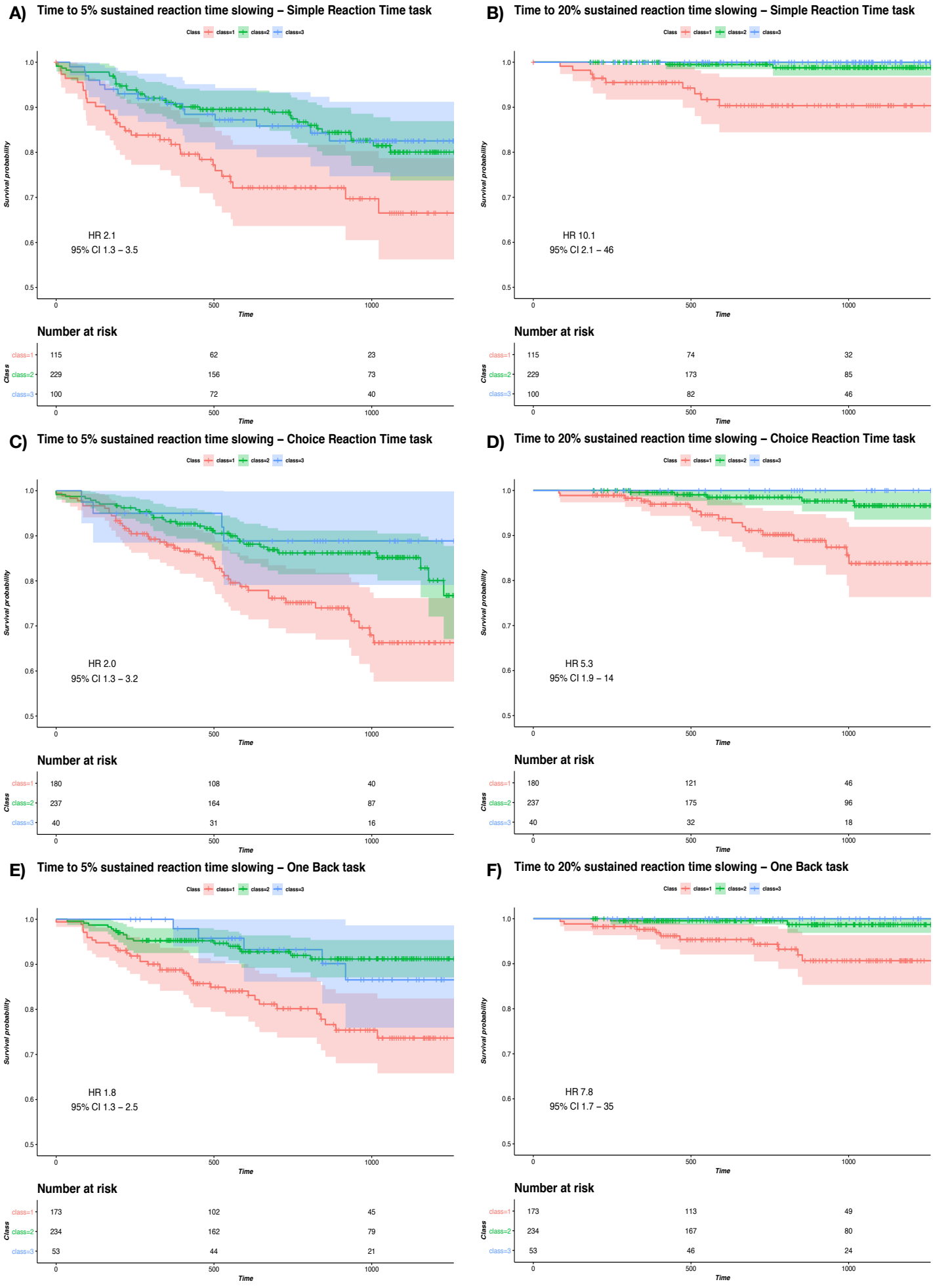

A)
Time to 5% sustained reaction time slowing – Simple Reaction Time task
Class class=1 class=2 class=3
Survival probability
HR 2.1
95% CI 1.3 – 3.5
Time
Number at risk
Class
class=1 115 62 23
class=2 229 156 73
class=3 100 72 40
B)
Time to 20% sustained reaction time slowing – Simple Reaction Time task
HR 10.1
95% CI 2.1 – 46
Number at risk
class=1 115 74 32
class=2 229 173 85
class=3 100 82 46
C)
Time to 5% sustained reaction time slowing – Choice Reaction Time task
HR 2.0
95% CI 1.3 – 3.2
Number at risk
class=1 180 108 40
class=2 237 164 87
class=3 40 31 16
D)
Time to 20% sustained reaction time slowing – Choice Reaction Time task
HR 5.3
95% CI 1.9 – 14
Number at risk
class=1 180 121 46
class=2 237 175 96
class=3 40 32 18
E)
Time to 5% sustained reaction time slowing – One Back task
HR 1.8
95% CI 1.3 – 2.5
Number at risk
class=1 173 102 45
class=2 234 162 79
class=3 53 44 21
F)
Time to 20% sustained reaction time slowing – One Back task
HR 7.8
95% CI 1.7 – 35
Number at risk
class=1 173 113 49
class=2 234 167 80
class=3 53 46 24

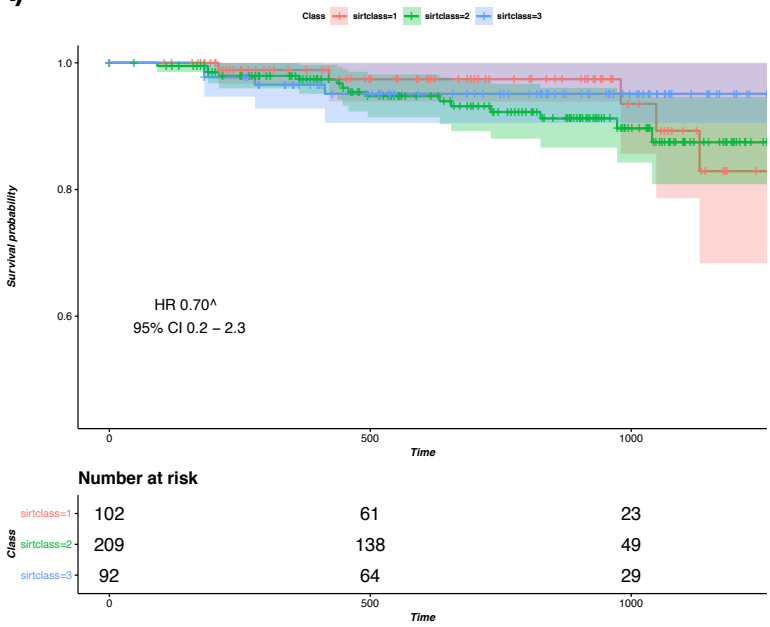
Figure 4: Time to sustained reaction time slowing threshold of 5% and 20%. (A, B) Psychomotor motor function task (SiRT); (C, D) Visual attention task (ChRT); (E, F) Working memory task (OBK). Hazard ratio (HR) is the hazard from moving from class 2 (green) to class 1 (red). No difference in hazard was found between class 2 and 3.

Time to 6-month confirmed disability progression

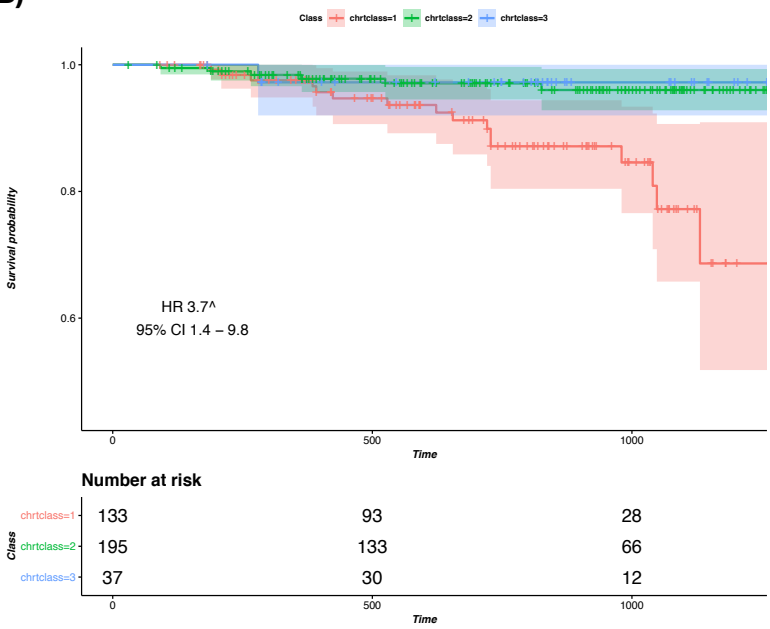
Results of the survival models for 6-month confirmed disability progression are shown in Figure 5. Participants in class 1 of the ChRT and OBK tasks were 3.7 (95% CI 1.4 – 9.8) and 2.6 (95% CI 1.1 – 6.4) times more likely to experience a confirmed disability progression than those assigned to class 2, in each respective model. There were no significant differences in disability progression between class 2 and 3 in the ChRT and OBK models. There was no significant association between assigned class and disability progression in the SiRT task.

There was no statistically significant difference in the probability to reach 6-month confirmed disability progression in participants assigned to class 1 on all tasks when compared to participants with discordant class assignation (SiRT: HR 1.6, 95%CI 0.60-4.2; ChRT: HR 2.3, 95%CI 0.90-5.7; OBK: HR 2.1, 95%CI 0.82-5.3).

A) Time to 6–month confirmed disability progression – Simple Reaction Time task



B) Time to 6–month confirmed disability progression – Choice Reaction Time task



C) Time to 6–month confirmed disability progression – One Back task

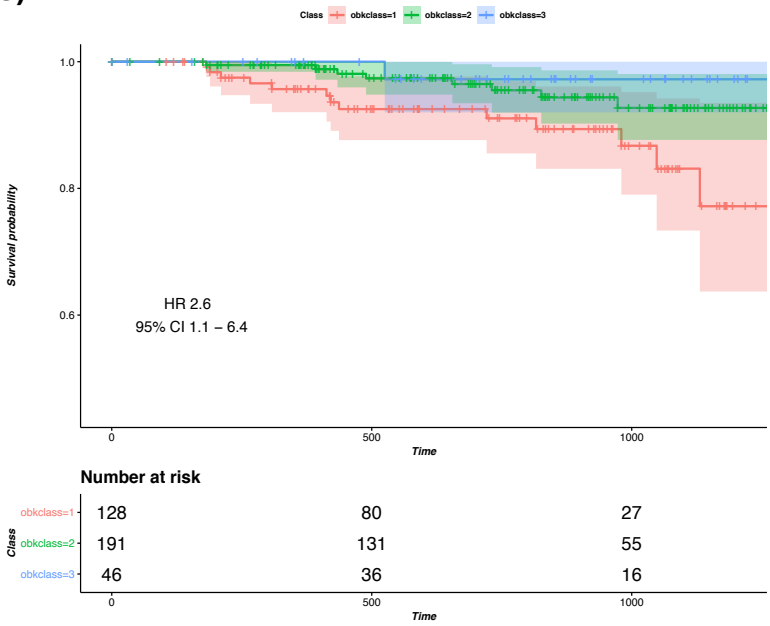


*Figure 5: Time to 6-month confirmed disability progression. (A) Psychomotor motor function task (SiRT); (B) Visual attention task (ChRT); (C) Working memory task (OBK). Hazard ratio (HR) is the hazard from moving from class 2 (green) to class 1 (red). No difference in hazard was found between class 2 and 3. ^ denotes shaped Accelerated failure time model coefficient (exp(-1 * shapeParameter * coef)).*

Discussion

In this study, we modelled reaction time trajectories in people with MS using Latent Class Mixed models to simplify heterogenous trajectories of performance into discrete 'classes' of individual trajectories. We detected a group of people with RRMS for each task (psychomotor function, visual attention, working memory), who had a high probability of marked and sustained reaction time speed changes over up to three years of data collection. In addition, using latent class modelling, we could identify a group of people with RRMS with an increased probability of experiencing a confirmed disability progression event within the period of follow up. We demonstrated that a restricted dataset of 5 repeat tests, predicts membership of the trajectory of reaction speed over 3 years. We used multinomial logistic regression and observed that baseline factors of a slower reaction time (all tasks), age (older in the SiRT model; younger in the OBK model) and higher EDSS (SiRT) predicted membership of the class most likely to experience cognitive worsening and disability worsening.

The use of latent class analysis allowed identification of 3 discrete groups of individuals in each task. Participants in all tasks were assigned to latent classes with high confidence (<90%). Despite the distinct slowing pattern of the predicted trajectory of the SiRT task, predicted latent trajectories of the ChRT and OBK tasks display a 'flat' or slightly negative slope. This may be due to the very modest posterior probability of participants not being correctly classified into class 1. Alternatively, it may reflect residual practice effects in these tasks and increased follow-up time could still see further increases in the probability of "threshold worsening" in class 1. We tested the modelling for consistency using a cross-validation approach. The SiRT modelling was most consistent in predicting latent trajectories, with training and test class trajectories being most similar (lowest mean root mean squared error). Whereas the ChRT and OBK models were more consistent in classifying participants into classes, with lower mean differences in numbers of participants classified into each class. This was consistent with the marginally higher posterior probabilities of class assignation seen with the latter models.

Our results are in line with our earlier work using seven tests of the Cogstate Brief Battery.{Maruff:2009io} In a cohort of RRMS, we showed that the simplest task, reaction time, was most likely to worsen over 12 months. The current study demonstrated a slower rate of change (in the first 12 months at least) than was shown by De Meier et al. This may reflect treatment evolution, where the early cohort was predominantly interferon-treated versus the current cohort of mostly high efficacy treated participants. It should be noted, however, that in the current study we found that therapy at baseline did not predict latent class membership. The rate and extent of cognitive decline is potentially modifiable with modern high efficacy therapies. This is likely because treatments such as fingolimod and alemtuzumab attenuate global and regional brain atrophy relative to interferon. Brain atrophy is associated with significant dysfunction in cognitive domains including working memory and executive function.

Early identification of patients most at risk of cognitive decline can inform choice of therapy or switch decisions. It can also prompt a more detailed neuropsychological evaluation and improve management of existing cognitive symptoms. Therefore, we looked at the accuracy of classification of participants into predicted latent trajectories in models with a short follow-up duration and between 3-5 follow up tests. Here, the psychomotor function task was clearly the most accurate of the MSReactor tasks with just 3 tests required to classify 81% of participants into the same class as the full model (rising to almost 90% for 5 tests). This finding is consistent with outcomes of computerised cognitive testing in healthy older adults. A series of 4 tests completed on the same day was predictive of future development of Mild Cognitive Impairment {Darby:2002gn}, though this utilised attenuation of practice effects for the prediction. Knowledge of baseline demographic and clinical features such as age, disease duration, disability and therapy use could assist in the early identification of patients at risk of cognitive changes. In this study, we compared inter-class differences between baseline demographic and clinical features. In the SiRT task, increased baseline age and slower initial task performance conferred slight increases in odds of being in the slowing trajectory. It is noted however that these slight odds are for single unit increases in baseline age or task performance. Larger increases in baseline age or reaction time confer vastly greater odds. Baseline EDSS was the strongest predictor of membership in the slowing class, with a 40% increase in odds which each unit increase in the disability score. In the ChRT and OBK tasks, slower task performance and younger age (in OBK only), but not EDSS, conferred small but significant odds of predicting membership into class 1. It is not known whether inclusion of

additional factors such as additional baseline clinical features, baseline magnetic resonance imaging (MRI) metrics, previous relapse history or even prior cognitive performance into the latent class model would improve the prediction of cognitive trajectories. This is the focus of ongoing work.

To date, cognition is rarely measured as a primary outcome in clinical trials due to low sensitivity to change and resource requirements of conventional neuropsychological testing. In this study, we could identify a group of patients with a higher probability of not just sustained reaction time slowing but also a higher probability of confirmed disability progression. Coupled with high accuracy when completing only 3 to 5 tests, this has practical implications in design of clinical trials and in particular, the identification of patients most likely to experience a cognitive and/or disability outcome.

Conventional and comprehensive cognitive assessment performed by trained neuropsychologists aim to measure cognitive impairment against a demographically adjusted normative control population yet can be impractical in clinical practice. Clinical neuropsychological assessment enables detailed profiling of cognitive impairment with valuable differential diagnostic information. On the other hand, computerised cognitive monitoring could provide non-specific but sensitive measures of changes in broad cognitive domains. The benefits of computerised cognitive screening is discussed in the literature{Merlo:2019fx}. The brevity, ease of use, home based test options, rapid stabilisation of practice-related effects and ability to deploy standardised tasks and data collection tools online, could allow regular cognitive monitoring to be implemented at scale. When used in conjunction with optional home-based testing with more than 80% uptake{Merlo:2019fx}, the MSReactor monitoring system enabled large numbers of tests to be completed over the period of follow up with high persistence and adherence to testing.

This study was not without limitations. Inclusion of baseline MRI metrics such as brain volume or lesion load in the regression analysis could have strengthened the study by potentially providing some insight into the pathophysiological predictors associated with a worsening cognitive trajectory. Secondly, only patients with RRMS were included in this study. The trajectories of cognitive change across the MS disease course, from preclinical Clinically Isolated Syndrome (CIS) to progressive forms, are of great interest and remain a key focus. Lastly, the lack of neuropsychological testing at baseline and at the end of follow up meant we are unable to describe the extent of baseline and end-of-study cognitive impairment which we predict would be greater in participants assigned to class 1.

One advantage of computerized batteries is the potential ability to measure subtle cognitive changes, even when a patient remains within the normal range of conventional tests. Even though the present study did not evaluate this hypothesis, we believe that early RRMS (or even CIS) presents the optimal period to begin cognitive monitoring at a time where subtle cognitive worsening is potentially modifiable. The clinical utility of automated self-administered cognitive assessment tools hold great promise for early identification and, potentially, modification of cognitive change in all MS phenotypes. Further work is needed to examine its effectiveness in improving cognition-associated adverse MS outcomes, such as employment and productivity measures.

Article information

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Author Contribution

DM conceived and designed the study. DM, JS was responsible for the statistical analysis. DM, JS, CZ, AVW interpreted the data. DM drafted the manuscript. DM, CB, TK, MG, JLS, TJK, MB, BT, KB, HB, AVW contributed to data acquisition and DM, CB, TK, CZ, MG, JLS, TJK, TK, MB, BT, DD, HB, AVW edited the manuscript.

General discussion, limitations, and future directions

Synopsis

There is an unmet need for efficient and reliable tools to monitor for cognitive changes in MS clinical practice. This thesis follows the implementation and longitudinal testing of a new computerised battery of RT tests into MS clinics across Australia. A better understanding of how such a tool fits within the busy MS clinic is imperative to facilitate monitoring of as many MS patients as possible. Understanding the end user impressions and experience in using the tool is important for maintaining the most effective monitoring intervention, but least disruptive to the patients, monitoring regime. Validation and sensitivity of the tool to measure clinically relevant changes in cognitive functioning is also crucial. Early detection of changes in cognitive functioning would result in a greater proportion of patients with previously undetected cognitive dysfunction being referred for more aggressive management.

The following section discusses the main findings and implications for clinical practice of the included work. I consider the limitations of the studies included in this thesis and propose potential future directions for this work.

Discussion

Monitoring of cognitive function in MS clinical practice using a computerised cognitive battery is practical and feasible.

In chapter one, I describe the implementation of the MSReactor computerised cognitive battery into two busy MS outpatient clinics. The scalability and brevity of the MSReactor computerised battery meant that we were able to enrol a large number of participants over a relatively short period of time and with minimal resources. Most participants self-administered the tasks in around ten minutes whilst waiting for their consultation and the testing was very well accepted by all participants. Most participants chose to complete home-based testing in addition to clinic testing, and adherence and persistence to testing in the community was high. We also identified factors that were associated with lower adherence to home-based testing including younger age and slower cognitive performance.

The findings from this study have some important clinical implications. Firstly, the ability to efficiently scale a self-administered cognitive monitoring program, such as MSReactor, within a busy MS outpatient clinic means that many patients (and their care team) have access to information regarding their cognitive functioning. This is in contrast to the current situation where, amongst the many aspects of MS management, changes in cognitive function may rarely be discussed. One important advantage of the MSReactor battery is the automatic scoring and collation of the tests, meaning that results are immediately available for the outpatient consultation. Very high acceptability of a screening tool, as seen with MSReactor, is crucial to the successful long-term implementation of a cognitive monitoring strategy. Cognitive dysfunction typically evolves over an extended period, so any approach for monitoring changes in function must facilitate patient adherence by being brief, enjoyable, and easy to perform. Additionally, the advantage of home- or community-based testing means participants are able to test in a familiar environment and perform a much higher frequency of testing.

MSReactor exhibits good psychometric properties for measuring changes in cognitive function over time.

The psychometric properties of the MSReactor battery as a cognitive monitoring tool were assessed. All MSReactor tests exhibited some practice effects with repeat testing, however these stabilised rapidly within three tests. Following this initial testing phase, serial MSReactor testing demonstrated excellent test-retest reliability. All MSReactor tasks were able to clearly discriminate between pwMS and healthy controls, with the psychomotor (processing) function having the largest effect size. Finally, criterion-related validity was assessed using comparisons against the conventional SDMT and an analogous electronic version, the PST. All MSReactor tasks correlated moderately concurrently with the SDMT. The MSReactor tasks also moderately correlated with the concurrent PST scores, independently of manual dexterity. In addition, the MSReactor test performances were moderately correlated with PST scores completed six months later.

The psychometric properties of the MSReactor cognitive battery have some clinical implications. We demonstrated that it exhibits good psychometric properties suited for its intended clinical role – for serial and high frequency administration to monitor for changes in broad cognitive functioning. Minimal learning effects that stabilise quickly mean that a pwMS'

baseline can be ascertained rapidly, resulting in a tool that can measure changes in function over time more quickly. The reliability or stability in repeat testing over short periods of time of the MSReactor tests is necessary to ensure confidence that any changes in function seen are not the result of inherent variability in the tests themselves. It was important to demonstrate criterion-related validity of the MSReactor battery to show that it measures some comparative neuropsychological constructs as other validated and commonly used cognitive screening tools. The moderate concurrent and predictive correlations seen between MSReactor and the SDMT and PST are concordant with the strength of correlation between the CBB and SDMT. This is indicative that the SRT, CRT and OBK paradigm of testing measure some overlapping cognitive constructs as the symbol digit tests, however some lack of correspondence remains. The magnitude of associations detected here was expected as performance on all neuropsychological tests require the coordination of multiple cognitive skills. Indeed, none of the tasks described here define a single neuropsychological construct. The lack of strong correspondence is likely due to these skills that do not overlap; for example, where the SRT task requires simple but speeded decisions, the symbol tests require more complex skills including visual memory and visual scanning.

An important characteristic of a test used to screen cognitive functioning, as opposed to diagnosing CI, is that it is highly sensitive to changes yet not so specific that it is very narrow in what it measures. Despite the lack of strong correspondence between MSReactor and the symbol digit tests in our study, all tests measure broad and commonly impaired cognitive domains in MS. In practice, any change in cognitive function detected by the screening test of choice should be first confirmed with a multi-domain cognitive battery such as the BICAMS, followed by referral to neuropsychological services if comprehensive testing is required. As a screening tool purposely designed to be integrated into clinical practice, MSReactor offers some important advantages over the SDMT or the PST such as self-administration, automatic scoring and being platform agnostic.

Subjective cognitive performance only weakly correlated with observed changes on MSReactor

In chapter three, I described the relationship between the subjective reporting of changes in cognitive function and observed changes in MSReactor task performance. In this study, I found

that depression was associated with the subjective reporting of cognitive function and this relationship sometimes confounded how a pwMS subjectively reports their MSReactor performance. However, some weak correlations between subjective performance and objective changes in MSReactor task performance were observed despite controlling for the effects of depression. At one year after initial testing, perceived RT only weakly correlated with observed changes measured in the psychomotor (processing) speed task, independent of depression. Perceived accuracy weakly correlated with measured changes in both the attention and working memory tasks; and subjective overall performance weakly correlated with changes in the working memory task.

These findings are largely consistent with the literature. In MS, discrepancies between traditional neuropsychological testing and perceived cognition are relatively common and may sometimes be explained by the presence of depression. We hypothesised that due to the ability of computerised cognitive tests to potentially detect more subtle changes in cognitive function (than conventional testing), we may also detect a lack of correspondence with perceived function. Our findings have some relevant clinical implications for using a computerised cognitive battery to monitor for changes in cognitive function as part of routine MS management. A typical outpatient consultation lasts 20-30 minutes during which time the clinician must make clinical observations, discuss results and treatment options, consider social concerns and many other aspects of MS management. They often rely on self-reported cognitive changes on which to base their clinical judgement decisions. The findings from this chapter demonstrate that RRMS participants could not reliably perceive changes in their cognitive performance, highlighting the need for frequent objective monitoring such as that achievable by the MSReactor tests. This finding does not obviate the need to include measures of subjective cognition, however. As shown here and in the literature, the presence of perceived cognitive difficulties may provide valuable insights into the psychological and everyday functioning status of pwMS.

Longitudinal MSReactor testing can identify worsening cognitive trajectories and predict disease progression

In chapter four, I modelled RTs collected with the MSReactor battery to identify distinct longitudinal trajectories of performance. Three distinct trajectories were identified for each

MSReactor task. In each task, a group of RRMS participants who were assigned into a 'worsening' longitudinal trajectory were identified. The participants assigned to this trajectory had a greater risk of sustained RT slowing of 5%, 10% and 20%; and also had a significantly increased probability of experiencing a confirmed EDSS progression event, relative to participants assigned to the other two classes. The results show that participants could be assigned to trajectories with up to 89% accuracy from just three to five tests per participant, when compared to the entire length of follow up. Finally, we show that a slower task performance, EDSS score and age at baseline all predicted assignation into the worsening trajectory.

The findings from this study have some important implications for integration of the MSReactor computerised cognitive monitoring program into MS clinical practice. The most fundamental of these is the demonstrated sensitivity of the MSReactor tests to measure subtle changes in performance over time. This offers the ability for clinicians to objectively observe and identify early cognitive dysfunction, at a time where it may still be modifiable with disease modifying therapies efficacious in slowing the rate of cerebral atrophy. Without this information, many pwMS with subtle changes in their cognitive functioning may go undetected, even with neuropsychological testing. Additionally, the baseline risk factors and the ability to assign participants into a longitudinal trajectory after just three to five tests, means the risk of cognitive decline and disability progression could be assessed early. This may strengthen the decision-making around therapy choice or even contribute to the definition of treatment failure for individual patients.

Summary

The MSReactor computerised cognitive battery is feasible to integrate into MS clinical practice. The administration of MSReactor is uncomplicated and requires minimal resources and time from the clinical care team. In addition to the ability to scale to monitor hundreds of individuals, the persistence and adherence to testing demonstrated that the battery was almost universally well accepted. MSReactor is not designed to replace conventional neuropsychological assessment which is cross-sectional and static; and where access in the public health system may be limited. MSReactor does however exhibit psychometric properties that are suitable for a serial monitoring tool designed to measure longitudinal changes in cognitive function. The MSReactor battery was sensitive to detect slowing in RTs within a

relatively short time frame. In routine MS clinical practice, there is a need for objective cognitive monitoring as the changes in function we measured with MSReactor were below the threshold at which pwMS could perceive them. This potentially offers the opportunity for earlier detection and management of MS cognitive symptoms, or referral to neuropsychological services. The ability of the MSReactor tests to identify a group of RRMS participants who are at increased risk of cognitive and disability progression also offers exciting implications for MS management. This finding potentially allows patients at higher risk of disability progression to be identified earlier and treatment escalation or switch be considered. This may also be particularly relevant in the selection of patients to participate in clinical trials. The primary outcome of interest in clinical trials of new MS therapies is invariably confirmed disability progression events. Inclusion of a test which can identify those at risk of disability and/or cognitive dysfunction progression, as well as monitor for cognitive changes throughout the trial, could result not just in cognitive change being included as a primary outcome but also significantly more efficient and cheaper clinical trials. Further, changes in cognitive function may be included in the definition of disease progression and treatment decision-making processes, and ultimately improve the management and outcomes of people living with MS.

Limitations

This body of research has some overarching limitations which warrant some discussion. Firstly, this research includes predominantly only people with RRMS. The usability of a web-based computerised battery may differ in persons with more advanced disease. Our findings show a slower baseline task performance was associated with a higher EDSS score and lower adherence to home-based testing. So it may be that those pwMS with more advanced disease or motor impairment find it more burdensome to complete regular MSReactor testing. In this scenario a test with vocal response may be more suitable. Further, the longitudinal change trajectories of people with more advanced MS may differ from those earlier in the disease course. Inclusion of the wider spectrum of MS (including the preclinical CIS) in future studies will provide important information about the feasibility of long-term active monitoring and the evolution of cognitive dysfunction over the entire MS disease course.

MSReactor is designed to be a brief cognitive monitoring tool to screen for changes in select domains, so it was important that the tasks were kept as efficient as possible. As such, the requirement for brevity must be weighed against the time for extended sampling. Although the

length of sampling for each task of the MSReactor battery is similar to comparable, validated batteries such as the Cogstate Brief Battery (between 30 and 35 correct responses for each task), we cannot rule out that less variability in the mean outcome measures would have enabled us to detect smaller longitudinal changes. A limitation of the home-based testing approach in these studies risks the introduction of invalid test results. Although participants were encouraged to perform the remote tests in a consistent and quiet testing environment, and accuracy-based measures to determine the integrity of the tests were taken (>70% correct), we cannot rule out variability in the results when remote testing. Studies of unsupervised testing in other computerised cognitive tests however have demonstrated reliability and comparable results to supervised testing (366, 401).

Another limitation for these studies is the lack of baseline and end of follow up neuropsychological assessment. Although this would be impractical with the numbers of participants included in these studies, the omission of comprehensive cognitive assessment meant we were unable to describe the extent of CI in the cohort using an accepted gold standard. We therefore could not describe the concurrent and predictive accuracy of MSReactor to formally established CI. Lastly, as a monitoring tool, MSReactor was designed to be brief and easy for pwMS to complete whilst targeting limited cognitive domains that are commonly impaired in MS. As a result, pwMS with dysfunction primarily in other cognitive domains such as executive function or verbal learning might not be detected by the MSReactor computerised tests. Further work in these areas would be appropriate.

Future research directions

The work completed in this thesis provides the basis for some exciting future research directions in the emerging field of digital cognitive biomarkers. Establishing clinically relevant change indices for the MSReactor scores is an important step for the translation of this approach into clinical practice. Understanding the relationship and dynamics between changes on the MSReactor tests and the evolution of disease burden, disability, and functional outcomes such as work productivity in pwMS will be one focus of my post-doctoral research. The prediction of individual patient-level cognitive trajectories is another area of research where clinical translation may offer great benefits to MS management. Defining the trajectory of MSReactor outcomes across disease will have clinical implications for management of pwMS. Monitoring for cognitive changes from early in the disease course is crucial, with the goal of the earliest

intervention, such as rehabilitation or treatment change, to prevent further impairment. Determining the sensitivity of the MSReactor tasks to measure temporary changes in disease state, such as during relapse or initiation of DMT, could potentially allow MSReactor to be included as a clinical trial outcome measure or included in the definition of treatment failure or NEDA. Although this thesis largely focused on the ability of MSReactor to monitor for longitudinal cognitive changes within an individual, the collection of normative data that represents the MS cohort in terms of ages, sex, education level and testing paradigm, would allow diagnostically meaningful inferences from any changes in function detected.

The depth and longitudinal structure of data collected by MSReactor when combined with clinical data, lends itself to the development of prognostic models harnessing machine learning computing. This approach would encompass a pwMS' past and current detailed clinical, imaging and MSReactor data to provide more accurate predictions of cognitive and disability progression. Development of these models is another focus of my post-doctoral work. Integration of MSReactor into the MSBase global outcomes registry offers exciting and unique opportunities to track these outcomes at a global level.

The long-term feasibility and acceptability of the MSReactor cognitive battery is another area of ongoing research that is crucial to understand the sustainability of implementing an active cognitive monitoring program across numerous MS outpatient clinics. Lastly, establishing the construct validity of MSReactor will demonstrate that the tests measure the broad intended cognitive constructs and future studies in this area are essential for the perceived overall validity of the battery.

Conclusion

This thesis addresses the existing cognitive monitoring gap in MS clinical practice. MSReactor is a highly scalable and practical solution to longitudinal cognitive monitoring in people with MS. It is reliable and sensitive to subtle changes in cognitive function over time. Further understanding of the predictive ability of the subtle neurological changes detected by these simple tests will have direct clinic impact. Translation of this approach into practice could transform the way all people with MS are monitored.

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