Anomia in people with Relapsing - Remitting Multiple Sclerosis: Investigating the nature and extent of the problem and taking steps toward better assessment and treatment.

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

2021

ERIKA P. CORDOVA LUNA

School of Biological Sciences

Table of Contents

Word Count: 47,940

List of Abbreviations

ACE-R: Addenbrooke's Cognitive Examination–Revised

AoA: Age of Acquisition

BNT: Boston Naming Test

CIS: Clinical Isolated Syndrome

CNS: Central Nervous System

D-KEFS: Delis-Kaplan Executive Function System

FDA-2: Frenchay Dysarthria Assessment 2

GM: Grey Matter

HA MS: Highly active multiple sclerosis

IPNP: The International Picture Naming Project

LIST OF ABBREVIATIONS

MRI: Magnetic Resonance Imaging

ms: Milliseconds

MS: Multiple Sclerosis

NART: National Adult Reading Test

PALPA: Psycholinguistic Assessments of Language Processing in Aphasia

PASAT: The Paced Auditory Serial Addition

PP MS: Primary Progressive Multiple Sclerosis

PR MS: Progressive Relapsing Multiple Sclerosis

PwMS: People with Multiple Sclerosis

RES MS: Rapidly evolving severe multiple sclerosis

RIS: Radiologically Isolated Syndrome

ROCFT: Rey-Osterrieth Complex Figure Test

RR MS: Relapsing-Remitting Multiple Sclerosis

RT: Reaction Time

SD: Standard Deviation

SDMT: Symbol Digit Modalities Test

SP MS: Secondary Progressive Multiple Sclerosis

SRFT: Salford Royal NHS Foundation Trust

VBM: Voxel Based Morphometry

WAB: Western Aphasia Battery

WAIS-R: Wechsler Adult Intelligence Scale-Revised

WM: White Matter

LIST OF FIGURES

LIST OF TABLES

Investigating the nature and extent of the problem and taking steps toward better assessment and treatment.

Erika P. Cordova Luna
The University of Manchester
Doctor of Philosophy, School of Biological Sciences, Faculty of Biology, Medicine and Health
July 2021

Abstract

Multiple Sclerosis (MS) is a neurodegenerative inflammatory disease characterised by demyelination and axonal loss in both, white and grey matter. It affects motor, sensory, cognitive and language functions. Language impairments have only recently been studied as a clinical manifestation, with word retrieval deficits as the most common symptoms. Anomia is also the most self-reported language feature between people with MS and even subtle deficits can affect communicative participation and quality of life.

This thesis investigated the extent and nature of anomia in people with Relapsing – Remitting (RR) MS through behavioural and imaging analyses and evaluated the use of a word retrieval software-based treatment as a form of self-management of anomic symptoms.

In order to explore the scope of anomia in the context of cognitive, linguistic and speech production skills, 151 participants with RR MS were assessed using general cognition tasks and a bespoke picture test which focused on accuracy and latency. Next, in order to understand the factors involved in the anomic symptoms, a wide array of neuropsychological and communication assessments were conducted with the RR MS participants (n=21). Later, the efficacy of a novel word retrieval software-based treatment for anomic symptoms was examined in participants (n=13), which focused on combined accuracy and speed intervention. Finally, grey matter (GM) volumes of 105 participants with RR MS were assessed and compared with healthy individuals as well their relationship with verbal fluency tests outcomes, as a means to a better understanding of the neural nature of verbal fluency in RR MS.

Results showed that participants with RR MS often present with anomic symptoms characterised as word retrieval inaccuracy and delayed latency. It was established that anomia could not be fully explained by speech deficits such as dysarthria and that difficulties in naming retrieval may have stemmed from a disruption in the systems of working memory and speed of information processing, and deficits in the semantic access, search and/or memory store. Furthermore, MRI on GM volumes suggested that low scores in verbal fluency tasks showed a general decline in information processing skills. Finally, we observed that word retrieval therapy produced gains in naming accuracy and latency and these could be generalised to connected speech task. However, the speeded therapy did not give an advantage for improving confrontational naming.

In conclusion, anomia is a common symptom in RR MS and could be described as a cognitive-communication disorder rather than a pure language deficit. Targeted early interventions could help to improve or maintain language abilities in people with RR-MS which may enhance their quality of life.

DECLARATION

Chapter 3 of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.
De Dios Pérez, B. (2017). *Anomia in people with relapsing-remitting multiple sclerosis* [Master's Thesis, The University of Manchester, United Kingdom]
De Dios Pérez, B., Cordova Luna, E., Cloutman, L., Rog, D., Preston, E., & Conroy, P. (2020). Anomia in people with rapidly evolving severe relapsing-remitting multiple sclerosis: both word retrieval inaccuracy and delay are common symptoms. Aphasiology, 34(2), 195-213.

COPYRIGHT STATEMENT

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and she has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made **only** in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further r information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=2442 0), in any relevant Thesis restriction declarations deposited in the University Library, The University Library's regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University's policy on Presentation of Theses.

DEDICATION

To

my husband Daniel

for his patience, laughter, love and wise words of support when most needed.

and

mi Mamá y Papá

porque gracias a ellos he llegado tan lejos.

Por su ejemplo de lucha incansable, apoyo y sobretodo por el amor infinito e incondicional que siempre he recibido.

ACKNOWLEDGEMENTS

Throughout the course of my PhD and the writing of this thesis I have received a great deal of support and assistance.

I would first like to express my deepest gratitude to my supervisor, Dr Paul Conroy, for his guidance and dedicated involvement in every step throughout my PhD. Thank you for your expertise, your patient support, care, and insightful feedback that pushed me to be a better researcher.

I would also like to thank Dr Lauren Cloutman, Dr David Rog and Dr Nils Muhlert for their valuable guidance thorough out my studies and the opportunities I was given to further my research.

I would like to acknowledge the Mexican Council of Science and Technology (CONACyT) which funded this project. Supporting scientific knowledge contributes to the function of a democracy, drives growth and innovation in any nation.

I would like to say a special thank you to all the participants with Multiple Sclerosis who generously took part in this research project. I truly appreciate your interest, eagerness and trust in this project.

Getting through my dissertation required more than academic support, I would like to acknowledge my colleagues and friends Nourah and Danka for their help, for the time spent together in the office and for the happy distractions that gave me a break from my research.

Finally, I wish to thank my family. My husband Daniel for being always there for me, for being my rock and never letting me doubt myself. Thank you for your kind words, laughter and encouragement. My parents, parents-in-law and my brothers, this work is a testimony to your unconditional love, I could not have done it without you.

THE AUTHOR

I graduated from the Anahuac University in Mexico City with a first class BA in Psychology. I was an intern at the National Institute of Neurology and Neurosurgery in Mexico City for two years where I assisted with neuropsychological assessments and participated in clinical research studies. Later, I worked as an assistant neuropsychologist at Hospital Medica Sur, where I supported with assessments and rehabilitation programmes in people with neurodegenerative diseases. Subsequently, I enrolled full-time on an MSc in Neuroscience in Neurodegeneration at King's College London. My master's research project investigated the impact of Ppt1 Deficient Glia upon Neurons in Infantile Neuronal Ceroid Lipofuscinosis. My MSc was fully funded by the Mexican Council of Science and Technology. After completion, I registered as a full-time PhD student at the University of Manchester. My PhD studies have been funded by the Mexican Council of Science and Technology and the University of Manchester.

CHAPTER 1

Thesis Overview

This thesis is presented in alternative format, core chapters are written in a style suitable for publication in a peer reviewed journal. In each chapter, a review of relevant literature is presented as well as the motivation for the work, research questions and methods are described, and results are discussed. Chapter 3 has already been published by a peer reviewed journal.

The overarching aim of this thesis was to investigate and enhance the current understanding regarding the extent, nature and treatment of anomia (difficulties retrieving words) experienced by people living with Relapsing-Remitting Multiple Sclerosis (RR MS). More specifically, the empirical chapters contained in the thesis attempted to achieve this goal in a logical, step-by-step manner with regard to addressing key questions in a coherent order: investigating how common these problems are; identifying both the superficial characteristics with regard to naming and deeper cognitive underpinnings; evaluating whether anomic symptoms be treated with established treatment methods; and lastly, considering the type of neurological deficits which lead to these symptoms.

Chapter 2 consisted of a comprehensive literature review on the broad topic of MS and the existing literature on language deficits in people with Multiple Sclerosis (PwMS), focusing on word retrieval. The review identified gaps in the literature pertaining to anomia and its treatment in MS, and made recommendations for future research. Following the review of previous research, Chapters 3 and 4 aimed to explore these communication deficits with specific focus on word retrieval difficulties and their interaction with other cognitive deficits in people with RR MS. Chapter 3 examined the extent of anomic symptoms in people with RR MS. The data regarding people with RR MS has been obtained through a previous and separate study, eventually reported by De Dios et al. (2020). Publication of this study required collection and direct statistical comparison with a sufficient sample of control participants (n=40), which was achieved within this PhD study. A replication of the screening method in Chapter 3 study was then conducted in order to extend and confirm its findings with a new group of participants (Chapter 4). Moreover, an in-depth neuropsychological and communication testing was also performed to understand the cognitive-linguistic-motor underpinnings of anomic symptoms in people with RR MS. Given the commonality of anomic

symptoms in PwMS, Chapter 5 utilised a novel computer-based and self-managed anomia therapy (QuickWord) The therapy used a combined accuracy and latency focused treatment and compared it with a standard (accuracy only) intervention in participants with RR MS. The overall aim was to explore the efficacy of the QuickWord therapy (both, the combined accuracy and speed -focused and the standard interventions) in improving word-finding abilities and any patterns of generalisation from naming gains to lexical retrieval in connected speech. Moreover, a self-rating communication questionnaire was given to the participants with RR MS in order to explore the kind of everyday communication problems they reported and perceived. In the need to improve the understanding of the underlying neural changes which lead to word-finding difficulties in people with RR MS, Chapter 6 analysed Magnetic Resonance Imaging (MRI) scans using an optimised voxel based morphometry (VBM) method to assess the grey matter (GM) volumes of a group of participants with RR MS and compared them with healthy control (HC) individuals. Also, given the prevalence of deficits in scores on verbal fluency tasks for our participants with RR MS, an association with verbal fluency test scores and GM atrophy was analysed. MRI scans and verbal fluency tests results of RR MS and HC groups were collected by the Cardiff University Brain Research Imaging Centre led by Dr Ilona Lipp and Dr Valentina Tomassini, whom agreed to participate in this study.

In the final Discussion Chapter, an overview of key issues from the literature review and the main findings of the four studies (Chapters 3-6) were reviewed. A discussion of the broader theoretical and clinical implication of these results was described. Finally, the thesis limitations were considered and potential directions for future research were explored.

CHAPTER 2

Topic Introduction

Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterised by demyelination and axonal loss (Friend et al., 1999; Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). MS affects all ages, but for most people symptom on-set usually begins in early adulthood (mean age of onset is approximately 28 years) with a female predominance, which makes it the most common cause of non-traumatic disability in young adults. Fifty percent of people living with MS will need some kind of help walking within 15 years after the onset of the disease (Weinshenker et al., 1989). In addition, 43% to 70% of people with MS will present with cognitive impairment at different stages of the disease (Chiaravalloti & DeLuca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991).

Clinical Course

MS presents across an array of diverse clinical courses as well as different degrees of disability accumulation at onset and throughout the course of the disease. The course of MS is characterized by relapses of acute neurological symptoms which lead to partial or complete progression (Confavreux & Vukusic, 2006). A relapse is defined as a newly, focal disturbance of neurologic function not associated with fever or infections and lasting for more than 24 hours, usually presenting optic neuritis, sensory deficits or cerebellar dysfunction. Return to normal functioning after a relapse typically occurs over days or weeks, or can produce continual remaining deficits. Disease progression is a steady and irreversible worsening of symptoms and signs over at least 6 months, often characterized by spinal symptoms (e.g., spasticity, paresis and gait ataxia) (Kamm, Uitdehaag, & Polman, 2014). New Magnetic Resonance techniques and evidence from pathology show that the early, diffuse, chronic and progressive axonal loss has a correlation with the progression and accumulation of disability (Confavreux & Vukusic, 2006).

In 1996, a Committee implemented an international survey of clinicians involved with MS and provided a consensus that described four clinical courses of MS: relapsing-remitting, secondary progressive, primary progressive and progressive relapsing. More than a decade later, the Committee described two new disease courses: clinically isolated syndrome (CIS) and radiologically isolated syndrome (RIS) (F. D. Lublin et al., 2014).

Clinically isolated syndrome (CIS): The term describes the first clinical episode in which a patient shows characteristics suggestive of an inflammatory demyelinating disease. The

episode should last for at least 24 hours. It usually affects optic nerves, the brainstem or the spinal cord (F. D. Lublin et al., 2014; Miller, Chard, & Ciccarelli, 2012).

Radiologically isolated syndrome (RIS): This is not technically considered an MS subtype. It is a situation where MS typical imaging findings are detected incidentally without clinical signs or symptoms (F. D. Lublin et al., 2014). However, the finding of asymptomatic lesions in the spinal cord places patients at a substantial risk of an eventual MS diagnosis (Okuda et al., 2011).

Relapsing-remitting MS (RR MS): This type is present in 80% of the patients during the early years of the disease, and has a female predominance. In this phase, the disease shows only relapses and remissions. Signs and symptoms develop gradually, stabilize and usually improve within weeks (Noseworthy et al., 2000).

Post hoc subgroup analyses of licensing studies on disease-modifying drugs have defined two subpopulations of RRMS: *Highly active multiple sclerosis* (HA MS) may be characterised as a patient who failed to respond to at least one year of treatment of a disease-modifying therapy or patients with an unchanged or increase relapse rate or ongoing severe relapses compared with the previous year (European Medicines Agency, 2014). *Rapidly evolving severe multiple sclerosis (RES MS)* according to the European Medicines Agency (2014) is defined as patients presenting "two or more disabling relapses in the past year, and one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI" (European Medicines Agency, 2014, p. 5)

Secondary progressive MS (SP MS): After the initial relapsing-remitting phase, gradual worsening of the disease may develop between or in the absence of relapses, and the recovery is often less complete resulting in the accumulation of disability. The transition from PPMS to SPMS is usually slow (Lublin & Reingold, 1996), with 75% of the RRMS patients changing to SPMS (Confavreux & Vukusic, 2006).

Primary progressive MS (PP MS): In 15% of patients, the disease gradually increases from onset presenting clear acute relapses with temporary minor improvements. PPMS patients are older at onset compared with RRMS and are predominantly males (Miller & Leary, 2007).

Progressive-relapsing MS (PR MS): The progressive phase is present from onset, and periods between relapses are characterised by sustained progression (Confavreux & Vukusic, 2006).

Symptoms

MS exhibits many symptoms throughout its clinical course, including visual loss, ataxia, spasticity, sexual dysfunction, bladder dysfunction, pain, cognitive impairment, and less commonly bowel dysfunction, paroxysmal symptoms and communication disorders (McAlpine & Compston, 2005). In addition, fatigue and depression are frequent comorbidities in MS (Ghaffar & Feinstein, 2007; Krupp, Alvarez, LaRocca, & Scheinberg, 1988). Many symptoms are manifested based on the progression of the disease and the extent and location of the lesions (Crayton & Rossman, 2006).

Negative symptoms: The presentation of symptoms such as blindness, paralysis, ataxia and numbness are caused by the loss of conduction due to demyelination and inflammation of the axon (Smith & McDonald, 1999), which suffers consequent physiological changes resulting in the block of conduction in the appropriate pathways (Sá, 2012; Smith & McDonald, 1999).

Positive symptoms: Symptoms like pain, spontaneous abnormal movement and sensory feelings are thought to be caused by ectopic impulses produced at the site of demyelination (Sakurai & Kanazawa, 1999).

Fatigue: People with MS not only suffer physical but also cognitive fatigue, and it is reported in 90% of the MS population (DeLuca, Genova, Hillary, & Wylie, 2008). Fatigue is a heterogeneous symptom and numerous factors can play a role in its pathogenesis (DeLuca et al., 2008). Primary fatigue may be associated with MS mechanisms such as inflammation, demyelination, or axonal loss (Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008). Neuroimaging studies also suggest that there is a higher energy demand in cortical and subcortical areas due to brain reorganization (DeLuca et al., 2008), that may result in an increase of fatigue perception in people with MS (Kos et al., 2008). Furthermore, fatigue can be a result of non-disease-specific factors (secondary fatigue) such as sleep problems, urinary problems, spasms, pain, anxiety (DeLuca, Yates, Beale, & Morrow, 2015), or even the effect of some pharmacologic treatments of MS (Kos et al., 2008).

Depression: Historically, depression in MS was thought to be a reaction to the stressful and chronic disease. However, numerous studies have suggested that depressive symptoms may have a specific CNS involvement (Siegert & Abernethy, 2005). For instance, Riccitelli et al. (2014) found severe microstructural alterations in the interhemispheric fibres of the frontal cortex in MS patients with depression symptoms compared with patients without the

symptoms. The lifetime prevalence of major depression is as high as 50% in MS patients (Sadovnick et al., 1996).

Cognitive symptoms: Although the white matter is predominantly affected in MS (Rao, 1996), demyelinating lesions involving the grey matter structures, especially in the cerebral cortex and to a less extent the deep grey nuclei, are also present, and along with white matter lesions may cause cognitive symptoms (DeLuca et al., 2015; Rao et al., 1991) or less frequently, epilepsy or aphasia (Sá, 2012).

Communication disorders: These are commonly present in MS. Usually, the most observed and studied are motor speech disorders such as dysarthria. However cognitive-linguistic dysfunction is also evident in some MS patients (Murdoch, 2000; Renauld, Mohamed-Saïd, & Macoir, 2016).

As a result of the unpredictable and progressive nature of the disease, there are not the same symptoms and the same disease course in each individual (Gordon, Lewis, & Wong, 1994).

Treatment

There is no cure for MS. However, over the past 20 years research has shown major advances in treatment of the disease. The approaches to treat the symptoms associated with MS are aimed at the reduction of inflammation, the immunosuppression or modulation of the immune system, and to maintain remission. Furthermore, research is also aiming for repair mechanism therapies directed to promote remyelination of the CNS and prevention of axonal loss and neuronal death (Anlar, 2009; McAlpine & Compston, 2005).

The main treatments for people with RR MS and SP MS are: corticosteroids to reduce inflammation and accelerate recovery (Miller et al., 2000); and, disease-modifying agents to reduce the relapses and delay progression of the disease (Cohen & Rae-Grant, 2012).

Cognitive impairment in MS

Researchers have become more aware of the prevalence, nature and impact of cognitive impairment in MS. These affect up to 70% of patients (Rao et al., 1991), and may be present at any stage of the disease (Amato, Ponziani, Siracusa, & Sorbi, 2001), even in clinically isolated syndrome (Feuillet et al., 2007).

Causes of lesions in MS are heterogeneous and they can affect cognitive functions through various mechanisms such as chronic inflammation and demyelination, oxidative stress, disruption in the blood-brain barrier, alterations in the brain metabolism and blood flow, and changes in the cortico-cortical and cortico-subcortical connectivity resulting from axonal injury and loss (DeLuca et al., 2015).

It has been shown that there is a weak correlation between the radiological extent of MS lesions and the level of cognitive impairment and clinical disability (Barkhof, 2002). There may be various factors underpinning this such as inappropriate clinical rating, neglect of the involvement of the spinal cord, underestimation of damage to the normal appearing brain tissue, masking effects of cortical adaptation (Barkhof, 2002), or cognitive reserve (Sumowski, Chiaravalloti, Wylie, & DeLuca, 2009).

According to the cognitive reserve hypothesis, the adverse effect of brain pathology on cognition is moderated among people with higher education or premorbid intelligence. Persons with higher cognitive reserve present a complex synaptic neural network, which allow them to require fewer cerebral resources to accomplish the same cognitive task than people with a lesser reserve as the neurologic disease advances and/or the task demands become more complex (Stern et al., 2005). This effect have been seen in Alzheimer's disease patients as well as MS patients (Bennett et al., 2003; Sumowski et al., 2009).

It has been shown that the onset of cognitive deficits in MS does not relate to the disease duration and does not follow the same severity course as the physical disability (DeLuca et al., 2015; Feuillet et al., 2007). However, a long-term study suggested that acute inflammatory lesions, physical disability and progressive disease course can predict the extent of decline in cognitive functions (Amato et al., 2001; Benedict et al., 2014). Despite the variation in cognitive deficits among patients, the most frequently affected functions in MS seem to be memory, efficiency in information processing (specially information processing speed), visual perception functions, executive functioning, attention, and to a lesser extent language (Chiaravalloti & DeLuca, 2008; DeLuca et al., 2015).

Attention: this deficit is seen in 12 – 25% of people with MS. The types of attention that seem to be the most often impaired are selective attention, which refers to the ability to focus on one type of information and ignore others, and divided attention referring to when the focus is divided or shared between two or more sources of information, or two or more mental

tasks (Davies, Jones, & Taylor, 1984; Rao et al., 1991). Calabrese (2006) reviewed different studies and observed that attention along with information processing deficits are seen early in the disease course, and may be one explanation for subsequent dysfunctions in memory or abstract reasoning (Calabrese, 2006).

Memory: 40% to 60% of patients with MS present with deficits in long-term memory (Rao et al., 1993; Rao et al., 1991), presenting with, in particular, an inadequate initial acquisition of information (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998). However, not all the components of memory are affected; verbal short term memory and implicit memory are generally undisturbed (Grafman, Rao, & Litvan, 1990; Winkelmann, Engel, Apel, & Zettl, 2007). Other factors also seem to be involved in the impaired process of encoding and storing information such as slow processing speed, difficulties ignoring irrelevant stimuli, executive dysfunction and perceptual deficits (Chiaravalloti & DeLuca, 2008).

Executive functions: this refers to abstract and conceptual reasoning, planning and problem solving and organisation. Whilst dysexecutive symptoms have been noted less frequently than other cognitive deficits, they have been reported in 19% of people with MS (Rao et al., 1991). Evidence shows that deficits in executive function are strongly related to dysfunction in information processing speed (Bergendal, Fredrikson, & Almkvist, 2007), and to the presence of depression (Channon, Baker, & Robertson, 1993).

Information processing speed: the efficiency on how we process information in the brain is composed of two elements: *working memory*, which is the capacity to store and work with information for a short period of time (Baddeley, 1992); and *processing speed,* which is the time it takes us to process information. Both are necessary to achieve successful performance in more complex cognitive functions such as language, reasoning, comprehension and learning (Chiaravalloti & DeLuca, 2008). Although both components seem to be affected in MS (Parmenter, Shucard, & Shucard, 2007), DeLuca et al. (2004) showed in a case-control study that deficits in information processing speed were much more common than in working memory in MS patients (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004). However, other studies have suggested that when the working memory demand increases, both processing speed and working memory become more impaired. Furthermore,

processing speed deficits may also affect other functions such as executive function (Denney, Lynch, Parmenter, & Horne, 2004).

Visual perceptual functions: these functions have not been fully investigated, but it is suggested that 19% of people with MS show poor performance in visuo-constructive and visuo-spatial abilities (Winkelmann et al., 2007). Optic neuritis, a common symptom in MS, can have a poor effect on perceptual processing. Although perceptual deficits not related to the neuritis may occur as well (Vleugels et al., 2000), there is a need for more research since data in this topic is inconclusive.

Impact of Multiple Sclerosis on Communication

When Charcot first described MS, he mentioned that speech disturbances were often found in the disease (Charcot, 1877). However, the main focus of MS research has been into physical symptoms and it has only been in the last two decades, with the help of neuroimaging, that attention has turned to cognitive impairment. Despite this, little research has been carried out into communication disorders associated with MS. Approximately half of the MS population presents with some kind of communication disorder (Hartelius, Runmarker, & Andersen, 2000), which limits their capacity to engage in everyday community life (El-Wahsh, Ballard, Kumfor, & Bogaardt, 2020). Firstly, we need to discern speech disorders from language disorders in MS.

Speech disorders

Speech is an integrated set of motor activities which combine neurocognitive, neuromotor, neuromuscular and musculoskeletal activities in order to innervate and activate respiratory, phonatory, resonatory and articulatory muscles to produce an acoustic signal to express thoughts and emotions (Duffy, 2013). Speech disorders have long been linked with MS, and are found in 40 - 50% of MS patients. The most common speech disorder in MS is dysarthria (Hartelius et al., 2000). Dysarthria is defined as "a collective name for a group of speech disorders resulting from disturbances in muscular control over the speech mechanism due to damage of the central or peripheral nervous system. It designates problems in oral communication due to paralysis, weakness or incoordination of the speech musculature" (Darley, Aronson, & Brown, 1969, p.246). The definition suggests that dysarthria is a movement disorder of neurological origin. Dysarthria has been found to occur at different

stages of the disease. However, it is not common in the initial stages (McAlpine & Compston, 2005). Dysarthria can be caused by the dysfunction of various components of the CNS. Darley *et al.* (1972) found that MS patients presenting with cerebral, cerebellar and brainstem disturbances showed severe dysarthric symptoms (Darley, Brown, & Goldstein, 1972). The most common abnormal speech features identified in the MS population from three countries were harshness, imprecise articulation, impaired respiratory support, impaired emphasis or stress patterns and impaired pitch variation or control (Murdoch & Lethlean, 2000).

Language disorders

Language is a cognitive ability and until the past decade there had been little research into the possible language problems in MS. There is a debate as to why language disorders in MS have not been extensively reported in the literature. This may be because the symptoms are very subtle and uncommon, or they are underdiagnosed, or it may be that researchers have simply ignored this function (Rao, 1986). Even subtle language disorders can have a big impact on MS sufferers, significantly affecting their quality of life (El-Wahsh et al., 2020; Klugman & Ross, 2002; Yorkston, Klasner, & Swanson, 2001). Klugman & Ross (2002) conducted a study in life quality and found that as many as 63% of the MS participants encountered poor communication abilities and language difficulties impacting their quality of life. Moreover, using a self-reported international survey, El-Wahsh et al., (2020) found that 75% of PwMS described some degree of language impairment, and 65.7% reported difficulties with word retrieval.

New neuroanatomical models have shown that brain structures and white matter pathways in both hemispheres play a key role in language processing (Hickok, 2013). Since MS affects the subcortical and cortical white matter (WM), hence interrupting WM pathways, it could be anticipated that damage in these structures and pathways in MS may result in language deficits. Also, it is possible that the disconnection of the cortico-subcortico-cortical loop by demyelination may cause a high-level language disruption (Lethlean & Murdoch, 1997). In spite of the new information in recent models of language, there is still an insufficient number of investigations that satisfactorily examine the language abilities of MS patients (Murdoch & Lethlean, 2000).

There is conflicting data in the literature about language deficits in people with MS. Early investigations into language processing in MS did not find significant language disturbances

or suggested that language problems are rare (Herderschee, Stam, & Derix, 1987; Rao, 1986). However, other studies did uncover deficits in language processing early in the course of the disease, and even in MS patients with preserved verbal intelligence (Friedman, Brem, & Mayeux, 1983; Jennekens-Schinkel, Lanser, van der Velde, & Sanders, 1990; Wallace & Holmes, 1993).

Friend et al. (1999) proposed that the contrasting findings in language deficits may be explained by a number of factors: the complexity of the language processing, the superficial assessment of language using abbreviated tests, the diversity of systems used to assess language functions, and/or the subtlety of the language process to disruption in the presence of cognitive impairment. Furthermore, Lethlean and Murdoch (1993) suggested that conflicting findings might be the result of a methodological problem in the selection of participants, where the participants in the reported studies present with different disease variables (usually separated into RR MS and chronically progressive MS (CP MS) clinical groups). They also observed that standard language tests included in neuropsychological batteries assessed only basic functional abilities and were not sensitive enough to demonstrate fine-grained language deficits. They, therefore, constructed a battery of tests focusing on subtle difficulties and high-level language in a study on MS. Measures of high-level language include comprehension of complicated commands, interpretation of figurative language, inferential reasoning and high-level verbal explanation capacity. The comparative study of the MS group against matched control participants revealed diverse language problems in all groups of MS participants and suggested that the presence of language deficits is not determined by disease course. However the CP MS group had more severe language problems than the RR MS group (Lethlean & Murdoch, 1993).

Different types of language deficits have been identified by various studies of language disorders in MS, labelled either as ‘aphasia’, naming difficulties, deficits in logic or grammatical constructions comprehension, difficulties with word fluency, verbal reasoning, word definitions, pragmatic deficits and the interpretation of absurdities, ambiguous sentences and metaphors (Amato et al., 1995; Carotenuto et al., 2018; De Dios Pérez et al., 2020; Friend et al., 1999; Lethlean & Murdoch, 1993; Renauld et al., 2016). However, the most common symptom reported in the literature has been word retrieval deficits (De Dios Pérez et al., 2020; Renauld et al., 2016), even in early stages of the disease (Brandstadter et al., 2020).

Typically, the literature has not described people with MS as having aphasia, despite several different forms of aphasic symptoms having been documented in MS literature. Occasionally, the literature has referred to the presence of Broca's aphasia in MS, and there have also been a few reported cases of conduction, transcortical, global and crossed aphasia (Achiron et al., 1992; Demirkiran, Özeren, Sönmezler, & Bozdemir, 2006; Friedman et al., 1983; Lacour et al., 2004). The term aphasia may have simply been used selectively to refer to more frank and severe language symptoms in MS, where in single case studies of aphasia, the presence of white matter plaques large enough to disrupt language pathways has been described. For instance, Friedman (1983) detailed an MS patient presenting with global aphasia, in which a computerised tomographic scan revealed large WM plaques in the left periventricular region, affecting connections from Broca´s and Wernicke´s areas and the arcuate fasciculus (Friedman et al., 1983). Moreover, Achiron et al. (1992) described two RRMS patients presenting severe non-fluent aphasia, a magnetic resonance imaging (MRI) scan showed extensive plaques in the left frontal region and the left centrum semiovale, suggesting the disruption of commissural, association and projection fibres.

Although the association between deficits in cognition and language in PwMS is not fully understood, increasing evidence suggest that these could coincide in the disease (Carotenuto et al., 2018; De Dios Pérez et al., 2020; Renauld et al., 2016)

2.9 Verbal Fluency

Verbal fluency is measured by the ability of a person to generate multiple single words from a given cue. Cues can be phonemic (a word starting with certain letter, e.g., 'p') or semantic (categories of words, e.g., *Animals)* (Baldo, Shimamura, Delis, Kramer, & Kaplan, 2001). A number of studies on language disorders in MS have used verbal fluency and naming tasks to assess participants, as those instruments are amongst the most sensitive to assess cognitive impairment (Henry & Beatty, 2006). Impairments in naming abilities or verbal production have also been shown to be independent of problems with dysarthria in both RR MS and CP MS (Friend et al., 1999; Murdoch & Lethlean, 2000; Rao, 1986). Verbal tests are usually used to measure verbal processing (the mental lexicon and lexical retrieval is accessed in order to retrieve words), and executive functions (participants need to focus on a particular task and select specific words according to a certain category) (Shao, Janse, Visser, & Meyer, 2014).

Nonetheless, information processing speed (including working memory) and attention can also be measured by verbal fluency tests (Elgamal, Roy, & Sharratt, 2011).

Various hypotheses have been offered to explain impaired performance of people with MS in fluency tasks. For example, deficits in verbal fluency may derive from executive functioning impairment in MS (Henry & Beatty, 2006), or from disruption of the semantic knowledge structure, or result from an impairment in the word retrieval process of semantic memory (Murdoch & Lethlean, 2000; Troster et al., 1998). Whilst some studies have found a notable frequency of executive disorders in people with MS (Foong et al., 1997; Marié & Defer, 2001), others have little evidence of executive dysfunction as a recurrent feature (Chiaravalloti & DeLuca, 2002).

Verbal fluency tests are usually divided in two categories: semantic and phonemic fluency as mentioned before (Lezak, Howieson, Bigler, & Tranel, 2012). Both categories demand comparable abilities, but each category also measures individual cognitive functions (Elgamal et al., 2011; Henry & Crawford, 2004a; Salthouse, Atkinson, & Berish, 2003). People with MS have been shown to consistently produce more errors on both phonemic and semantic fluency tests against control participants (Henry & Beatty, 2006). Phonemic fluency has mainly been associated to attention and executive functions (Bryan & Luszcz, 2000; Shao et al., 2014) whilst semantic fluency has been linked to lexical access and semantic memory (Henry & Crawford, 2004a; Kraan, Stolwyk, & Testa, 2013). Henry and Beatty (2006) have suggested that equal impairment on measures of phonemic and semantic fluency tasks could possibly reflect executive function, while greater impairment of semantic fluency may be indicative of semantic memory dysfunction. In addition, studies in dementia have suggested that impairment of semantic fluency might be due to a compromised semantic store, while impairment of phonemic fluency may be the result of a compromised lexical or phonemic memory (Butters, Granholm, Salmon, Grant, & Wolfe, 1987). Furthermore, following a study of patients with frontal lobe lesions, Baldo and Shimamura (1998) suggested that impairment in both phonemic and semantic fluency reflect inefficient organisation and development of retrieval strategies for searches through lexical and semantic memory. A meta-analysis on studies of verbal fluency and focal cortical lesions on different neurological disorders by Henry and Crawford (2004a) found that verbal fluency (both phonetic and semantic) was associated with frontal structures, however semantic fluency was also linked to temporal structures. Also, Robinson et al. (2012) considered that the temporal cortex supports semantic word

retrieval while frontal regions support phonetic word retrieval. Various studies of the frontal cortex have presented reduced word fluency associated more with left frontal lesions compared with right-sided lesions and mainly for phonemic fluency (Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981; Robinson et al., 2012; Stuss et al., 1998). In MS, an MRI study on cortical thinning revealed that the participants with MS had lower verbal fluency performance than controls and manifested widespread cortical thinning. Also, on a global level, cortical thinning predicted the performance in verbal fluency. On a regional level, verbal fluency deficits correlated with the left-sided thinning of the anterior cingulate cortex (Geisseler et al., 2016).

It is important to assess both fluency tasks as the differentiation may be the clue to determining whether the errors on the phonemic and semantic tasks might be associated with executive function impairments and/or semantic memory dysfunction. However, we need to be careful not to interpret and individual's semantic or lexical abilities on a single verbal fluency test as the nature of the deficit causing the poor performance is not well known (Kennedy & Murdoch, 1990). In addition, other extra-linguistic elements such as impaired initiation, working memory, attentional deficits or depression, among others, may interfere with the efficiency of completing a verbal fluency task (Cherktow & Bub, 1990).

Anomia

Anomia or word-finding difficulties are a deficit of expressive language (Goodglass & Kaplan, 1972). Anomia frequently occurs in people with damage in the left hemisphere and aphasia, but it can also occur in healthy people from time to time, for instance, struggling to think of an intended word during an everyday conversation (Raymer & LaPointe, 2005). The most common form of this is the tip-of-the-tongue state, when the person knows there is a particular word to express an idea but cannot recall its phonological form (Laine & Martin, 2013). Anomia can affect the ability to retrieve verbs and adjectives but it is usually associated with problems in retrieving nouns (Raymer & Rothi, 2008). According to different models, word retrieval requires semantic (the speaker has an idea to express) and phonological (the speaker chooses a suitable word to express that idea) processes (Raymer & Rothi, 2008), and both semantic and phonological representations of a word are retrieved independently of each other in different brain areas and in specific time windows for each process (Indefrey & Levelt, 2004; Laine & Martin, 2013). Hence, brain damage in different parts of the brain will

convey different types of anomia and anomic errors. According to Laine and Martin (2013), there are three types of word retrieval deficits:

Semantic anomia: This naming disorder includes comprehension problems with the same concepts that the individual finds difficult to name. It includes incomplete, incorrect or imprecise semantic representations (Hodges, Graham, & Patterson, 1995). Comprehension and production deficits also affect auditory, visual and tactile object recollection, as well as the production of oral and written word responses (Laine & Martin, 2013).

Word form anomia (phonological output lexicon): Here, word-finding difficulties are due to an impaired access to the output lexicon or the lexical representations, whereas semantics are preserved (Lambon Ralph, Sage, & Roberts, 2000; Lorenz & Ziegler, 2009). The anomia presents with intact comprehension and normal performance on word production tasks that do not require semantic support, such as repetition and oral reading (Laine & Martin, 2013).

Disordered phoneme assembly: This title describes problems in various post-lexical processes of the cognitive-motor act. It includes substitutions, additions, exchanges and omissions of phonemes or phoneme combinations which surface in output (Laine & Martin, 2013).

A number of naming errors can be present when anomia occurs, for instance, the complete inability to retrieve a word, or paraphasias, when an inappropriate word is retrieved (Goodglass, Kaplan, & Barresi, 2001). Semantic paraphasias are impairments where the mistaken word meaning is related to the intended word (e.g., saying 'cow' for sheep) (Caramazza & Hillis, 1990). It can also be seen when participants try to compensate for their word-retrieval deficit, and they produce semantic word errors (Nickels, 2001). Another type of errors is phonologic paraphasias, where the error word is related to the intended word in the sound characteristics (e.g., saying 'capple for apple). Neologisms can also occur where the intended word may not be identifiable at all (e.g., saying 'fulan' for window) (Raymer, 2011). The presence of anomia has been found from early MS to the progressive forms of the disease (Brandstadter et al., 2020; De Dios Pérez et al., 2020; Renauld et al., 2016). Using naming tests, Beatty and Monson (1989) found impaired naming abilities in more than 40% of participants with CPMS and in 20% with RRMS. Nonetheless, in self-reported studies over 60% of PwMS had experienced anomia as the most common language symptom, affecting their quality of life (El-Wahsh et al., 2020; Johansson, Schalling, & Hartelius, 2020; Klugman & Ross, 2002). A systematic review of language impairments in MS also found word retrieval impairments as the most common symptom (Renauld et al., 2016). Successful word retrieval

needs accuracy and speed in response time, De Dios Perez et al. (2020) found that participants with RR MS had inaccuracies and low response latency in naming tests.

Beatty and Monson (1989) also found that participants with MS showed a wide range of impairments in accessing semantic and lexical information, such as increased latency and reduced precision when naming familiar words where the target was evoked by visual, semantic or phonologic cues; and ineffective searches of their semantic memories. However, the reasons for the impairment in naming abilities remained unclear. Nevertheless, their later studies found intact lexical priming in people with MS, suggesting the presence of a lexical accessing impairment instead of a semantic organisation impairment (Beatty & Monson, 1990).

Lethlean and Murdoch (1994) carried out a comprehensive study on naming abilities where they examined the effects of variables on naming abilities and the nature of naming errors produced by a group with MS. The variables included disease course, disease duration, age, and education level. Their findings confirmed the existence of naming impairments in these participants with MS, where the CP MS group showed more naming deficits than the RR MS group. They also suggested that disease course was not a reliable predictor of naming deficits in MS, and they did not find a relationship between naming scores and subject variables. In this study, MS participants made more naming errors than the control group, in particular semantic errors, such as sematic paraphasias and circumlocutions for the target. Based on their findings, the authors suggested the existence of a semantic accessing deficit as an explanation for the large rate of semantic errors of the MS group (Lethlean & Murdoch, 1994). As Lethlean and Murdoch (1994) did not have confirmation of lesion sites occurring in the MS group, they could only speculate. But they suggested that the presence of significantly more semantic paraphasias in the MS group compared with the control group was due to a cortical-subcortical interruption in their communication, which is necessary for normal naming function. This interruption disturbs the ability of an individual to monitor verbal output and later to access words efficiently from the lexicon (Lethlean & Murdoch, 1994; Murdoch & Theodoros, 2000). De Dios et al. (2020) also found more semantic errors in the confrontation naming tests. There are still relatively few studies on anomia in MS; hence explanation of the nature of anomia in MS is worth further study.

Assessment and Therapies for Anomia

As previously stated, word finding deficits are commonly found and reported in people with MS. Normally, they are assessed along with other cognitive functions. This can mean that they are given a superficial analysis. It is important, therefore, to have an in-depth evaluation focused on language to explore subtle deficits in MS.

Participant characteristics should be considered when evaluating the naming abilities of an individual, such as age, education, overall health status, premorbid performance level, as well as language and cultural background (Laine & Martin, 2013).

Assessing cognitive functions is relevant to identify the source of the language impairment as the evaluation can present with theories about the structure and functioning of mental processes such as the ones mediating word retrieval (Basso, 1993; Berndt, 2013).

A cognitive model can help researchers to diagnose a word processing deficit. However, it is necessary to keep in mind two arguments proposed by Basso (1993). Firstly, when a functional lesion is identified in a cognitive model, the lesion can only be as specific as the feature of the model allows; the more detailed the cognitive model the more detailed the diagnosis. Secondly, some components of the cognitive model overlap with each other. In other words, some functions of the cognitive components will be utilised in more than one task. Hence, it is important to evaluate any language process in all of the cognitive tasks that participate in that process (Basso, 1993).

An effective assessment of word-finding ability is particularly significant in understanding the nature of anomia. Severe anomic problems such as circumlocutions or neologisms are simple to identify in a conversation. However, mild word-finding problems can be masked by the use of everyday language stereotypical phrases or expressions. Consequently, mild anomia may only be seen in more challenging speaking tasks that require retrieval of specific words or on naming tests (Laine & Martin, 2013).

Picture naming tasks are the most frequent tools used to assess word retrieval ability. In these tasks, a specific lexical item must be retrieved, minimising the possibilities for covering the deficit with circumlocutory answers. Other methods for assessing anomia can include narrative speech tasks, where a participant has to describe events in a cartoon or tell a story; and analysis of conversational speech samples (Laine & Martin, 2013). These forms of assessment provide the researcher with an overall score which is an indicator of severity and the opportunity to analyse errors patterns and cueing effects that impact on the subject's

performance, resulting in valuable information about the mechanisms of the naming problem. Their use has been shown to present valid and rich means of assessment of word-retrieval (Herbert, Hickin, Howard, Osborne, & Best, 2008). Besides specific picture-naming tests, there are aphasia test batteries which have high consistency measures. They include visual confrontation naming tasks, word comprehension and lexical processing tasks (Shewan & Kertesz, 1980; Spreen & Risser, 2003)

In order to investigate the underlying mechanisms of anomia, naming tests alone should not be used. The assessment should also be accompanied with word comprehension tasks and phonological output tasks such as repetition and reading (Laine & Martin, 2013).

It has been reported that even the subtle difficulties in retrieving and producing words could cause people some kind of distress and frustration leading to a restriction in participation in everyday activities (Yorkston, Baylor, & Amtmann, 2014). Hence the need for remediation in word production is important for people living with the communication impairment. Treatments for anomia are widely used in people with neurological disorders, specifically aphasia and aim to improve word retrieval by correcting or completing the activation of semantic or phonologic information (Kiran & Bassetto, 2008). There are many approaches or therapies for naming disorders such as strategic, re-organisational or compensatory approaches and, facilitation, repair and re-teaching approaches (Nickels, 2002b). There is strong evidence of the efficacy of anomia therapies in single-case studies and case-series studies, however it is hard to predict an accurate outcome of a therapy with each specific person (Fillingham, Sage, & Lambon Ralph, 2006; Nickels, 2002b). Still, language treatment therapies for word production deficits in MS remain relatively scarce. Since MS is a neurodegenerative and fluctuating disease, a compensatory treatment over a restorative one has been proposed (Kristensson et al., 2021). Anomia treatment typically involves picture repetition, where the individual is presented with an image of an item and its verbal name, then the person is asked to repeat it back. The repetition of the item enters its phonological form and the image of the item gives a semantic cue (Howard, 2000). Standard single-item picture naming can be successful, however some limitations in its efficacy can arise. Generalisation to untreated items in the therapy can be unreliable (Nickels, 2002a) and although generalisation on the treated and untreated items can occur (Best et al., 2013), they might not always translate to significant improvements in everyday conversations (Carragher, Conroy, Sage, & Wilkinson, 2012; Conroy, Sage, & Lambon Ralph, 2009b). Also, Conroy et al.

(2018) suggested that in order to achieve generalisation on a naming therapy, word retrieval needed to be quick and accurate. They used and compared a combined speed and accuracy treatment to a standard accuracy therapy and found significant generalisation of treated items to connected speech following both therapies, but with significantly greater maintenance of treatment effects following speed and accuracy focused intervention. Moreover, several studies suggest that short-term highly intensive training leads to substantial and durable improvements in language functions, rather than less frequent therapy during a longer period of time (Barthel, Meinzer, Djundja, & Rockstroh, 2008; Breitenstein et al., 2017).

Conclusion

Multiple sclerosis is an inflammatory disease of the CNS. The average at onset of this chronic disease is 28 years old, gradually disabling people for potentially several decades of life. The most common symptoms are physical and cognitive deficits, and communication problems which bridge both of these symptom types, have been frequently noted. Research has focused primarily on physical and cognitive symptoms, but little research has been done to define the nature and basis of communication disorders associated with MS. Despite this, as much as 63% of MS patients have experienced language difficulties which affect their quality of life. In fact, only in the past two decades has attention turned to communicative impairments, but it has mainly focused on speech problems such as dysarthria, in spite of the fact that, of all the language problems presented in the MS population, anomia remains the most common. The reasons behind the lack of awareness of language disorders may be due to the subtlety of the deficits, the inefficacy of the methodology or the insensitive assessments. Nevertheless, the advent of new technologies such as neuroimaging is providing a new perspective on functional models of language processing and language disorders on in-vivo patients, thereby increasing our awareness and understanding of them. It is particularly relevant to comprehend and detect the extent and nature of language deficits in people with MS, as the anticipation and preventative treatment of language deficiencies in MS may lead to better rehabilitation outcomes, thereby reducing the impact of the disease on longer term quality of life.

Aim of the thesis

The overarching aim of this thesis is to investigate and enhance the current understanding regarding the extent, nature and treatment of anomia (difficulties retrieving words) experienced by people diagnosed with Relapsing-Remitting Multiple Sclerosis. More specifically, the empirical studies presented will examine the relative contribution of language and other cognitive skills to anomic symptoms in RR MS and how they interact over the course of the disease and to explore therapy effects with respect to improved accuracy and efficiency of word retrieval.

CHAPTER 3

Anomia in people with Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis: both word retrieval inaccuracy and delay are common symptoms

De Dios Pérez, B., et al. (2020). "Anomia in people with rapidly evolving severe relapsing-remitting multiple sclerosis: both word retrieval inaccuracy and delay are common symptoms." Aphasiology **34**(2): 195-213.

Abstract

Background: Multiple Sclerosis (MS) is a neurodegenerative disease that produces plaques throughout the central nervous system. MS can present in four different clinical courses. Of these, Relapsing-Remitting MS (RR MS) is the main clinical course, especially at early stages of the disease. Rapidly evolving severe (RES) RR MS is a form of RR MS in which an individual has two or more disabling relapses in one year and evidence of increasing lesions on two consecutive MRI scans. MS affects the cortical and subcortical pathways of the brain leading to impairment in both physical and cognitive skills. Speech, language and communication deficits more broadly, have been acknowledged in the MS literature, but relatively little research has focused on these symptoms.

Aims: To examine communication deficits in people with (RES) RR MS, with specific focus on anomic symptoms – difficulties in word retrieval, examining measures of both accuracy and latency (time intervals for accurate word retrieval).

Methods & Procedures: A communication screening assessment was conducted with 100 participants with (RES) RR MS. This screening assessment consisted of the ACE-R cognitive screen, a bespoke picture naming task, reading words aloud from the National Adult Reading Test (NART) and the Pyramids and Palm Trees Test. The picture naming task obtained timed naming responses for sixty pictures of objects from the International Picture Naming Project (IPNP). Results for participants with MS (PwMS) were compared to matched neurotypical control participants (n = 40) and normative test data.

Outcomes & Results: The group mean performance for PwMS was below the lower end of the neuro-typical control range for the cognitive screen and picture naming tasks. The reading aloud and semantic association mean scores were within the neuro-typical range but towards the lower end of this range. Anomic symptoms for PwMS presented as both lapses in word retrieval and reduced speed of word retrieval. Word retrieval latency was on average 26% slower for PwMS. Within the anomic symptoms, there were instances of inaccuracy (42% of participants) as well as slow naming latency (31% of participants) in retrieving words. There was evidence of mild dysarthria for 33% of participants. Regression analyses suggested the anomic symptoms were most strongly associated with semantic processing deficits.

Conclusions: Anomic symptoms are common in (RES) RR MS, and present as inaccuracy as well as slow word retrieval latency. The prevalence and cognitive nature of anomic symptoms require further research across the range of presentations of MS.

Introduction

Multiple Sclerosis (MS) is a neurodegenerative disease characterised by the presence of inflammatory lesions and plaques in both the white and grey matter of the brain (Bagert, Camplair, & Bourdette, 2002). At early stages of the disease, the most common and recognisable symptoms are usually physical ones, i.e. motor and or sensory deficits, resulting in disabilities affecting visual processing, and a lack of motor coordination and/or fatigue (Finkelsztejn, 2014). Despite the perception of MS as a disease predominantly leading to physical disability, cognitive symptoms can appear at any phase of the disease (Rao, 1986). In fact, cognitive impairment have been reported to affect approximately 40–70% of people with MS (Chiaravalloti & DeLuca, 2008). Both physical and cognitive symptoms are caused because of the brain atrophy produced by demyelination (Achiron et al., 1992; Amato et al., 2007).

In early descriptions, Charcot reported that "speech disturbances" also commonly presented in MS (Charcot, 1877). Despite this, relatively little research has been carried out into speech/communication disorders associated with MS. More recent research has indicated that approximately half of the MS population presents with some kind of communication disorder (Hartelius, Runmarker, & Andersen, 2000), which limits their capacity to engage in family and community life. The most common speech disorder in MS is dysarthria (Hartelius et al., 2000), defined as "a collect name for a group of speech disorders resulting from disturbances in muscular control over the speech mechanism due to damage of the central or peripheral nervous system." (Darley, Aronson, & Brown, 1969). Though dysarthria has been found to occur at different stages of the disease, it is suggested that it is not common in the initial stages (McAlpine & Compston, 2005). Dysarthria can be caused by the dysfunction of various components of the central nervous system. Darley, Brown, and Goldstein (1972) found that people with MS presenting with cerebral, cerebellar and brainstem lesions showed severe dysarthric symptoms (Darley et al., 1972). The most common abnormal speech features identified in the MS population were vocal harshness, imprecise articulation, impaired respiratory support, impaired emphasis or stress patterns and impaired pitch variation or control (Murdoch & Theodoros, 2000).

Dysarthric symptoms tend to be more readily identifiable in MS relative to language disorders. Whether or not there are frank language disorders in people with MS, in the absence or in combination with dysarthria, has been a source of controversy because of conflicting results found in different research studies. However, it has been increasingly recognised that impaired language processing can be one of the cognitive deficits associated with MS (Gerald, Murdoch, & Chenery, 1987; Lethlean & Murdoch, 1997). The presence of language deficits in people with MS can be explained, to a certain extent, by damage to certain neuroanatomical tracts that support language processing (Shu et al., 2011). Several research studies have implicated the involvement of lesions of cortical areas and white matter pathways in language processing deficits in people with MS (Friend et al., 1999; Laakso, Brunnegård, Hartelius, & Ahlsén, 2000). MS can cause damage in cortical areas, as well as white matter tracks such as the arcuate fasciculus, which has also been thought to impact on language processing, leading for example to severe problems repeating words (Fridriksson et al., 2010). The thalamus and basal ganglia may also be affected in MS which are brain regions thought to be highly implicated in language functions (Laakso, Brunnegård, Hartelius, & Ahlsén, 2000; Mesulam, 2003), specifically verbal learning and verbal fluency (DeLuca, Yates, Beale, & Morrow, 2015). There is a question as to why language disorders in MS have not been extensively reported in the literature. This may be because the symptoms are very subtle and uncommon, or they are underdiagnosed (Rao, 1986), perhaps masked by clinical attention directed to more overt physical and dysarthric symptoms. However, Klugman and Ross (2002) reported that 63% of MS participants encountered poor communication abilities and language difficulties impacting their quality of life (Klugman & Ross, 2002).

Anomia is the term used to refer to problems in retrieving words including any difficulty in either word production accuracy or speed of retrieval. Anomic symptoms are reasonably easy to measure and can be seen as a marker for wider deficits in language processing. Anomia has been reported in people with MS (Beatty & Monson, 1989; Drake, Allegri, & Carra, 2002; Tallberg & Bergendal, 2009) though symptoms are thought to vary according to factors such as clinical course of the disease (e.g., Relapsing-Remitting versus Primary Progressive). Some findings indicate that anomia can appear at early stages in the disease process (Friend et al., 1999). However, the nature of the anomia associated with MS is not clear, in terms of the language processing levels which typically become impaired. A recent study investigated noun

and verb retrieval in people with Relapsing Remitting Multiple Sclerosis (RR MS) (Kambanaros, Messinis, Nasios, Nousia, & Papathanasopoulos, 2017) and concluded that verb retrieval was more severely impaired than noun retrieval. The authors suggested that there were specific linguistic underpinnings to these symptoms with disconnections between semantic and phonological lexicons (Kambanaros et al., 2017).

Anomic symptoms have been widely discussed in stroke aphasia literature (Goodglass, Kaplan, & Barresi, 2001a). Anomia frequently occurs in people with damage in the left hemisphere and aphasia, but it can also occur in healthy people from time to time, for instance, struggling to think of an intended word during an everyday conversation (Raymer & LaPointe, 2005). The most common form of this is the tip-of-the-tongue state, when the person knows there is a particular word to express an idea but cannot recall its phonological form (Laine & Martin, 2013). Anomia can affect the ability to retrieve verbs and adjectives but it is usually associated with problems in retrieving nouns (Raymer & Rothi, 2008). According to cognitive models of language processing, word retrieval requires semantic (the speaker has an idea or concept to express) and phonological (the speaker chooses a suitable word to express that idea) processes (Raymer & Rothi, 2008), and both semantic and phonological representations of a word are retrieved in different brain areas and in specific time windows for each process (Indefrey & Levelt, 2004; Laine & Martin, 2013). Hence, damage in different brain regions will be expressed as different types of anomia or anomic errors. According to Laine and Martin (2013), there are three types of word retrieval deficits (Laine & Martin, 2013):

1. *Semantic anomia*: This naming disorder tends to include comprehension problems for inaccurately named items which is reflective of incomplete, incorrect or imprecise semantic representations (Hodges, Graham, & Patterson, 1995). Comprehension and production deficits also affect auditory, visual and tactile object recollection, as well as the production of oral and written word responses (Laine & Martin, 2013).

2. *Word form anomia (phonological output lexicon*): Here, word-finding difficulties are due to an impaired access to the output lexicon or the lexical representations, whereas semantics are preserved (Lambon Ralph, Sage, & Roberts, 2000; Lorenz & Ziegler, 2009). The anomia presents with intact comprehension and accurate performance on word

production tasks that do not require semantic support, such as repetition and oral reading (Laine & Martin, 2013).

3. *Disordered phoneme assembly*: This describes problems in various post-lexical processes of cognitive-motor processing. It includes substitutions, additions, exchanges and omissions of phonemes or phoneme combinations which surface in output (Laine & Martin, 2013).

The presence of anomia has been found in people with both RRMS and chronic progressive MS. Beatty and Monson (1989) found impaired naming abilities in more than 40% of people with chronic progressive MS and in 20% with RR MS (of a total of 34 participants with MS in total). In this study, anomic deficits were not entirely reduced by cueing. They also found that participants showed a wide range of impairments in accessing semantic and lexical information such as increased latency and reduced precision when naming familiar words where the target was evoked by visual, semantic or phonologic cues, and ineffective searches of semantic memory.

Lethlean and Murdoch (1994) carried out a comprehensive study on naming abilities where they examined the effects of variables on naming abilities and the nature of naming errors produced by a group of people with MS (n = 60). The variables included disease course, disease duration, age, and education level. Their findings confirmed the existence of naming impairments in people with MS, where the chronic progressive group showed more naming deficits than the RRMS group. They also suggested that disease course is not a reliable predictor of naming deficits in MS as they did not find a relationship between naming scores and subject variables. In this study, participants with MS made more naming errors than the control group, in particular semantic errors such as semantic paraphasias and circumlocutions for the target. Based on their findings, the authors suggested the existence of a semantic accessing deficit as an explanation for the large rate of semantic errors of the MS group (Lethlean & Murdoch, 1994). As Lethlean and Murdoch did not have a confirmation of lesion sites occurring in the MS group, they speculated that the presence of significantly more semantic paraphasias in the MS group compared with the control group was due to a cortical-subcortical interruption in their communication, which is necessary for normal naming function. This interruption disturbs the ability of an individual to monitor verbal output and

later to access words efficiently from the lexicon (Lethlean & Murdoch, 1994; Murdoch & Theodoros, 2000).

In summary, our understanding of speech, language and communication deficits in MS as reflected in the current literature is very partial, with overlapping and interacting symptoms of motor and cognitive symptoms in a heterogeneous disease making for a clouded picture, which is reflected in both the theoretical and clinical literature. With specific reference to anomia, everyday interaction requires rapid and fluent access to a substantial vocabulary. Yet, this ease of access can be subtly limited by the gradual onset of MS. If undetected, these deficits can have a negative impact in the professional and social life of people with MS. Sensitive and time-efficient assessment of anomia in people with MS may lead to earlier treatment and more effective cognitive rehabilitation, thereby reducing the impact of the disease and enhancing quality of life. Further research is clearly warranted to explore anomic deficits and broader communication disabilities in people with MS.

This study aimed to investigate the extent and nature of anomic symptoms in people with Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis (RES RR MS) with respect to both accuracy and reaction time (RT) in a picture naming assessment task. In order to progress our understanding of anomia and communication skills more broadly, we aimed to recruit 100 participants to ensure a range of performance and numerically stronger findings. Given the literature briefly reviewed here, we hypothesised that anomic symptoms as measured by low accuracy scores and slow latency scores would be common. In order to interpret anomic performance in the context of wider cognitive, linguistic and speech production skills, we also implemented the following tests: the Addenbrooke's Cognitive Examination–Revised (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006); the National Adult Reading Test (NART) (Nelson & Willison, 1991); and, the Pyramids and Palm Trees-PPT (Howard & Patterson, 1992). These were respectively: a cognitive screening tool devised in the UK; a reading words aloud test which we also used to screen for dysarthria; and a test of picture semantic associations. Complimenting picture naming scores with these wider performance measures would allow us to arrive at some preliminary hypotheses as to the nature of anomic symptoms with respect to the relative contribution of motor, cognitive and linguistic skills.

Methods

Participants

One hundred participants with (RES) RRMS were successfully recruited for the study. These were 68 females and 32 males. Their mean and standard deviation of their age was 40.85 (8.97), with an average of 7.58 (5.95) years living with MS. The average years of education was 14.86 (2.4). In order to directly compare the performance of the participants with MS with control participants, we recruited 40 neurotypical participants, who were spouses or family members of the participants with MS. These were 25 females and 15 males, with an age mean and standard deviation of 38 (11.18) and average years of education was 15.12 (2). Differences between the MS group and Control group in terms of age, education and gender were examined using Mann-Whitney U. The group of participants with MS and the control group did not differ significantly with respect to age (U = 1611.0, Z = 1.796, p = .073 r= 0.15), education (U = 1824.50, Z = 823, p = .410, r = 0.069), or gender (U = 1890.0, Z = 620, p = .535, r = 0.052)

This study obtained approval from the National Health Service Research Ethics Committee (REC) (15/NS/0126). The inclusion criteria were definite diagnosis of MS, as confirmed by neurological diagnosis, age over 18, native English speakers and enough mobility in the upper limbs to allow participants to fill in the questionnaires. Informed consent was obtained from all participants prior to participation in the study. All participants with MS were assessed at Salford Royal Foundation Trust, North West England, during their infusion of natalizumab (TYSABRI) under the care of the Neurology team. This medication is commonly prescribed as treatment for people with (RES) RR MS. The infusion does not produce any type of cognitive side effects that can have a negative influence in the performance of the participants.

Screening assessment

The behavioural assessments included:

1. The Addenbrooke's Cognitive Examination–Revised (Mioshi et al., 2006). This cognitive screen was used to assess the presence and severity of symptoms of cognitive impairment. An advantage of the ACE-R lies in the relatively wide range of cognitive domains that are addressed (e.g., attention and orientation, memory, verbal fluency, language, visuospatial skills), which helps to obtain a general measure of the cognitive status of the participants. The ACE-R (Mioshi et al., 2006) has been used in previous MS studies, proving to be sensitive in detecting cognitive impairment in people with MS (Connick, Chandran, & Bak, 2013; Hamilton et al., 2009). In both studies, participants performed slightly above the cut-off of the control range (score 88) with a mean and standard deviation of 90.9(8.3) and 91.17(6.49) in Connick et al. (2013) and Hamilton et al. (2009), respectively.

2. Picture naming task. A bespoke picture naming task was developed to assess both accuracy and response latency of word retrieval. Picture naming tasks have been widely used to investigate anomia in people with MS (Beatty & Monson, 1989; Drake et al., 2002; Tallberg & Bergendal, 2009). The task developed for this study was displayed on a laptop computer screen. The stimuli were pictures selected from the International Picture Naming Project-IPNP (Bates et al., 2000), along with the simultaneous presentation of a beep sound (for RT analyses). Before the picture appeared, a fixation dot was presented in the centre of the screen for one second where the picture was to appear to ensure the participant was looking at the correct location. There was a six seconds interval between the presentations of pictures for the participant to name the picture that appeared on the screen. The RT of this task was measured for every correct word. The RT was obtained by measuring the length of time from the beep at the picture onset to the onset of correct word production in audio-recordings of the task. The task consisted of sixty pictures of objects selected from the IPNP (Bates et al., 2000). Three other pictures also from the IPNP (Bates et al., 2000) were displayed at the beginning of the task to familiarise participants with the procedure before task commencement.

These sixty pictures were selected and divided into four sets of fifteen pictures each, based on the RT in milliseconds (ms) required to name the picture, obtained from the normative data provided by the IPNP (Bates et al., 2000). RT was chosen to divide the groups so that deficits in processing speed and naming latency could be assessed and compared with the control group as well as accuracy. The four different RT groups were:

Group A: 15 pictures with a RT <800 ms;

Group B: 15 pictures with a RT between 801-1000 ms;

Group C: 15 pictures with a RT between 1001-1220 ms;

Group D: 15 pictures with a RT between 1220-1500 ms.

Psycholinguistic variables associated with language performance were also obtained from the normative data of the IPNP (Bates et al., 2000), specifically frequency, age of acquisition and number of phonological syllables. The words included in each subtest and the information about their psycholinguistic variables can be found in the appendix.

The frequency of the words referred to the number of times a word is used in oral language, measured in occurrences per million (Bates et al., 2000). Another variable of interest was age of acquisition, the average age at which people usually learn a word. Age of acquisition values are divided into three groups: Group 1, with value equal to 1, is for words learned between 8 and 16 months; Group 2, with a value equal to 2, is for words learned between 17 and 30 months; Group 3, with a value of 3, is for words learned with more than 30 months (Bates et al., 2000). Finally, word length was measured as number of phonological syllables.

As can be seen in Table 3.1, the group mean frequency decreases as the RT of the group increases. The average age of acquisition of each group increases as the RT of the group increase. The length of phonological syllables is the same for groups A, B and C, and it increases for group D.

Z-scores were computed for the raw accuracy and RT data so as to allow us to compare these sets of scores from different normal distributions. RTs were calculated for accurate naming responses only.

1. The National Adult Reading Test (NART) (Nelson & Willison, 1991) consists of fifty irregular words displayed on a screen of a computer which participants are asked to read aloud. The NART (Nelson & Willison, 1991) has been widely used to assess premorbid intelligence in people with different types of neurological diseases, including a research study that used it with people with MS (Friend & Grattan, 1998; Friend et al., 1999). However, there is evidence with the American version of this test (NART-R) that suggests that this task cannot be used to estimate premorbid intelligence in people with MS because of the language deficits associated with the disease (Friend & Grattan, 1998). For this reason, in the present research study this test has been used to detect the presence of dysarthria reading isolated words (as it involves reading aloud) and as a measure of reading skills, and has not been utilised as an estimate of general intellectual functioning. To assess the level of dysarthria of each participant, the Therapy Outcome Measure for Dysarthria was used (Enderby, John, & Petheram, 1997). This allowed scoring of the severity of the problem across a five point scale. The descriptors of this five point scale are: "0" profound dysarthria, "1" severe/moderate dysarthria, "2" moderate dysarthria, "3" moderate/mild dysarthria, "4" mild dysarthria, and "5" no dysarthria (Enderby et al., 1997). Two speech and language therapists listened to audio-recordings of participant performance on the NART in order to independently assess for the presence and severity of dysarthric symptoms. Where there were discrepancies between the two speech and language therapists who made these clinical assessments, this was within 5. These instances were resolved through review and discussion between the two therapists.

2. The Pyramids and Palm Trees-PPT (Howard & Patterson, 1992) was used to assess semantic processing of concepts. Participants need to access the meaning of the pictures that are presented to them, and to establish a semantic relationship between two of the pictures. For example, for the target picture glasses, participants chose between a picture of eye or ear and point to the one with the strongest meaning association. Although to our knowledge there is no evidence of the use of this test in people with MS in the literature reviewed so far, this was used as an accessible task designed to assess semantic knowledge, impairments of which may contribute to language deficits such as anomia.

Table 3. 1. Values of the psycholinguistic variables for each group of words in the Picture Naming task.

Psycholinguistic variables	Group A	Group B	Group C	Group D
Frequency mean	3.51	2.90	2.15	1.63
Frequency S.D.	1.80	1.24	1.37	0.75
Age of Acquisition mean	1.27	2.13	2.4	2.73
Age of Acquisition S.D.	0.70	0.99	0.91	0.70
Number of Syllables mean	1.73	1.73	1.73	2
S.D.	0.70	0.70	0.70	0.92

Multiple Regression analyses were used to examine correlations between main results for the behavioural assessments included in this study; i.e. picture naming accuracy, ACE-R, P&PT, NART.

Results

Table 3.2 shows the group level mean and standard deviation scores of the participants with MS (PWMS) and the neuro-typical control participants we also recruited in the behavioural assessments. Table 3.2 also provides (in the final 2 rows) the control cut-off scores (i.e., the lower threshold for performance within the neuro-typical range – x2 S.D. from the mean) for both the control participants we recruited for this study (n = 40) and control data provided within the published assessments we used. The scores of the PWMS fell below the lower end of the neuro-typical performance range for the cognitive screen and picture naming tasks as follows:

- ACE-R: PWMS = 87.37, control cut-off = 90.89;
- Picture Naming: PWMS = 52.02, control cut-off = 52.52;

Table 3. 2. Overview of the mean scores for participants across the different tasks.

TASK	ACE-R Overall	ACE-R Attention Orientation	ACE-R Memory	ACE-R Verbal Fluency	ACE-R Language	ACE-R Visuospatial Skills	PICTURE NAMING	NART	PYRAMIDS & PALM TREES
Max Score	100	18	26	14	26	16	60	50	52
PwMS Group Mean	87.37	16.25	21.85	10.72	23.79	14.77	52.02	34.41	48.91
PwMS Group S.D.	7.17	1.45	3.61	2.34	2.01	1.54	5.21	8.36	2.52
Control Group Mean	96.13	17.9	24.08	12.85	25.48	15.83	57.08	39.88	50.83
Control Group S.D.	2.62	0.3	1.95	1.12	0.68	0.5	2.28	3.98	1.05
Difference between mean scores (Control Group > MS Group) %	8.76 8.76	1.65 9.16	2.23 8.57	2.13 15.21	1.69 6.5	1.06 6.62	5.06 8.43	5.47 10.94	1.92 3.69
Cut-off for control range (mean -2 S.D.)	90.89	17.3	20.18	10.61	24.12	14.83	52.52	31.92	48.73
Published cut-off for control performance *	88	17	18	9	24	15	52	26	49

For the other two tasks, reading aloud and semantic processing skills, the scores of the participants with MS (PwMS) fell within the neuro-typical control range though towards the end of this range as follows:

- NART: PwMS = 34.41, control cut-off = 31.92;
- Pyramids & Palm trees: PwMS = 49.91, control cut-off = 48.73.

The control participants recruited for this study performed at higher levels than the control data provided within the ACE-R assessment (cut-off = 90.89 compared to 88) and the NART (cut-off = 31.9 compared to 26); yet, the mean score for the participants with MS fell below this alternative cut-off of 88 (ACE-R: MS group = 87.37). Furthermore, our controls cut-off scores were similar to the normative data provided within the Picture Naming and PPT (cut-off = 52.52 compared to 52 and cut-off = 48.73 compare to 49 respectively). Beyond group means, there was substantial variability in performance across the participants with MS, as suggested by the markedly higher standard deviations for the group of participants with MS in Table 3.2.

More fine-grained analyses of these results are provided here, in the order in which the assessments were presented in the Methods:

1. ACE-R: Looking at individual performances, 61% of PWMS performed below the control cut-off score for the task (90.89), which is indicative of the presence of some degree of cognitive impairment. In fact, some participants performed below 70 points, reflecting more marked cognitive impairment. The range of ACE-R scores in numerical/rank order is displayed in Figure 3.1. According to the Mann Whitney U, there is a statistical difference between the control and PwMS groups regarding the total scores in the ACE-R (U= 376.0, p= .0001, r = 0.634), showing a medium effect size.

Table 3.2 shows the mean score and SD in the global task and in the five separate subtests for the PWMS in the ACE-R. Below the name of each subtest appears the maximum possible score for each subtest, as well as the control cut-off representing impaired performance. In terms of the relative difficulty of each sub-test of the ACE-R, this is best reflected in the percentage of PWMS scoring below the control cut-off. This was 50% for Attention Orientation (U =

420.0, *p* = .0001, r = 0.642), 22% for Memory (*U* = 1228.0, *p* = .0001, r = 0.642), 28% for Verbal Fluency (*U* = 875.0, *p* = .0001, r = 0.444), 36% for Language (*U* = 915.0, *p* = .0001, r = 0.435), and 17% for Visuo-spatial skills (*U* = 1154.0, *p* = .0001, r = 0.375). Overall, while these data showed a statistically significant difference in every sub-task, attention/orientation and language tasks were the most challenging for the PWMS in relative terms.

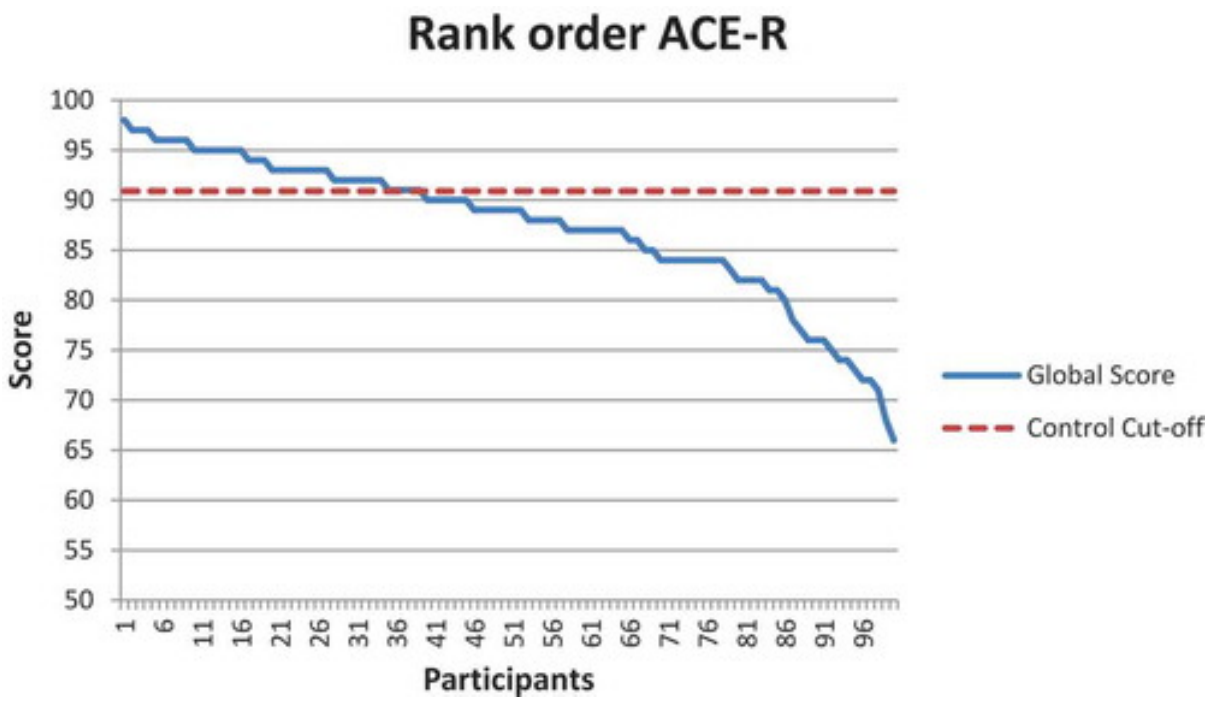


Figure 3. 1 ACE-R Total scores rank order in participants with MS.

2. Picture naming task: Performance was measured in terms of both naming accuracy and RT. Amongst the PWMS, there was again substantial variability in performance. The mean accuracy was 52.02 correct naming responses, which was broadly the same value as the cut-off scores provided both within the IPNP dataset from which the stimuli had been sourced (52) and in the matched control data (n = 40) (52.52) (see Table 3.2). The range of picture naming accuracy scores in numerical/rank order is displayed in Figure 3.2.

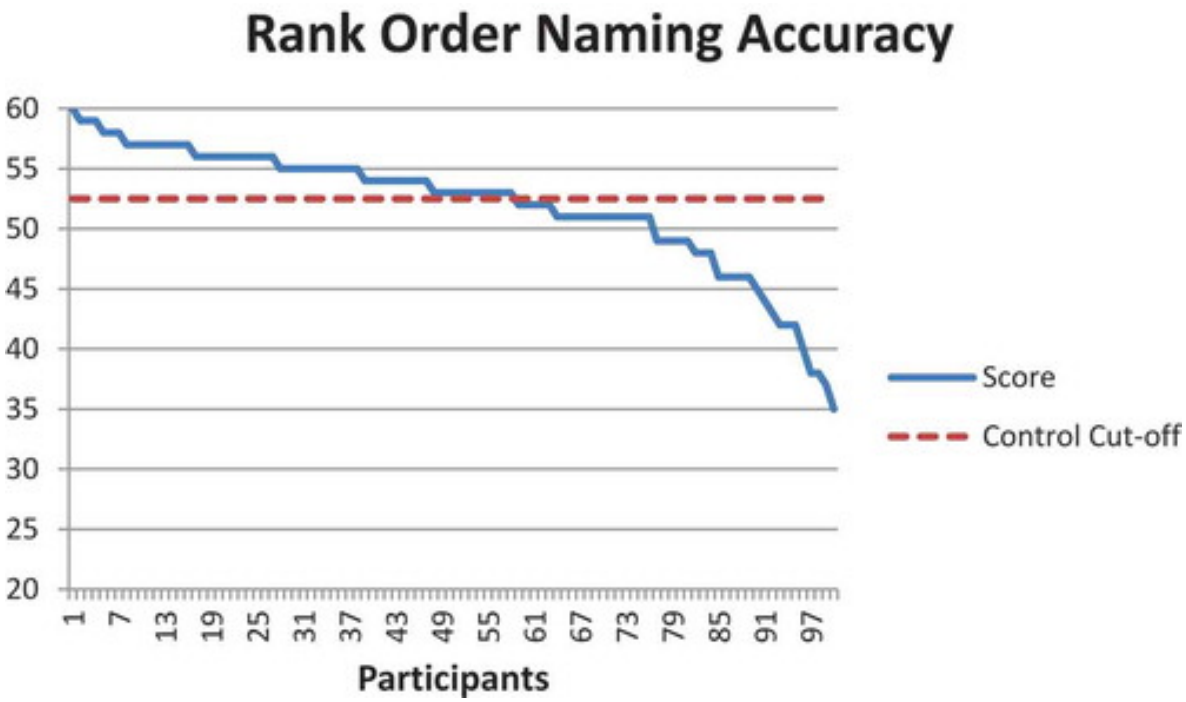


Figure 3. 2. Naming test accuracy rank order in participants with MS.

RT results are shown in Table 3.3. These show poorer performance for PwMS with regard to naming speed who were, for the global naming task, on average 26% slower than the control data (1307 ms versus 1035 ms) and 28% slower than that reported in the normative data (1307 versus 1020 ms). The global RT of the data we collected for the study (n=40) was visibly similar to the normative data from the IPNP as shown above, though with more variability in performance across the control participants (SD 148 ms), possibly reflecting their higher overall age compared to the normative data age group.

As well as noting the difference in RT for the global task, it was also informative to analyse the difference in the RT between subgroups of words. For Group A (easiest word group:

relatively high frequency and early AoA), mean RT for participants with MS was 20% slower than the mean RT of our control data for this subgroup. The difference according to the Mann-Whitney U was found to be significant (U=26.00, p=0.0001, r= .65). For Group B, participants with MS were 35% slower and again this was significant (Mann-Whitney U, U=17.00, p=.0001, r=.72). For Group C, the RT for participants with MS group was 26% slower, and again statistically significant (Mann-Whitney U, U=47.00, p=.006 r=.50). Finally, for Group D, although the same pattern was evident with a 13% slower group performance for participants with MS, this did not reach statistically significance (Mann-Whitney U, U=67.00, p=.061 r=.34). Group B was the subgroup of words with the largest RTs for participants with MS compared to the control's subgroup RTs (35% slower). Subgroup D (relatively difficult words) had the longest RTs for participants with MS compared to the rest of the subgroups. Both subgroups C and D had a reasonably similar level of naming accuracy with 75% and 77% for participants with MS respectively, which showed that the RT were not differentially affected by accuracy.

Table 3. 3 Picture Naming Reaction Time Results (in ms) – Group means (and S.D.s).

	Participants with MS(n= 100)	**Control Participants(n= 40)**	**Normative data from IPNP**
Global RTs for Picture Naming Task (n= 60)Difference in %	1307 (211)	1035 (148) 26%	1020 (52) 28%
Word Group A (n= 15)Difference in %	894 (71)	742 (98) 20%	742 (31) 20%
Word Group B (n= 15)Difference in %	1108 (170)	821. (106) 35%	890 (59) 24%
Word Group C (n= 15)Difference in %	1557 (287)	1236 (333) 26%	1104 (58) 41%
Word Group D (n= 15)Difference in %	1670 (315)	1480 (418) 13%	1345 (58) 24%

Z-scores were computed for the raw accuracy and RT scores. The Mann-Whitney descriptive statistics showed that the accuracy of PWMS was lower (median= 53) than the control data

(median=57.5). The difference according to the Mann-Whitney U was found to be significant (U=.64100, p=.0001, r=.53). Overall, the results revealed that anomia was evident in many participants with regard to naming accuracy and of speed of word retrieval.

As well as considering naming speed and accuracy, we also examined naming errors as these can often be informative in terms of highlighting weak aspects of language processing on cognitive neuropsychological models. Naming errors were categorised based on the classification used by Martin, Dell, Saffran, and Schwartz (1994). Description of error types are found in Table 3.4. The participants with MS generated a total of 748 (12%) errors (see Table 3.5). The most frequent error type was semantic paraphasia which occurred 55% of the time (Table 3.5). In fact, the variants of semantic error combined accounted for 65% of errors (n=471). After semantic, the most common error type was 'no response', in which for 21% of errors (n=156), there was no verbal response within the 6000 ms time limit. Next, perceptual errors (perceptually related and part perception) totalled 15% of errors (n=115) and lastly sound based errors (formal phonemic paraphasias, literal paraphasias and neologistic) accounted for only 0.8% of total errors (n=6).

Table 3. 4 System for error analysis on naming test.

Type of Error	Description	Example
Correct	No error	
Semantic paraphasias	Inaccurate words with semantic relationship to the target word.	*Horse* for *goat*
Semantic description	Multiword description of the target word	*You use it to cut paper for scissors*
Semantic super-ordinate	A word that use to stand for a whole category of things.	*Fruit* for *banana*
Semantic negation	An answer indicating what the answer in not	*It is not an orange* for *apple*
Wild paraphasia	A response word with no relation to the target	*Chair* for *foot*
Formal phonemic paraphasias	Word that shares <50% of phonological elements of the target	*Hoot* for *foot*
Neologistic	Abstruse non-word	*Batelli* for *squirrel*
Perceptually related	A similar visual representation of the target	*Circle* for *ballon*
Partly perception	Name only a part of the picture	*Ankle* for *foot*
No response	No verbal response within the 6 second time window	

Table 3. 5. Error analysis of naming test in 100 participants with RR-MS.

Total naming attempts	6000
Correct naming attempts	5252
Error Types	Number
Semantic paraphasias	413
Semantic description	29
Semantic super-ordinate	21
Semantic negation	1
Wild paraphasia	7
Formal phonemic paraphasias	5
Literal paraphasias	0
Neologistic	1
Perceptually related	44
Partly perception	71
No response	156
TOTAL ERRORS	**748**

3. NART: The results of the NART (Nelson & Willison, 1991) indicated that 33% of PWMS presented with mild dysarthric symptoms. This indicates that the naming deficits described above may not have been solely the result of articulatory motor deficits. Inter-rater agreement for the dysarthria ratings was at 92%. Overall, participants with MS were accurate in reading words aloud and did not present severe difficulties in the task. In fact, their mean performance (34.4) was above the lower end of the neuro-typical performance range (cut off = 31.9). Only 11% of participants with MS had any difficulty reading aloud according to these single word reading data. The range of NART scores in numerical/rank order is displayed in Figure 3.3. Mann Whitney U showed a significant difference between the control group and PWMS (U = 1193.0, p = .0001, r = 0.315).

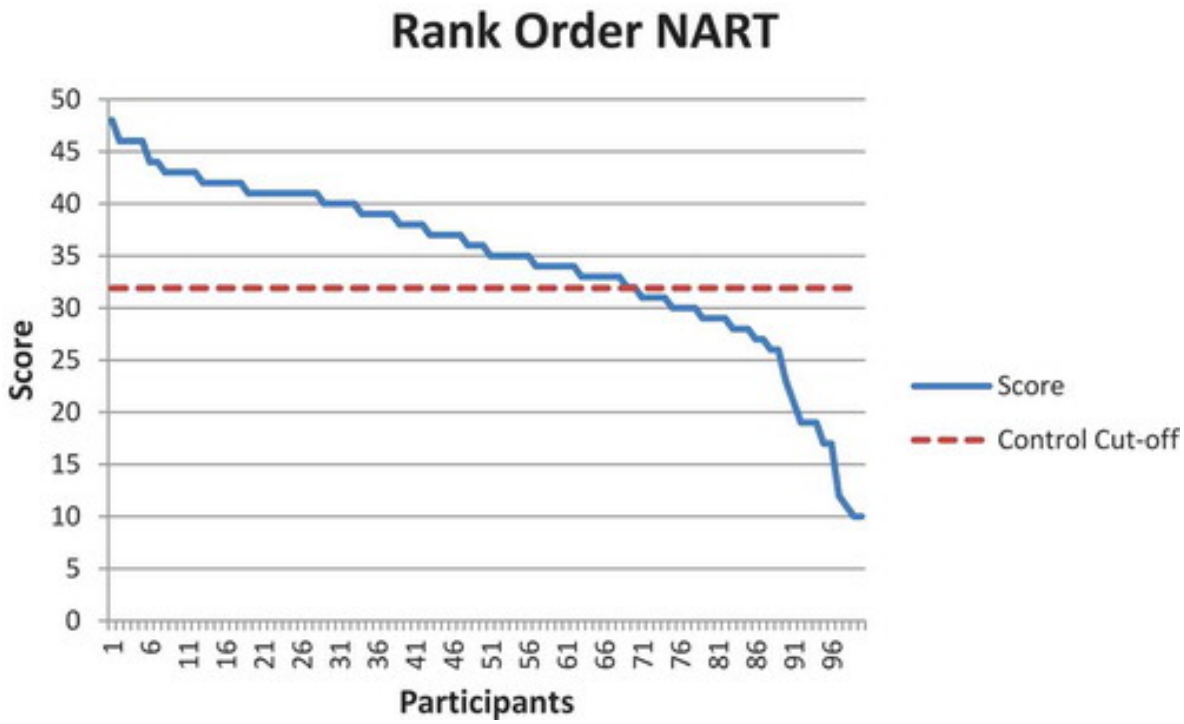


Figure 3. 3. NART scores rank order in participants with MS.

4. Pyramids and Palm Trees Test (P&P): The average number of correct responses for PWMS group was 48.91 which is just above the lower end of the control range (48.73) for this task. Looking at individual participant performance, 32% of PWMS showed clinical performance (performance below cut-off score) suggestive of some degree of semantic processing impairment. The range of P&P scores in numerical/rank order is displayed in Figure 4. Mann Whitney U showed a significant difference between the control group and PWMS (*U* = 976.0, *p* = .0001, r = 0.406).

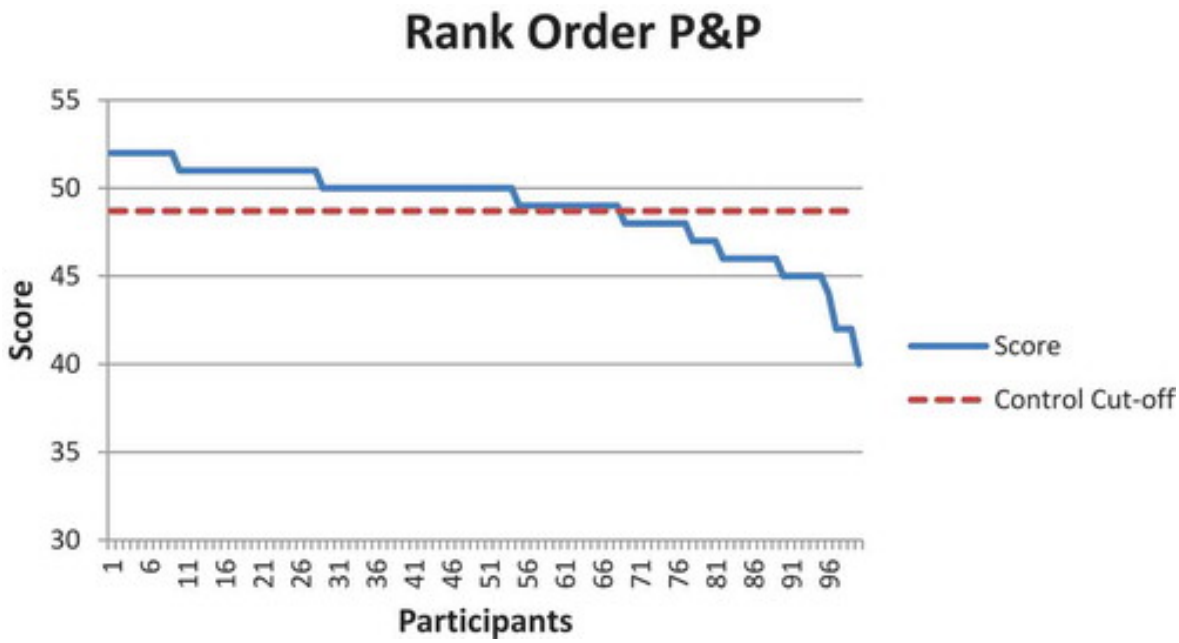


Figure 4. P&P scores rank order in participants with MS.

Comparison across assessments

Multiple Regression analyses were conducted using the stepwise method. A significant model emerged F (2,97) = 36.418, p<p< .0005. The association between the accuracy in Picture Naming Task and the accuracy of the explanatory variables (ACE-R, NART, PPT) was moderately weak (Multiple R = 0.655). Only the PPT (Howard & Patterson, 1992) and the ACE-R (Mioshi et al., 2006) were significant in the model. Together, these variables (PPT, ACE-R) accounted for 42.9% of the variance (R^2 = .429, p < .0001). Both variables positively related to the picture naming task scores. The regression coefficient for the PPT was 0.89 (95% CI = 0.53–1.24); for the ACE-R it was 0.24 (95% CI = 0.12–0.37). The confidence limits did not encompass a negative value. Therefore, it can be concluded that the population regression coefficients for both the PPT and the ACE-R were positive (PPT: t = 4.969; p < .0001; ACE-R: t = 3.878; p < .0001). The standardised regression coefficients showed that PPT was a stronger predictor than the ACE-R. However, both variables were related to the picture naming task score.

Discussion

This study aimed to address the lack of clarity in existing literature as to both the extent and nature of anomia in people with Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis (RES RR MS), in the context of speech, language and cognitive deficits. The key findings regarding the presence of speech/language deficits in a reasonably large cohort of people with RES RR MS were that anomic deficits in word retrieval speed and accuracy were evident, together with some degree of semantic and cognitive impairments, as well as less frequent and predominantly very mild symptoms of dysarthria. But crucially, there was a large variability within the performance of the 100 participants with RRMS that we recruited to the study.

Regarding the overall cognitive status of the participants with MS, cognitive impairment in more than one cognitive domain was highly prevalent. More than 60% of participants presented with at least mild cognitive impairment, and some presented with more severe cognitive deficits. Within the anomic symptoms, there were more instances of inaccurate

naming (in 42% of participants) as opposed to slow naming latency (31% of participants) in retrieving words. Inaccurate and slow naming were related as evidenced by the frequency of semantic errors suggesting partial semantic activation underpinning both error types. The presence of dysarthria in some cases (33% of participants) may have had some negative effect on word retrieval skills. However, deficits in semantic processing skills were found to be strongly related to the word retrieval problems and were the largest contributor to anomic symptoms in this study.

The results showed that individuals with RR MS did indeed often present with anomic symptoms, as evidenced by word retrieval inaccuracy and delayed latency. These results confirm and extend previous literature findings firstly by extending the sample size substantially to 100 participants providing a more robust statistical sample. Secondly, within this sample, we have focused solely on RRMS in contrast to previous anomia studies which combined relapsing-remitting and progressive sub-variants of MS (e.g., Beatty & Monson, 1989; Lethlean & Murdoch, 1994). The results are in line with previous findings that have aimed to delineate the nature and extent anomic deficits in people with (RES) RRMS (Kambanaros et al., 2017). As in Beatty and Monson (1989) and Lethlean and Murdoch (1994), semantic deficits were evident in both semantic processing scores (32% clinical performance on the P&P) and as suggested by the overwhelming dominance of semantic errors, particularly semantic paraphasic errors, indicative of partial semantic processing for lexical access. It seems likely that, for many people with MS, the lesions caused by the disease can hamper the processes involved in the access of semantic knowledge, increasing the severity of the anomic symptoms. The existence of many non-responses in naming may also have been indicative of slowed lexical processing, specifically in the semantic domain and/or executive search strategy domain, as previously noted by Sepulcre et al. (2011).

Our study was also noteworthy in having taken a more integrative approach to naming and language processing by screening for motor speech symptoms of dysarthria, given the potential for such symptoms to impede the rapid and effortless production of words in confrontation naming. We did not find any evidence for the presence of severe dysarthria in reading single words in isolation. This is arguably inconsistent with the literature, which suggests that approximately 40% of people with MS suffer from this deficit (Sorensen, Brown, Logemann, Wilson, & Herndon, 1994). However, we did uncover reasonably frequent

instances of mild dysarthric symptoms only. Typically, these were symptoms like weak phonation, low voice volume and reduced articulatory precision in production of multi-syllabic words. In themselves, such symptoms appear unlikely to impact on RT for word onset of naming. Indeed, slow latencies were evident across many participants with MS with no dysarthria symptoms. Clearly the relationship between naming response times and dysarthria is complex and warrants further research.

In summary, these results have strongly indicated that MS can and does commonly produce naming deficits as part of a wider cognitive-linguistic presentation of broader executive-attentional and semantic processing symptoms. A substantial proportion of the participants with (RES) RR MS presented with mild to moderate anomic symptoms but within a complex interactive picture of frank semantic, cognitive and motor speech/dysarthric symptoms. These word retrieval deficits are likely to have strongly impacted those affected, and anecdotally, a number of participants did report suffering from anomic deficits in their everyday personal and social lives. It is difficult to estimate the percentage of the population with MS that suffers from language deficits and more specifically naming problems, however, these have been found to be widely present in the current sample of participants.

The main limitation of this study was that although the sample of participants had a considerable size (n = 100), the use of a communication screening tool, by definition, only offered limited insights into the extent and nature of the symptoms under investigation. As a development from this broad-but-shallow approach, it should be informative in future work to conduct more extensive and focused neuropsychological and motor speech assessments in fewer of the participants who are presenting with frank language deficits including anomic symptoms. Furthermore, future research could also very usefully compare the findings from this sample of people with RR MS, with similarly large samples of people with other MS subtypes, particularly secondary progressive presentations which could be anticipated to represent marked deterioration in cognitive and motor skills from those captured in the current data. On the other hand, all participants included in this study presented (RES) RRMS and were treated with natalizumab (TYSABRI). It would be equally be useful to extend the communication screen utilised to people with less severe onset of RRMS with a lighter lesion load. Other limitations of this research study relate to the relative lack of information about the level of physical disability and stability of the disease. It will be important to measure this

variable to see if it correlates with other variables such as type of MS or performance in certain tasks. Although some participants did present with physical disabilities to a certain extent, these symptoms did not interfere in their performance in the behavioural assessments.

Lastly, as well as understanding the deficits under discussion, future research should also aim to develop sensitive and time-efficient assessments and, most importantly, evaluate treatment programmes through which people with MS can reduce the disabling consequences of anomia and related communication deficits. With regard to language assessments, comparing the relative contribution of naming tests to other types of testing such as verbal fluency tasks in understanding language processing in RRMS will be key. Furthermore, the development of tailored patient reported outcome measures should enable us to understand the relationship between language deficit measures and functional consequences of these symptoms for activity-related quality of life. With respect to treatment, speed of word retrieval has been proposed as a useful treatment target in stroke aphasia research (Conroy, Sotiropoulou Drosopoulou, Humphreys, Halai, & Lambon Ralph, 2018), so applying this treatment approach with people with RRMS may have considerable rehabilitation potential.

CHAPTER 4

Anomia in Relapsing-Remitting Multiple Sclerosis: A replication and extension of previous findings.

Introduction

MS is characterised by demyelination and axonal injury and can affect the brain and/or the spinal cord, causing a wide range of symptoms, including physical disabilities, cognitive impairments and language disorders (Noseworthy et al., 2000). The estimated prevalence of MS in England is 190 cases per 100,000 population, and total of 105,800 MS sufferer (Public Health England, 2020); moreover, it is the most common chronic disabling disease of the central nervous system in young adults (Weinshenker et al., 1989).

There are different standardised MS clinical courses, according to its clinical, imaging and biomarker characteristics (Lublin et al., 2014). RR MS is the most common clinical form with 85% of cases at onset (Huisman et al., 2017) and it follows periods of attack of symptoms (relapses) with periods of remission (Lublin et al., 2014). RES RRMS has a particularly rapid disease progression and it is defined as two or more disabling relapses in one year, and one or more lesions showing in magnetic resonance imaging (MRI) (European Medicines Agency, 2014)

Cognitive impairment is common in MS affecting up to 70% of the patients (Amato, Zipoli, & Portaccio, 2006). The most frequently affected functions are memory, efficiency in information processing, visual perception functions, executive functioning and attention (Chiaravalloti & DeLuca, 2008; DeLuca, et al., 2015). Cognitive impairments have been widely investigated in MS, although language deficits have not been thoroughly researched to date, even though language problems and poor communication skills more broadly are found in 40 - 60% of MS patients, negatively impacting their quality of life (Hartelius, Runmarker, & Andersen, 2000; Yorkston et al., 2003 (El-Wahsh et al., 2020). Dysarthria, a neurological muscle movement disorder, and/or deficits in cognition are symptoms that can interfere with communication skills. Studies into communication disorders have been usually focused on the speech rather than the language deficits probably as a result of subcortical demyelination and axonal loss (Jeffery, Absher, Pfeiffer, & Jackson, 2000). However, language impairments in MS such as word retrieval or verbal production have been found to be independent from dysarthria (Friend et al., 1999; Murdoch & Lethlean, 2000; Rao, 1986).

Early investigations into language deficits in MS did not find frank symptoms of disordered language processing akin to aphasic symptoms (Rao, 1986; Rao, St Aubin-Faubert, & Leo, 1989), although often these studies were not solely aiming to investigate language functions

and, consequently, the methods and tools used to test language might not have been sufficiently sensitive (Friend et al., 1999; Peyser, Rao, LaRocca, & Kaplan, 1990). However, subsequent research has revealed language deficits in MS patients with different disease courses. Specific symptoms have included impaired naming, comprehension, and verbal fluency (letter and category fluency) (Beatty et al., 1989; Friend et al., 1999; Gerald, Murdoch, & Chenery, 1987; Henry & Beatty, 2006; Kujala, Portin, & Ruutiainen, 1996; Lethlean & Murdoch, 1993, 1994 (Gerald et al., 1987). A recent systematic review (Renauld et al., 2016) found an impairment of various higher language abilities in people with MS, yet no conclusions were drawn since the methods used in the studies varied widely.

Tallberg and Bergendal (2009) confirmed that language symptoms such as anomia in MS were common but often subtle and that some patients reported a subjective experience of an impaired ability although this was difficult to verify in standard assessments of language. Given the crucial role of verbal communication in everyday social, vocational and family life, it has been noted that even mild communication impairments lead to major lifestyle changes characterized by substantial limitations in communicative participation (Klugman & Ross, 2002; Yorkston et al., 2001).

The nature of cognitive-linguistic deficits such as anomia, in terms of the underlying impairments in thinking which cause behaviours such as lapses in word retrieval or inefficient, audible word searches, continues to be debated. Marié and Defer (2001) described 21 patients with significant impairments in executive processes, working, episodic and procedural memory, whereas short term memory, language and global intellectual efficiency were not impaired. However, different studies with people with MS have confirmed the existence of naming errors (Beatty & Monson, 1989; Lethlean & Murdoch, 1994), though the nature of anomia remains poorly understood. Naming tests have been widely used in patients with MS (Beatty & Monson, 1989; Friend et al., 1999; Gay Snodgrass, 1984; Henry & Beatty, 2006; Lethlean & Murdoch, 1993, 1994), frequently observing the presence of naming impairments (Drake, Allegri, & Carrá, 2002; Henry & Beatty, 2006; Lethlean & Murdoch, 1994). The process of correctly naming a picture involves well organised perceptual, semantic and lexical cognitive analyses (Snodgrass, 1984; Warren & Morton, 1982). In Lethlean & Murdoch's (1994) study, the MS group of participants was significantly less accurate in naming pictures than a control group. Moreover, they suggested that errors in naming tests

in people with MS derived not only from impairments at the levels of the perceptual and the semantic system, but also by a dysfunction in the lexical semantical access.

A recent and comprehensive attempt to capture and characterise the extent and nature of anomic symptoms in people with RR MS (De Dios Pérez et al., 2020), in the context of screening of wider cognitive skills, provides a starting point for trying to understand the neuropsychological origins of anomic symptoms in this clinical population. De Dios Pérez and colleagues recruited 100 participants with RR MS and implemented language and cognitive screening tasks. The tasks administered assessed presence of dysarthria, general cognitive abilities (attention, memory, verbal fluency and visuospatial skills), naming skills and semantic memory. Most of the participants presented different levels of cognitive impairment in more than one domain. Although the study found evidence of mild dysarthria amongst some participants, its prevalence was minimal and did not explain all the word retrieval problems observed. The presence of anomic symptoms in these participants was reported as lapses in naming accuracy and delays in naming latency, i.e., on average, participants showed 26% reduced speed of word retrieval than the control group and 42% of the participants presented inaccurate naming. Although this study had some limitations with regard to its explanatory power with respect to in-depth neuropsychological profiles (as only cognitive screening data were obtained), the findings suggested that underlying semantic deficits were related to word retrieval difficulties symptoms and made the major contributor to anomic symptoms in an explanatory model. There was no significant correlation between test scores and years with MS in participants.

Although the De Dios Pérez et al. (2020) study has progressed our broad understanding of the incidence of anomia in people with RR MS, even a sample size of 100 participants can benefit from replication research to ensure the robustness of the findings. Furthermore, as a complement to the broad but shallow data gathering approach evident in the De Dios Pérez et al. (2020) study, a narrow but deeper methodological approach to neuropsychological assessment of anomia and its cognitive underpinnings may advance our understanding of these symptoms further. In summary, anomia in MS has been underestimated and under-defined and requires further research across the MS range of presentations. This research should aim to better understand the deficits that lead to anomic symptoms, develop sensitive and time-efficient assessments and evaluate treatment programmes through which people with MS can reduce the disabling consequences of anomia and related deficits. With this

broad aim in mind, the present study aims to answer the following research questions in relation to anomia in people with RR MS:

1. Can we replicate the incidence and severity of anomic symptoms reported in the De Dios Pérez et al. (2020) study, in a similar study implemented with a different set of participants from the same clinical setting?
2. What explanatory factors can be identified in relation to the nature of anomic symptoms by conducting a fuller neuropsychological and communication assessment of participants?
3. Are there any implications for clinical treatment of anomic symptoms to emerge from these data? Specifically, what proportion of participants present with sufficiently marked symptoms, in the context of wider cognitive-linguistic deficits, to justify a tailored programme of treatment to alleviate the severity of these symptoms?

Methods

Participants: Replication Study

Fifty-one adult participants with RR MS volunteered to participate in the study. Twenty-nine females (56.8%) and 22 males (43.1%) with a mean age and standard deviation of 39.4 years (10.6), 7 (4.2) mean years living with MS and average years of education of 14.7 (2). Three of these participants had already volunteered for the De Dios Perez (2020) study, 18 months before participating again in the present study. These participants were recruited and tested at the MS Neurology clinic at Salford Royal Hospital Foundation Trust (SRFT) in North West England whilst they were going through an intravenously modifying drug treatment (Natalizumab). This treatment does not produce any influence in the cognitive performance of the participants. The diagnosis of clinically definite or laboratory-supported definite MS was made by the patient's consultant neurologist at the SRFT according to the McDonald criteria (Polman et al., 2011). Forty control participants were used to directly compare the performance with MS participants. These were 25 females (62.5%) and 15 males (37.5%), with an average age of 38 (11.2) and average years of education of 15.1 (2). Mann-Whitney U tests revealed that the RR MS group did not differ significantly from the control group by gender (U = 962.5, Z = .540, p = .589 r= 0.05), age (U = 914.0, Z = 0.848, p = .396 r= 0.08) or education (U = 877.5, Z = 1.158, p = .247 r= 0.12). See table 4.1 for RR MS group's demographic information. The control participants were the same group recruited by De Dios Perez et al. (2020) who were spouses or family members of the De Dios Perez et al. (2020) study as well as other volunteers at the SRFT.

Inclusion criteria for both MS participants and controls included being over 18 years of age, native English speakers and having enough mobility in the upper limbs and being able to read to allow participants to fill in the questionnaires. Exclusion criteria were history of other serious neurologic trauma, history of (or current) substance abuse, and severe motor or visual impairments that precluded testing. A convenience sample was used in the replication study where all participants provided written informed consent by filling out the Study 1 Consent Form. The study was reviewed and approved by the North East - Newcastle & North Tyneside 2 Research Ethics Committee (Ref: 17/NE/0242).

Table 4.1. Demographic information for RR MS group.

Participant	Age	Gender	Handedness	Education in years	Diagnosis	Years since diagnosed	Occupation
1	32	Female	Right	16	RES MS	6	Sales and consumer support
2	49	Female	Left	12	RES MS	11	None
3	31	Female	Right	16	RES MS	9	None
4	21	Female	Right	14	RES MS	4	None
5	48	Female	Right	12	RES MS	5	Customer Services Manager
6	27	Male	Right	13	RES MS	6	Self-employed
7	27	Female	Left	14	RES MS	6	None
8	37	Female	Right	17	RES MS	3	Self-employed
9	53	Male	Right	19	RES MS	8	Retired
10	46	Female	Right	16	RES MS	4	Teacher
11	46	Male	Right	14	RES MS	0.25	None
12	51	Female	Right	15	RES MS	3	None
13	39	Male	Right	14	HA MS	11	None
14	42	Female	Right	13	RES MS	8	Office
15	32	Male	Right	15	RES MS	2	None
16	26	Male	Right	17	HA MS	2	Nurse
17	27	Male	Left	16	RES MS	8	Employed
18	32	Female	Right	16	HA MS	11	None
19	29	Male	Right	15	RES MS	7	Desk job
20	54	Female	Right	18	RR MS	2	Finance Manager
21	61	Female	Right	14	RR MS	11	Part-time job
22	57	Female	Right	13	RES MS	9	None
23	44	Male	Right	18	HA MS	17	Employed
24	46	Female	Right	12	RES MS	9	None
25	63	Male	Right	15	RR MS	11	Transport support officer
26	44	Female	Right	12	RR MS	7	None
27	34	Female	Right	15	RES MS	5	Nurse
28	50	Male	Right	10	RES MS	4	Retired
29	48	Female	Right	16	RES MS	11	None
30	41	Male	Left	12	RES MS	11	None
31	28	Female	Left	16	RES MS	7	Part-time job
32	56	Female	Right	13	RES MS	6	Operations Manager
33	40	Male	Right	17	RES MS	16	None

34	47	Female	Left	16	RES MS	15	working
35	35	Male	Right	17	RES MS	16	Project Manager
36	36	Male	Right	15	RES MS	13	Project Manager
37	38	Female	Right	13	RES MS	14	None
38	27	Male	Right	14	RES MS	4	Glass worker
39	22	Female	Right	13	RES MS	4	Student
40	42	Male	Left	11	RES MS	7	Part-time cleaner
41	32	Male	Right	11	RES MS	3	None
42	27	Male	Right	17	RR MS	0.16	IT
43	28	Female	Right	14	RES MS	4	Working
44	45	Female	Right	16	RES MS	7	Working
45	51	Female	Right	13	RES MS	4	None
46	38	Male	Left	16	RES MS	8	None
47	47	Male	Right	17	RES MS	5	None
48	45	Male	Right	17	RES MS	0.83	Part-Time
49	32	Female	Right	15	RES MS	5	Working
50	21	Female	Right	16	RES MS	1	Working
51	35	Female	Right	16	RES MS	5	Part-time
Mean	**39.39216**			**14.7451**		**6.985098**	
SD	**10.59611**			**2.017989**		**4.2366415**	

Participants: In-depth Neuropsychology Study

As a follow-up to the replication screening study, we subsequently aimed to recruit approximately half of the participants for an in-depth neuropsychological study. Though aiming for 25 participants, ultimately 21 participants from the replication group volunteered to participate in the second part of the study. These were 11 females (52.4%) and 10 males (47.6%). Mean age 43.9 years (9.0), mean education 15 years (1.9). Selection of these participants was on the basis of their performance on accuracy and reaction times on naming tests in the replication study. Participants were not in exacerbation at the time of the study and were able to complete questionnaires, read and answer questions on their own to ensure the value of the results obtained. A convenience sample was used in the study where all participants provided written informed consent in the Study 2 Consent Form. Participants

were assessed at their homes during three to four separate sessions of a maximum of 1.5 hours each day. Exclusion criteria for this study included participants with native language other than English, presence of severe dysarthria (sufficient to make words produced unintelligible), severe visual impairments, history of other serious neurologic trauma, history of (or current) substance abuse that precluded testing.

Materials and Procedures: Replication Study

The methods utilised by de Perez Dios et al., (2020) were replicated in terms of the communication screen which was used. In order to gather information about the extent and nature of anomic symptoms in a sample of RRMS participants a brief interview and four different language and cognitive assessments were used.

Interview

The interview was aimed to establish initial rapport with the participants and to elicit specific demographic information including age, handedness, gender, education, time of diagnosis and treatment. Information provided by participants was confirmed in their medical records.

Behavioural tasks

Tests of language and cognitive function were administered to assess naming abilities, verbal fluency, semantic memory, writing, comprehension, reading and the presence or not of dysarthria in patients with MS. In addition, attention, memory, visuospatial and perceptual abilities were tested. The neuropsychological tests were chosen with consideration to the capacity and challenges of the participants with MS, as well as to capture a general profile of the speech, language and cognitive skills of the participants. The tests were relatively brief to administer (40 – 60 min) and cognitive/ physical strain was kept to a minimum in order to reduce fatigue. The assessments chosen were not timed and involved oral responses, limited writing and pointing.

The following tests were administered:

- *Addenbrooke's Cognitive Examination Revised*

The Addenbrooke's Cognitive Examination Revised (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) was used in this replication study. The ACE-R is a revised version of the Addenbrooke's Cognitive Examination (ACE) (Mathuranath, Nestor, Berrios, Rakowicz, &

Hodges, 2000). ACE-R is a sensitive screening cognitive test developed initially to assess and differentiate various subtypes of dementia from early stages (Mioshi et al., 2006). However, in various studies the ACE-R has been proved to be sensitive to detect cognitive impairments in people with MS (Connick, Chandran, & Bak, 2013; Hamilton et al., 2009). Moreover, O'Gorman et al. (2010) using the ACE detected cognitive dysfunction associated with subcortical atrophy in RR-MS patients (O'Gorman, Freeman, & Broadley, 2010). The test takes an average of 16 minutes to administer and score. The ACE-R is divided in 5 different subtests, each one representing a cognitive domain and with a specific score.

The domains include: *attention/orientation* (18 points): the participants were asked questions which show their orientation in time and space, they are also asked the registration of three words and they were requested to do serial mental subtractions and spell backwards. *Memory* (26 points): the participants were asked to recall the three words they previously were requested to register, also they had to immediate recall a fictitious name and address and after 10 minutes, and to answer four general knowledge questions. *Verbal fluency* (14 points): the participants were asked twice to generate as many words as they could, first starting with the letter "P" of the alphabet and lastly with a semantic category (animals). *Language* (26 points): in order to evaluate written and verbal comprehension, participants were showed a written instruction and asked to follow it as well as a verbal command; to evaluate written ability they were asked to write a sentence; they were also asked to repeat words and phrases, to recognise and name objects and to read a list of words. *Visuospatial skills* (16 points): to measure these abilities patients were asked to copy overlapping pentagons, a wire cube and to draw a clock face with numbers and hands at ten past five, they were also requested to count dots inside a square and to identify incomplete letters.

The addition of the points of all subtests is 100, which is the highest score (Mioshi et al., 2006). The cut-off scores used were <88 points that gives 94% sensitivity and 89% specificity for dementia (Mioshi et al., 2006)

- *International Picture Naming Project Naming Test*

The International Picture Naming Project (IPNP) is a series of picture-naming studies carried in seven different languages in order to build databases and provide norms for names produced and reaction times (Bates et al., 2000; Bates et al., 2003). The norms include age-of-acquisition, word frequency, familiarity, goodness-of-depiction, and visual complexity (Bates et al., 2000; Szekely et al., 2004). The IPNP contains 520 black and white line drawings

of common objects that can be used in cross-linguistic studies in various clinical populations (Bates et al., 2000; Szekely et al., 2004).

Fifty-five picture stimuli out of the 60 stimuli previously chosen by De Dios Perez et al. (2020) were used for the replication study in order to assess lexical access (recognition and retrieval skills) in participants with RR MS. Five pictures were removed from the original study list (n=60) as both the RR MS participants and the control group found them ambiguous or visually confusing and had failed to successfully identify those stimuli. Nicholas et al. (1989), after finding that healthy neuro=typical control participants also misnamed some stimuli, suggested being cautious about assigning naming errors due to the participants' disorder. Pictures removed were 'canoe', 'priest', 'beaver', 'mosquito' and 'hoe'; common errors for these words in both groups (MS and control) were "boat", "monk", "squirrel", "insect" and "rake", respectively.

The pictures were chosen based on the RT in milliseconds (ms) required to name the picture, then divided into four groups in order to assess naming latency, processing speed and accuracy. Furthermore, psycholinguistic variables related to language performance such as age of acquisition (average age at which usually people learn a word), frequency (the number of times a word is used in oral language, measured in occurrences per million) and length of phonological syllables in the word were also considered when selecting the pictures. The RT in the four groups were: *Group A* with a RT <800 ms and 15 picture stimuli; *Group B* with a RT between 801 – 1000 ms and 15 picture stimuli; *Group C* with a RT between 1001 – 1220 and 13 picture stimuli; *Group D* with a RT between 1221 – 1500 ms and 12 picture stimuli. The words included in each group as well as the variables they were decided upon can be found in the appendix.

The shortest RT stems from the higher frequency of these words and the earliest stage of life when the word was learnt. Consequently, Group A has the lowest mean RT (<800 ms), the highest mean frequency (3.51) and the earliest mean age of acquisition (1.27) compared with Group D that has the highest mean RT, the lowest mean frequency and the latest mean age of acquisition. It is expected that participants will find easier to name words from Group A overall the other groups and find it harder to name the pictures from Group D over all the other groups.

The stimuli were presented to the participants in a laptop screen using PowerPoint. The pictures from the four groups were distributed randomly, however were presented to all the participants in the same order. The participants were shown the pictures one after the other, along with a simultaneous presentation of a sound used for RT analyses. A fixation dot is also shown in the centre of the screen to ensure the participants' attention to the screen before the image is presented. The picture stayed in the screen for six seconds before moving to the next picture automatically.

The participants were audio-recorded in order to gather data as to signs of possible dysarthria and also to measure their RT to naming the pictures. The latency and accuracy of participants' naming responses were compared to the ones of healthy controls obtained from the IPNP database (Bates et al., 2000). The maximum score was 55 points (1 point per picture).

- *National Adult Reading Test*

The National Adult Reading Test (NART) (Nelson, 1982) was designed as an assessment tool for the estimation of premorbid level of intellectual ability of adult patients with dementia. Nowadays, the NART is widely used as a comparison of premorbid intellectual function between patients suffering brain damage and healthy controls (Bright, Jaldow, & Kopelman, 2002). However, various studies have questioned the use of the NART as a premorbid intelligence estimate in different neurologic populations. Patients with alcoholic Korsakoff Syndrome, scored significantly lower than matched controls (Crawford, Parker, & Besson, 1988; O'Carroll, Moffoot, Ebmeier, & Goodwin, 1992). Similar findings were seen in patients with Huntington Disease, schizophrenia and depression among others (Crawford et al., 1988; O'Carroll, 1995). Longitudinal studies using the NART in Alzheimer patients found decrements in NART performance, suggesting that the NART is not sensitive enough at later stages of the disease (Cockburn, Keene, Hope, & Smith, 2000; Fromm, Holland, Nebes, & Oakley, 1991; Taylor, 2000). In addition, NART showed to produce lower premorbid intelligence estimates in a study with patients with mild dementia and language deficits (Stebbins, Gilley, Wilson, Bernard, & Fox, 1990) and in a study with MS patients with language impairments (Friend & Grattan, 1998). The results of the studies question the validity of the use of the NART for the estimation of premorbid level of intellectual ability in patients with possible language deficits. Thus, the present study used the NART as a quick tool to help us screen for the presence of dysarthria.

Fifty words with atypical phonemic pronunciation were presented individually to the participant in a computer screen. The participants were required to read each word aloud. The responses were audio recorded for later analysis. The level of dysarthria of each participant was assessed using the five- point scale Therapy Outcome Measure (TOM) (Enderby, John, & Petheram, 2013). The analysis was carried out by a trained speech and language therapist. The five- point scale analysis are the following:

0 = Profound dysarthria. There are evident profound problems. The patient is unable to produce any distinguishable sounds. There are no signs of oral motor control and no signs of respiratory support for speech.

1 = Severe dysarthria: The patient shows severe and inconsistent articulatory and prosodic impairment. Mostly open vowel sounds with some consonant approximations. The speech is effortful and slow with severe restriction of respiratory support and limited motor control.

2 = *Severe/moderate dysarthria*: The patient has most consonants attempted, but poorly represented acoustically, prosodic impairment and difficulty controlling speed of speech either slow or increasing in speed. Breath support consistent but weak. There is limitation of oral motor control.

3 = Moderate speech dysarthria: The patient presents consistent omission or distortion of articulation of consonants variability of speed, some limitation of oral motor control and prosodic abnormalities.

4 = Mild dysarthria: The patient shows light or occasional omission or mispronunciation of consonants, slight occasional difficulty with oral motor control, prosody, or respiratory support.

5 = No dysarthria

- *Pyramids and Palm Trees (PPT)*

The Pyramids and Palm Trees (PPT) (Howard & Patterson, 1992) was used to assess detailed semantic knowledge by asking participants to make explicit meaning associations between object concepts. This test employs non-verbal communication to obtain semantic knowledge. According to Raymer & Rothi (2008), word retrieval requires semantic and phonological processes. The PPT is frequently utilised in dementia, aphasia, agnosia and language processing research (Caine & Hodges, 2001; Hodges et al., 1999; Martin, Schwartz, & Kohen, 2006; Wierenga et al., 2008).

The PPT is composed of 52 items; each item contains three pictures of different objects. The participant was presented with three pictures, one above the others and was asked to match the top picture (e. g., hands) to one of the other two pictures above (e.g., gloves and slippers) with the one which is most closely associated (e.g., slippers).

The maximum score is 52 (1 point per item). The cut off of score used is 49.

All assessments were administered according to standardised procedures and they follow the next order: ACE-R, IPNP, PPT, NART.

Materials and Procedures: In-depth Neuropsychology Study

A comprehensive neuropsychological battery was implemented with a subset of participants in order to contextualise language deficits, particularly anomia, within wider profiles of cognition. This neuropsychological battery was administered over 4 sessions of testing, lasting a maximum of 1.5 hours each, at the participant's home. On the untimed tests, participants were given as much time as they needed to complete a task. Further, on the timed tasks, participants were asked to work as quickly as possible and performance time was recorded in addition to errors produced. All the tests were administered according to standardised procedures in the same order for every participant (See table 4.2). The tests were chosen with consideration to the capacity and challenges of the participants with RR MS. Each test was relatively brief to administer and the physical strain was kept to a minimum in order to reduce fatigue and keep the interest.

Table 4.2. Neuropsychological battery detailed in sessions.

Session 1	**Session 2**	**Session 3**	**Session 4**
Frenchay Dysarthria Assessment (2nd ed.)	Rey Complex Figure Test	Boston Naming Test (BNT)	96 - Synonym Judgement
Matrix Reasoning (Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II))	Symbol Digit Modalities Test (SDMT)	Digit Span Forward and Backward	Non-Word Repetition (PALPA)
Corsi blocks	Colour-Word Interference Test	Trail Making Test (DKEFS)	Verbal Fluency Test (DKEFS)

Design Fluency (Delis-Kaplan Executive Function System (D-KEFS))	Western Aphasia Battery (WAB)	Rhyme Judgement (Psycholinguistic Assessments of Language Processing in Aphasia, 1st Edition (PALPA))	Cookie Theft Picture Description task
Naming Test (International Picture Naming Project (IPNP))			

Speech and Language Tests

Tests of speech/language function were conducted to assess various verbal cognitive and speech functions in participants with RES RRMS as a part of an in-depth neuropsychological battery. The functions assessed included naming abilities, verbal fluency, semantic memory, writing, comprehension, reading and the presence or not of dysarthria.

- *Frenchay Dysarthria Assessment 2 (FDA-2)*

The FDA-2 (Enderby, 1980) is a validated rating scale used for the assessment of dysarthria. It consists of seven sections such as reflexes, respiration, lips, palate, laryngeal tongue and intelligibility. The FDA-2 can be administered in 30 minutes.

Participants were given a set of tasks for each section of the test (e.g., in the respiration section the participant was asked to take a deep breath in through the mouth and let out through the mouth as audibly and slowly as possible). Items in FDA-2 are scored from “a” (normal) to “e” (unable to undertake task). However, the FDA-2 was adapted by replacing alphabetic coding with numeric scoring. Scores for ‘Normal’ function (a) were 9 points, for ‘mild’ (b) were 7–8 points, for ‘moderate’ (c) corresponded 5–6 points, for ‘severely abnormal speech’ (d) were from 3–4 points and for ‘no function’ were 1–2 points . For each of the eight FDA items, the mean was calculated to give a final score. (Max score 9 points). The degree of dysarthria was rated with the help of a qualified and experienced speech and language therapist.

- *Boston Naming Test (BNT)*

The BTN (Kaplan, Goodglass, & Weintraub, 1978) is a visual naming tool to assess word retrieval skills. The original version consisted of 85 simple line pictures. Nowadays, the BTN

shortened version with 60 items (Kaplan, Goodglass, & Weintraub, 2001) is one of the most commonly administered naming tests (Butler, Retzlaff, & Vanderploeg, 1991) in clinical settings. Pictures in the BNT are simple line, black and white objects.

Participants were assessed using the 60-item BNT. They were presented with each picture given up to 20 seconds to name the line drawings that ranged in familiarity (e.g., house, sphinx). Stimuli were presented in a laptop screen using a PowerPoint presentation and participant's answers were audio recorded for later analysis of reaction times and accuracy. One point was given for each correct answer (Max score = 60). BNT can be administered in 10 minutes. RES RRMS participant's scores were compared with normative data for the BNT (Tombaugh & Hubiey, 1997).

- *International Picture Naming Project Naming Test (IPNP)*

The IPNP naming test used in the replication study was administered again in order to assess semantic and lexical access. (Refer to the replication study). The pictures were presented in a laptop screen as a Powerpoint presentation. A fixation dot and a beep sound appeared simultaneously before each picture. Stimuli stayed on the screen for 6 seconds before moving to the next picture automatically. All answers were voice recorded for later analysis.

Classification of naming errors for IPNP and BNT

Naming errors on the naming tests were categorised based on the classification used by Martin, Dell, Saffran, and Swartz (1994) and Chenery (1993). The description of error types is found in the Table 3.4.

- *96-Synonym Judgement Task*

The 96-Synonym Judgement Test (Jefferies, Patterson, Jones, & Ralph, 2009) was used to assess verbal comprehension (Almaghyuli, Thompson, Lambon Ralph, & Jefferies, 2012; Hoffman, Rogers, & Lambon Ralph, 2011). Participants were presented with a probe word, the target and two unrelated distractor words and asked to select the word closest in meaning to the probe word (e.g., WINTER (probe) clothes, sea, **summer** (target)). Each item was presented in a power point slide with the probe word above the rest of the words. Participants had no time limit to give an answer. Responses were registered in the Synonym Judgement Test scoresheet. Participant's results were compared to control data used for this task

(Almaghyuli et al., 2012). One point per correct item was given with a maximum score of 96 points. Test administration time is 10-20 minutes.

- *Western Aphasia Battery-Revised (WAB-R)*

The WAB (Kertesz, 2007), is a validated instrument that assess primary aspects of language functions such as fluency, information content, auditory comprehension, repetition and naming. The WAB-R is often used as a diagnostic tool which allows classification of a patient into eight aphasic syndromes (Risser & Spreen, 1985). It can be administered in 60 – 90 min. Fluency and information content of speech were measured by asking the participant conversational questions (e.g., How are you today?) and by asking to describe as completely as possible a black and white picture (Max score: 20 points). Auditory verbal comprehension was measured by asking the participant yes or no questions (e.g., Is your name Smith?), by asking to point different objects, pictures, colours and body parts and by asking the participant to follow some commands (e.g., Raise your hand) (Max score: 80 points). Repetition was assessed by recording the participant's answers to repetition of target words and phrases (Max score: 100 points). Naming and word finding were measured by naming different objects, word fluency (category: animals), completion of sentences (e.g., The grass is __.) and answering questions (e.g., What colour is snow?) (Max score: 100 points).
Raw scores for all subtests were added and multiplied by two. The result translates into the Aphasia Quotient (AQ) score. The AQ compiles the performances across the five language functions, and it is the value of the person's aphasic deficit regardless the type of impairment. An AQ of 0-25 is very severe; an AQ 26-50 is severe, an AQ of 51-75 is moderate, an AQ of 76 and above is mild. The WAB-R also includes the Aphasia Classification Criteria Table to determine the aphasia type based on WAB-R scores (Kertesz, 2007).

- *Cookie Theft*

The Cookie Theft Picture from the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1983) was used to assess participants' descriptive discourse. Participants were asked to describe everything they saw happening in the black and white action picture. Answers were audio recorded, timed and transcribed verbatim for later analysis. There was no time limit, recording was stopped after 10 seconds of silence or when the participant verbally expressed that the task was completed. The test was measured in information units

which has been found to be the most sensitive measure of change in people (Tomoeda & Bayles, 1993). An information unit refers to the smallest non-superfluous significant fact or inference (Giles, Patterson, & Hodges, 1996). Control data by Giles, Patterson and Hodges (1996) was used to compare our MS participants.

- *Non-Word Repetition*

Non-Word Repetition is a task included in the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) subtest 8 (Kay, Lesser, & Coltheart, 1996). This task assess auditory-perceptual sub-lexical phonological encoding processes (Munson, 2006), as well as short-term memory (Baddeley, 2000). Participants were asked to repeat unfamiliar yet word-like sound forms after the examiner (e.g., splant). One point per correct item was given with a maximum score of 30.

Cognitive Tests

These tests were administered to represent a general profile of the cognitive functions in people with RES RR-MS, such as attention, memory, executive functions, information processing speed, visuospatial and perceptual abilities.

- *Rey-Osterrieth Complex Figure Test (ROCFT)*

The Rey Osterrieth Complex Figure Test (ROCFT) (Osterrieth, 1944; Rey, 1941) has been widely used to assess attention, memory, visuospatial abilities and executive functions in people with MS (Dimitrov et al., 2015; Gmeindl & Courtney, 2012; Longoni et al., 2015). The ROCFT is an intricate, black and white asymmetrical stimulus.

The participant was asked to copy a complex geometric figure using a pen on a blank sheet of paper. Immediately after completion of the copy task, the figure and copy were removed. After three minutes of the completion of the copy task, the participant was asked to reproduce the figure from memory on a blank sheet of paper. Finally, after 30 min, the participant was asked to reproduce again the image in a blank sheet of paper in order to measure delay recall. None of the tasks had a time limit; however, the length of time took to complete each one was recorded. Scores were compared with ROCFT normative data (Max score: 36 points on each task).

- *Matrix Reasoning*

The Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II; Wechsler, 2011) Matrix Reasoning (MR) subtest measures spatial ability, fluid and visual intelligence (which manifests learning and novel problem solving) and perceptual organisation (McCrimmon & Smith, 2013). MR has been shown to be sensitive to cognitive symptoms of brain injury such as stroke and dementia (Ryan et al., 2005). The subtest comprises 30 coloured incomplete matrices presented in the test's stimulus book. Participants were asked to view an incomplete matrix or series and select the response option from a selection of five items at the bottom that completes the matrix. The task was discontinued if the participant had three consecutive failures. There was no time limit for this task, scores were compared with the MR WASI-II normative data (Max score: 30 points).

- *Verbal Fluency*

The Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, Kramer, Delis, & Kramer, 2001) is a standardised tool that has been proved to be sensitive in assessing executive functions including inhibition, planning and problem solving, impulse control, flexibility of thinking, formation of concepts, abstract, verbal and spatial thinking (Drew, Tippett, Starkey, & Isler, 2008; Homack, Lee, & Riccio, 2005). The D-KEFS comprise nine tests that than can be administered as a group or individually. In order to test phonemic and semantic fluency on the RES RRMS participants the Verbal Fluency test was used. This test includes two tasks, a verbal and category fluency.

Participants were asked to generate as many words as possible in 60 seconds in each trial; answers were recorded by the examiner. For letter fluency, participants performed three trials with letters F, A and S and were asked to exclude proper names, numbers and the same word with different endings. For category fluency, participants performed a trial with male names. Scores for letter fluency was the addition of the correct answers in the three trials (F, A, S) and for category the number of the correct responses (male names). Administration time is 5 minutes. Participants' scores were compared with the test's normative data.

- *Trail Making Test*

The Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (Delis et al., 2001) consists of a series of 5 conditions: visual scanning, number sequencing, letter sequencing,

number-letter switching and motor speed. The primary executive function task is Number-Letter Switching which assesses flexibility of thinking. The rest of the conditions assess the person's visual scanning, number and letter sequencing and motor speed skills. In the Visual Scanning task participants, were asked to cancel all the 3s that appeared on the worksheet, ignoring other distractor numbers. In the Number Sequencing task, participants were asked to connect the numbers 1 to 16 with a line using a pen, ignoring distractor letters also on the worksheet. In the Letter Sequencing task, participants were asked to connect the letters A – P, having distractor numbers on the worksheet. In the Number-Letter Switching task, participants had to switch back and forth between connecting numbers and letters in order from 1A to 16P on the worksheet (e.g., 1-A-2-B-3-C…). In the last task, Motor Speed, participants were required to connect circles by tracing over a dotted line as fast as they could. In all five tasks, it was requested that participants work as accurately and quickly as possible. There was no time limit; however, all the tasks were timed. Times on each task were converted into normative scores.

- *Design Fluency Test*

The D-KEFS Design Fluency Test (Delis et al., 2001) assesses motor planning-initiation, cognitive flexibility and fluency in generating motor sequences (Suchy, Kraybill, & Larson, 2010). The test consists of three trials: Filled Dots, Empty Dots and Switch in which the participant task is to create different designs by connecting dots in 60 seconds. In Filled Dots participants were asked to create as many novel designs by connecting filled dots in a series of five dots matrices. In Empty Dots, the instruction is the same as the previous task but connecting empty dots and in the Switch task participants were asked to switch between connecting filled and empty dots. In all three tasks, participants were instructed to work as quickly and accurately as possible, with a time limit of 60 seconds on each task.

- *Colour-Word Interference Test*

The D-KEFS Colour-Word Interference Test (Delis et al., 2001) is based on the Stroop test (Stroop, 1935) which measures selective attention, inhibition, cognitive flexibility and verbally mediated processing speed (Homack et al., 2005; Rabin, Paolillo, & Barr, 2016). Three trials were presented to the RES RRMS participants: Colour Naming, Word Reading and Inhibition.

In the Colour Naming task, participants were shown a page containing a series of green, red and blue squares and asked to name the colours as fast and accurate as they could. In the Word Reading task, participants were presented with a page with the words “green”, “red” and “blue” printed in black ink, then they were asked to read as fast as possible the words. Lastly, in the Inhibition task, participants were presented with the words “green”, “red” and “blue” printed in inappropriate ink colours (e.g., word “green” printed in red ink) and they were instructed to say the colour of the ink in which each word was printed as accurate and fast as possible. All tasks obtained a time to completion score and required responses to all stimuli.

- *Symbol Digit Modalities Test (SDMT)*

The Symbol Modalities Test (SDMT) (Smith, 1982) is one of the most widely used test on patients with MS as an sensitive and practical screening test, to measure working memory and processing speed abilities in clinical settings (Benedict et al., 2002; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007).

The SDMT is a pen and paper task containing a key with nine different symbols corresponding to the numbers one to nine and a series of the symbols with blank boxes under them to write down the corresponding number. Participants were given the blank worksheet and were asked to write down the correct number for each corresponding symbol as quick and accurate as they could. Participants were given 90 seconds to complete the task. The score was calculated by totalling the number of correct answers in the time given.

- *Corsi Block Tapping Test*

Originally designed by Corsi (1972), the Corsi Block Tapping Test is a span task used to assess visuospatial short-term memory (Kessels, Van Zandvoort, Postma, Kappelle, & De Haan, 2000). The test consists of nine squares presented in a computer screen. Participants were instructed to pay attention to the squares on the screen tapped by the examiner and to repeat immediately after the examiner was finished in the correct sequential order. Two trials were given per sequence of the same number of blocks; the length of the sequences was increased if at least one sequence was repeated correctly. The task was discontinued two of the same length sequences were tapped incorrectly. Total scores were obtained by calculating the

length of the last repeated sequence and multiplying it by the number of correct trials with a maximum score of 144. Scores were compared to Kessels et al. (2000) normative data.

- *Digit Span Forward and Backward*

The Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) includes two verbal digit span tasks and was used to measure attention and immediate auditory recall (forward) and working memory (backward). In the first forward span task participants were asked to listen to a digit span and then immediately repeat it forward. The digits increase on each trial, from three to four digits until nine digits. In the second backward task, participants were instructed to listen to a digit span then asked to repeat the digits backward (e.g., 2-5-3: answer: 3-5-2). On both tasks, digits were gradually increased in length. Participants had two trials per each span and the task was discontinued when they failed to repeat correctly the two trials of one span. One point was given for each list recalled with a max score of 14 points on the forward task and 12 points for the backward task. Scores were compared to Jefferies and Lambon Ralph's (2006) control data.

- *Rhyme Judgement*

Rhyme Judgement is a task also included in the PALPA (subtest 15) (Kay et al., 1996), which assesses phonological processing (phonological awareness, decoding and phonetic memory) (Waldron, Whitworth, & Howard, 2011). This task required the participants to retrieve names of black and white pictures from their phonological output lexicon. Participants were presented with two pictures and asked to look at them and, without naming the pictures aloud, deciding whether the picture names rhymed by saying only "yes" or "not". The test contains 40 trials and one point was given for each correct answer.

Results

Replication study results

Descriptive statistics for the screening tests and subtests for both study groups (MS and Control) are presented in Table 4.3. Also included in 4.3 are the control cut-off values for the study control participants and the published control data included in the assessments used.

The mean scores of the MS group in the overall cognitive screen (ACE-R) fell well below the control group mean of 96.13 and below the lower end of the neuro-typical performance (MS group = 89.88, control cut-off 90.89). For the naming accuracy task, the MS group mean score was at the lower end of the neuro-typical performance (MS = 51.67, control cut-off = 51.6). The NART test was used as a quick screen of dysarthria instead of a measure of estimated premorbid intelligence; however the MS group had lower scores than the healthy control group (36 vs 40 respectively). Since both groups were matched by age and education, this could be attributed to the MS group language deficits as shown in the Friend and Grattan (1998) study using the NART in people with MS. For the PPT, the MS group mean was toward at the end of this range (MS = 48.98, control cut-off = 48.73). A variability in performances across MS participants can be seen in the ACE-R and NART tasks as suggested by the high standard deviations for the MS group (SD = 5.63 and 6.26 respectively).

Table 4.3. Mean performance on the screening test and subtests.

TASK	ACE-R Attention Orientation	ACE-R Memory	ACE-R Verbal Fluency	ACE-R Language	ACE-R Visuo-spatial Skills	ACE-R Overall	PICTURE NAMING	NART	PYRAMIDS & PALM TREES
Max Score	18	26	14	26	16	100	55	50	52
MS Group Mean and SD	17.47 (0.7)	21.84 (3.04)	10.90 (1.69)	24.24 (1.87)	15.43 (0.90)	**89.88 (5.63)**	**51.67 (2.73)**	**36.05 (6.26)**	**48.98 (1.76)**
Control Group Mean and SD	17.9 (0.3)	24.08 (1.95)	12.85 (1.12)	25.48 (0.68)	15.83 (0.5)	**96.13 (2.62)**	**53.98 (1.19)**	**39.88 (3.98)**	**50.83 (1.05)**
Difference between mean scores (Control Group > MS Group)	**0**.43	2.24	1.95	1.24	0.4	6.25	2.31	3.83	1.85
Difference in percentage	2.38%	8.61%	13.92%	4.76%	2.5%	6.25%	4.20%	7.66%	3.5%
Cut-off for control range (mean – 2 S.D.)	17.3	20.18	10.61	24.12	14.83	90.89	51.6	31.92	48.73
Published cut-off for control performance	17	18	9	24	15	88	52	26	49

A more detail analyses of each assessment is presented below.

- ACE-R: The control cut-off for the overall score (90.89) was higher that the normative data provided (88), reflecting the age matching of these participants to the MS group. Having noted the MS group mean score falling toward the end of the cut off normative data range (published cut-off = 88, MS group 89.88) and below the matched control cut off score (control = 90.89, MS group 89.88), it is important to consider the range of performance across the participants with MS. In terms of individual performances, 45% of the MS group fell below the matched control cut-off score in the cognitive test as can be seen in Figure 4.1. Mann-Whitney U showed that the difference in the overall scores between the two groups (MS and Control) was significant (U = 284.5, Z = 5.9, p = .0001, two tailed) including a medium effect size (r = .618).

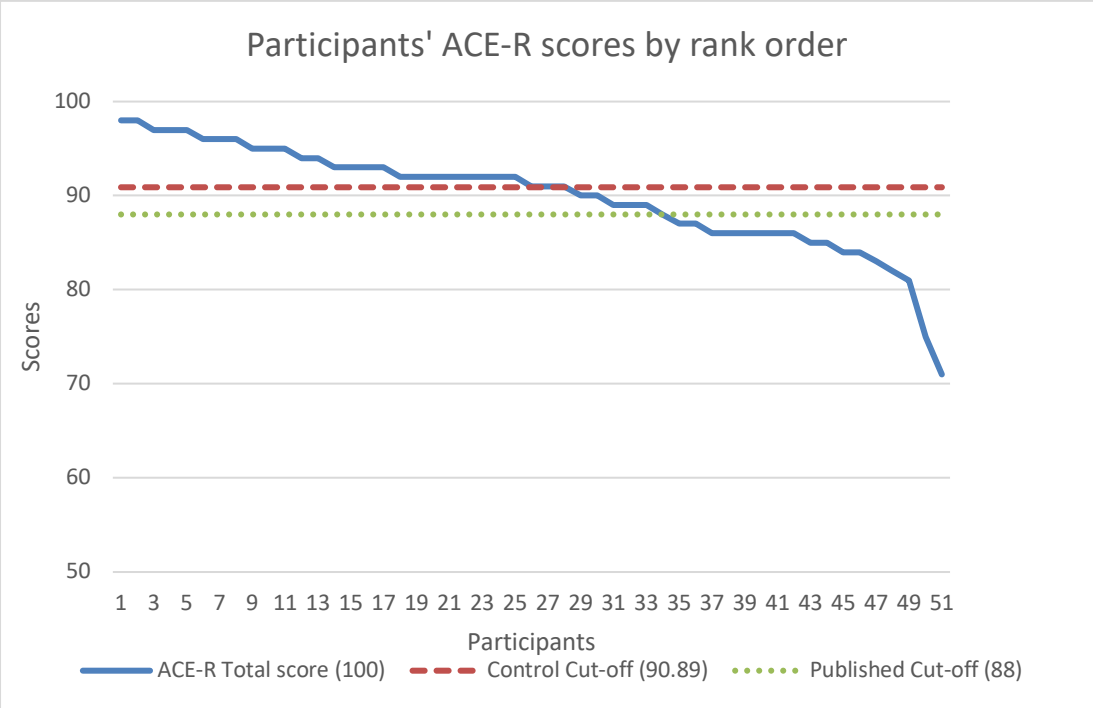


Figure 4. 1 Individual participants' scores ranked by order in the ACE-R

Looking at the ACE-R subtests, Figure 4.2 shows the mean scores for both the MS and matched control group. All subtests in the cognitive examination were within the neuro-typical

performance; nonetheless, attention and orientation, verbal fluency and language tasks scores fell towards the control cut-off score (See Table 4.3).

To compare performance on each subtest, the statistical comparison were as follows:

- Attention and orientation (U = 674.0, Z = 3.5, p = .0001, r = .366, two tailed).
- Memory (U = 554, Z = 3.8, p = .0001, r = .398, two tailed).
- Verbal Fluency (U = 365.5, Z = 5.3, p = .0001, r = .555, two tailed).
- Language (U = 562, Z = 3.8, p = .0001, r = .398, two tailed).
- Visuo-spatial abilities (U = 797.5, Z = 2.4, p = .018, r = .241, two tailed).

A significant difference was therefore observed in all subtests scores between the matched control and the MS group. As noted before, language, attention and orientation, and verbal fluency abilities respectively were where more participants presented difficulties.

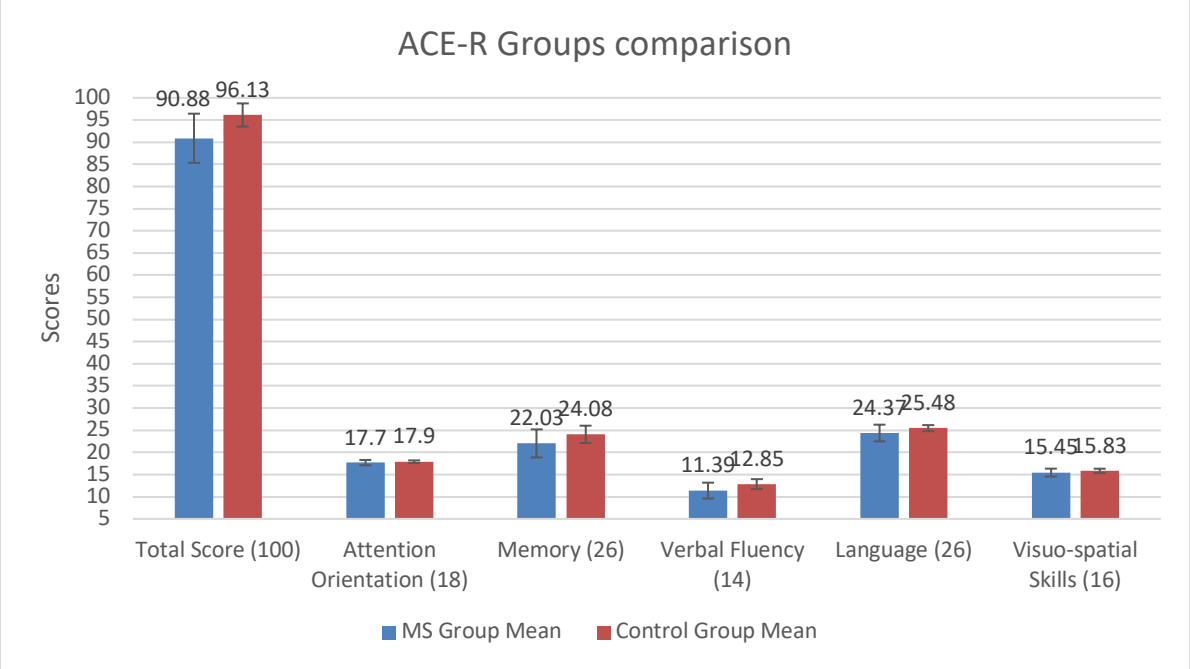


Figure 4. 2. Comparison between MS and healthy control groups in the ACE-R test.

- Picture Naming Test: This test was measured according to accuracy and reaction times (RT) to the presentation of the stimuli. Having noted the overall pattern of MS participants performing at the same level of the matched control cut-off accuracy scores (MS = 51.67, control cut-off = 51.6) and lower than the published control data (MS = 51.67, published cut off = 52) (See Table 4.3), we also observed a strong variability in performances in the RES

RRMS group when compared SD with the matched control group (SD = 2.73 vs 1.19 respectively). When looking at individual performances, 39.2% of the participants obtained lower scores than the control cut-off (See Figure 4.3) compared to a 3.3% in the control group that scored lower than the cut-off. According to Mann-Whitney U, performance in the naming accuracy task differs significantly between MS group and the control group (U = 434, Z = 4.8, p = .0001, two tailed) having a medium effect size (r = .50).

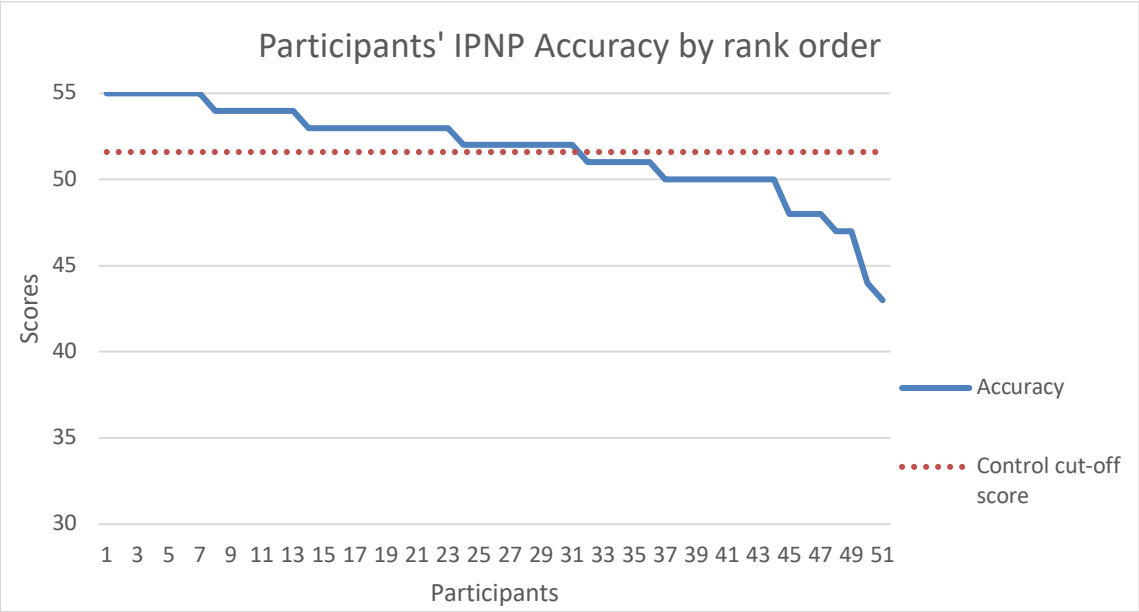


Figure 4. 3 Naming task individual participants' accuracy.

The time in milliseconds (ms) that it took the MS group to correctly name the items in the overall task and word subgroups compared to the control group, is shown in Table 4.4. Participants with MS were slower to name the pictures than the control group in the overall task/sum of word groups (RES RRMS = 1177.7 ms, control 977.4 ms). Likewise, participants with MS performed slower than the IPNP normative data. The MS group and the control group RT means were statistically significantly different (Mann Whitney U = 490, Z = 4.2, p = .0001, two tailed, r = .50). Picture names had been divided into four word-groups of increasing psycholinguistic complexity for a more fine-grained analysis (Group A, which was easiest to name - high frequency and early age of acquisition, to Group D, which was the most difficult for word retrieval). Analysing each word group, the RTs were significantly different when comparing the MS group with the control group, except for Group D. The latency differences (MS>control) in percentage between word groups were: 14% for Group (U = 38, Z = 3, p =

.001, one tailed, r = .54); 27% for Group B (U = 30, Z = 3.4, p = .0001, one tailed, r = .6); 26% for Group C (U = 38, Z = 2.4, p = .016, one tailed, r = .48); and 18% for Group D (U = 32, Z = 2.3, p = .02, one tailed, r = .48). Four correlation analyses on the same dependent variable would indicate the need for a Bonferroni correction of ($\alpha_{altered}$ =.05/4) = 0.0125. Mann-Whitney was used since control Group C is not normally distributed.

Table 4.4. Naming task RTs (ms) comparison between groups.

	RES RRMS Group	**Control Group**	**Normative Data**
Global RTs for Naming test (n_ 55) *Difference in %*	1177.7 (271.4)	977.4 (143.7) *20.5%*	1015.3 (246.8) *16%*
Word Group A RTs (n=15) *Difference in %*	844.2 (75.2)	742.3 (98) *14%*	742 (31) *14%*
Word Group B RTs (n=1) *Difference in %*	1043.6 (155.1)	821.3 (105.6) *27%*	890 (59) *17%*
Word Group C RTs (n=13) *Difference in %*	1442.4 (304.3)	1145.8 (245.8) *26%*	1139.2 (81.5) *27%*
Word Group D RTs (n=12) *Difference in %*	1548.7 (220)	1314.3 (224.6) *18%*	1365.6 (128.4) *13%*

Error analyses were also conducted in order to have a better understanding of the psycholinguistic mechanisms in charge of word production. The same error classification used by Perez De Dios et al., (2020) was employed in the current study (Chenery, 1993; Martin, Dell, Saffran, & Schwartz, 1994) and can be found in Table 4.5**.** As mentioned before, participants with MS were less accurate than the control group with a total of 180 errors in the naming task (See Table 3.4). In Table 4.5, it can be observed that semantic errors accounted half of the total error types (51%), with 44% of semantic paraphasias (n=79), 4% of semantic descriptions (n=8) and 3% of semantic super-ordinate (n=6). The second most common error in participants with MS was a 'no response' to the stimulus presented with 26% of the total error types (n=47), followed by perceptual errors (perceptually related, partly percept) with 21% of the total error types (n=37). Phonemic errors very infrequent, accounting 1.5% of the error types (n=3).

Table 4. 5. Error Analysis on Naming Test in participants with MS.

Error Types	**Number**	**% of the total errors**
Correct naming attempts	*2625*	
Semantic paraphasias	79	44%
Semantic description	8	4%
Semantic super-ordinate	6	3%
Semantic negation	0	0%
Wild paraphasia	2	1%
Formal phonemic paraphasias	1	0.5%
Literal paraphasias	0	0%
Neologistic	0	0%
Perceptually related	14	8%
Partly perception	23	13%
No response	47	26%
TOTAL ERRORS	**180**	

- NART: This test was used to detect dysarthria using the TOM 5-point scale by a trained speech and language therapist. Ninety-four percent of the participants had no audible dysarthric symptoms (score 5 on 5 point scale) and 6% presented with mild dysarthric symptoms (only three participants rated 4 points). From those three participants, the first one showed intermittent consonantal articulation; the second presented low volume,

phonatory break and vocal tremor; and the last one showed pitch breaks, sonatory creak and intermittent voice harshness.

- Pyramids and Palm Trees (PPT): On this test, the MS group had a mean score of 48.98, which is just above the control cut-off score (48.73) (see Table 4.3). When looking at individual semantic process performance, 31.4% of MS participants scored below the control cut-off. The MS group and the control group RT scores appeared to be statistically different according to Mann-Whitney U (U = 384, Z = 5.2, p = .0001, two tailed, r = .55).

Comparative Results.

Demographic data in both studies (present and De Dios Perez et al. 2020) were comparable as shown in table 4.3. According to Mann-Whitney, none of the MS groups differ significantly from each other on age (U = 2327, Z = 0.88, p = 0.38 r= 0.07) or education (U = 2485.5, Z = 0.258, p = 0.796 r= 0.02).

Table 4. 6 Demographic characteristics of MS participants in De Dios et al., (2020) and the present study.

Mean (SD)	De Dios Perez et al. 2020	Present Study
Sex	68 % Female, 32% Male	57% Female, 43% Male
Age	40.85 (8.9)	39.4 (10.6)
Education	14.86 (2.4)	14.7 (2)
Years with MS	7.58 (5.9)	7 (4.2)

The results in the cognitive tests in the present study were strikingly similar to the De Dios et al. (2020) findings (See Fig 4.4). Overall, the De Dios group performed slightly poorer in most of the screening tests compared to the MS group in this replication study as shown in Table 4.7. Both groups fell below the matched control cut-off score in the cognitive examination and both performed towards the control cut-off score in the semantic test (PPT). On the Mann-Whitney U tests, groups did not differ significantly from each other on ACE-R (U = 2063.5, Z = 1.9, p = 0.055 r= 0.15) and PPT (U = 2309.5, Z = 0.96, p = 0.337 r= 0.07).

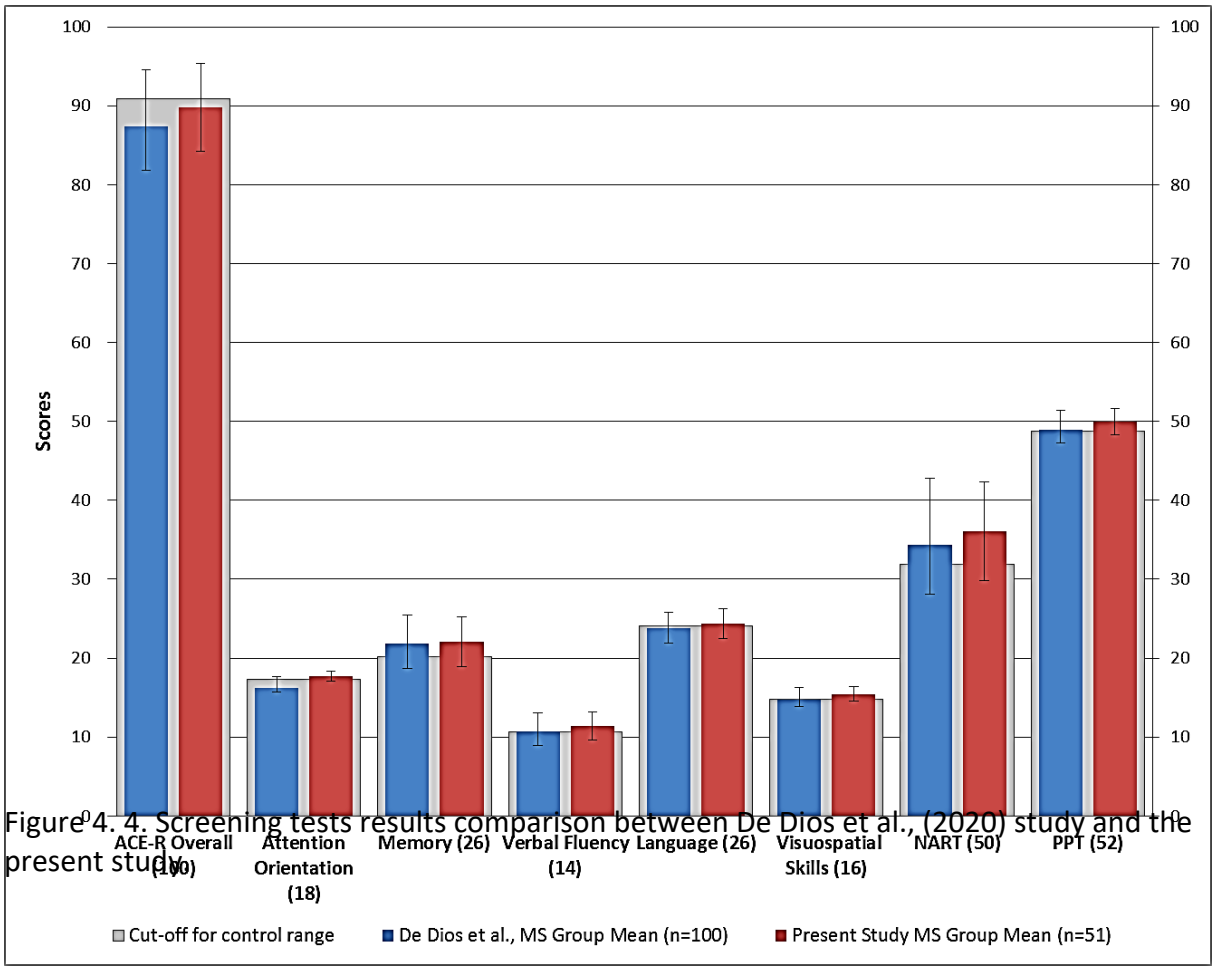


Figure 4. 4. Screening tests results comparison between De Dios et al., (2020) study and the present study.

Table 4.7. Comparison of the cognitive tests means between De Dios Perez et al. (2020) and the present study.

TASK	ACE-R Overall (100)	Attention Orientation (18)	Memory (26)	Verbal Fluency (14)	Language (26)	Visuospatial Skills (16)	NART (50)	PPT (52)
De Dios et al., MS Group Mean and SD (n=100)	**87.37 (7.17)**	16.25 (1.45)	21.85 (3.61)	10.72 (2.34)	23.79 (2.01)	14.77 (1.54)	**34.41 (8.36)**	**48.91 (2.52)**
Present study MS Group Mean and SD (n=51)	**89.88 (5.6)**	17.7 (0.6)	22.03 (3.17)	11.39 (1.79)	24.37 (1.89)	15.45 (0.89)	**36.05 (6.26)**	**49.94 (1.65)**

Cut-off for control range	90.89	17.3	20.18	10.61	24.12	14.83	31.92	48.73
Difference in % between groups	2.5%	8%	0.6%	4.7%	2.2%	4.2%	3.2%	1.9%

In terms of naming skills, results were also similar between both studies; again the De Dios group showed slightly lower scores than the present MS group. In terms of accuracy, both groups performed at the same level of the matched healthy control cut-off (De Dios MS group 52 vs cut-off 52.5 and Present MS group 51.6 vs cut-off control 51.6) (See Table 4.8). Presented in Table 4.3.2.B are the naming mean global and word groups' reaction times for both MS study groups. When compared with the control global mean reaction times the De Dios et al. group had a difference of 26% and the present study MS group had a difference of 20.5%. Table 4.9 also shows the difference in % of each word groups compared to the healthy control group. Overall, our replication study had reasonably similar findings as the De Dios et al., (2020) study. In replicating methods, with 51 participants with RR MS (48 of whom had not taken part in the previous research, and were new recruits to this research), these results confirm the observations of De Dios et al, that anomic symptoms are common in (RES) RRMS, and present as inaccuracy as well as slow word retrieval latency. The next part of the current study will further investigate the nature of anomic symptoms in RR MS.

Table 4. 8 Naming test accuracy scores comparison between De Dios Perez et al. (2020) study and the present study.

TASK	De Dios et al., (2020) Naming Test Accuracy	Present Study Naming Test Accuracy
Max Score	60	55
MS Group Mean and SD	**52.02 (5.21)**	**51.67 (2.73)**
Control Group Mean and SD	**57.08 (2.28)**	**53.98 (1.19)**
Difference between mean scores (Control Group > MS Group) %	5.06 **8.43%**	2.31 **4.20%**

Cut-off for control range (mean – 2 S.D.)	52.52	51.6
Published cut-off for control performance *	52	52

Table 4. 9. Reaction Times for Naming Test Word Groups: comparison between De Dios et al. and the present study.

	Participants with MS De Dios Perez et al. 2020 (n = 100)	**Participants with MS present study (n = 51)**	**Control Participants (n=40)**
Global RTs for Picture Naming Task (n = 60) (n=55)	**1307 (211)**	1177.7 (271.4)	1035 (148) 977.4 (143.7)
Difference in %	**26%**	**20.50%**	
Word Group A (n = 15)	894 (71)	844.2 (75.2)	742.3 (98)
Difference in %	**20%**	**14%**	
Word Group B (n = 15)	1108 (170)	1043.6 (155.1)	821.3 (105.6)
Difference in %	**35%**	**27%**	
Word Group C (n = 15)	1557 (287)	1442.4 (304.3)	1236 (333) 1145.8 (245.8)
Difference in %	**26%**	**26%**	
Word Group D (n = 15)	1670 (315)	1548.7 (220)	1480 (418) 1314.3 (224.6)
Difference in %	**13%**	**18%**	

Results: In-depth neuropsychology study

Participants were selected across both the cohort from the De Dios Perez et al. (2020) and the present study (n=151) with 9 participants volunteering from the former and 12 from the latter groups. MS participants had a mean age and standard deviation of 43.9 years (9.0) and average years of education of 15 (1.9). When compared to the control group, there was no significant difference on education between MS participants (U = 311, Z = 0.78, p = .93). However, there was a significant difference between the MS participants and the control group on age (U = 3.12, Z = 3.12, p = .02). Participants for the in-depth neuropsychology study were chosen based on their performance on accuracy and reaction times in the naming test,

with a combination of lower end and highest end scores designed to allow range of anomia performance to be interpreted across a wide array of cognitive and communication focused forms of testing (Fig 4.5 & 5.6).

The whole cohort of participants had a mean of 51.2 (4.0) for accuracy and a mean of 1232.8 (282.3) for reaction times in the naming test. Twenty-one participants volunteered from that cohort with a mean of 50.1 (3.0).

Descriptive statistics for the in-depth neuropsychological assessments (n=21) were divided into Speech and Language tests and Cognitive tests.

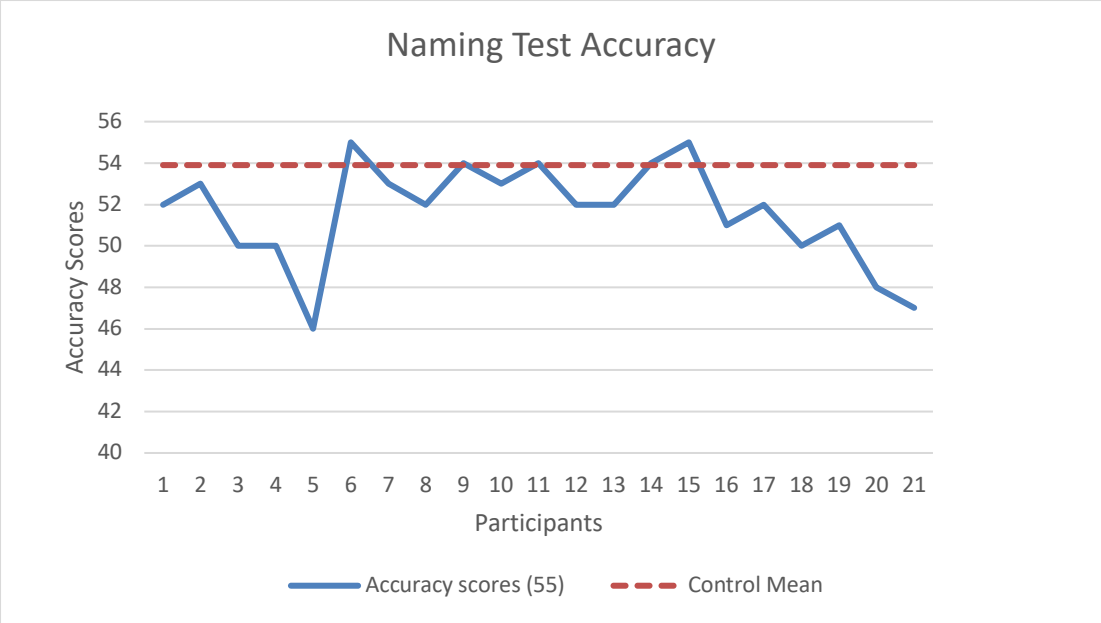


Figure 4. 5. Performance on accuracy in Naming test for the chosen MS participants.

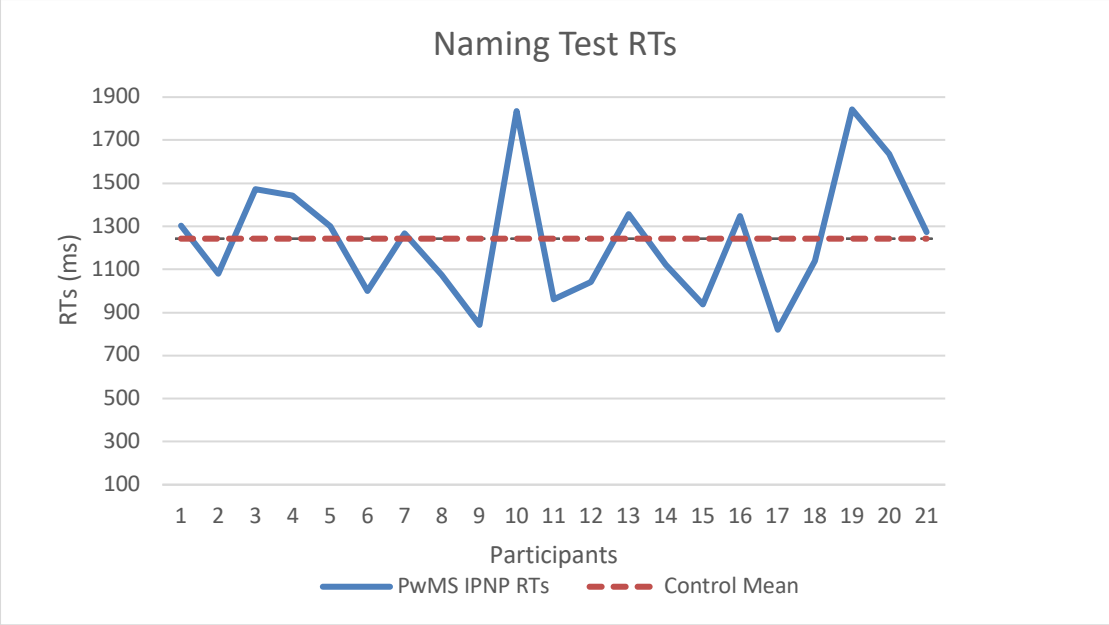


Figure 4. 6. Performance on reaction times in Naming test for the chosen MS participants.

Speech and language assessments data

To obtain a measure of motor speech and oro-motor skills, participants were assessed with the FDA-2. The MS group had a mean score of 8.9 (SD 0.2) in the test. 90.5% of the participants presented with normal speech function and 9.5% (2 participants) presented with mild abnormalities such as mild problems with respiration and palate, mild difficulties on lips and tongue movement and mild laryngeal phonation (See Table 4.10)

Language tests were compared with published normative data; however, data for some tests such as reaction times for the Boston Naming Test were not available.

As shown in Table 4.11, the MS group scores fell below the published normative and control mean data in most of the assessments, only the WAB-R was above the mean normative data. Furthermore, most of the language tests had more than half of the MS participants performing below the mean normative data with the exception of the WAB, which had only 23% (Fig 4.7). This implied that for many participants with MS, they performed within the control range, but towards the lower end of that range.

Table 4.10. MS group subtests and overall scores in FDA-2

PART	*REFLEXES*	*RESPIRATION*	*LIPS*	*PALATE*	*LARYNGEAL*	*TONGUE*	*INTELLIGENCE*	*TOTAL RESULTS*
1	9	9	9	9	9	9	9	**9**
2	8.3	9	9	9	9	9	9	**9**
3	8.3	8	8	9	8	8	8.3	**8**
4	8.3	8.5	8.6	8.3	9	8.7	8.3	**8.5**
5	9	9	9	9	8.75	9	9	**9**
6	9	9	9	9	9	9	9	**9**
7	9	9	9	9	9	9	9	**9**
8	9	9	9	9	9	9	9	**9**
9	9	9	9	9	9	9	9	**9**
10	9	9	9	9	9	9	9	**9**
11	8.7	9	9	9	9	9	9	**9**
12	9	9	9	9	9	9	9	**9**
13	9	9	9	9	9	9	9	**9**
14	9	9	9	9	9	9	9	**9**
15	9	9	9	9	9	9	9	**9**
16	8	9	9	9	9	9	9	**9**
17	7.7	9	9	9	9	9	9	**9**
18	8.7	9	9	9	9	9	9	**9**
19	9	8.5	9	9	9	9	9	**9**
20	9	8	8.6	9	9	9	9	**9**
21	9	9	8.8	9	9	8.8	9	**9**

Table 4. 11**.** Mean (SD) row scores for group comparison on the language assessments.

	IPNP RTs (ms)	**IPNP Accuracy (55)**	**Boston RTs (ms)**	**Boston Accuracy (60)**	**Cookie Theft (IU)**	**WAB-R (100)**	**Non-Word Repetition (30)**
PwMS Mean (SD)	1242.7 (290.1)	51.6 (2.5)	1553.9 (318.6)	47.6 (7.1)	47.9 (21.4)	99.1 (0.9)	29.1 (1.8)
Norm Data/Control mean (SD)	977.4 (143.7)	53.9 (2.1)	N/A	55.5 (3.9)	46.6 (23.8)	98.4 (2)	N/A
Cut-off	1264.8	51.6	N/A	47.7	N/A	96.4	N/A

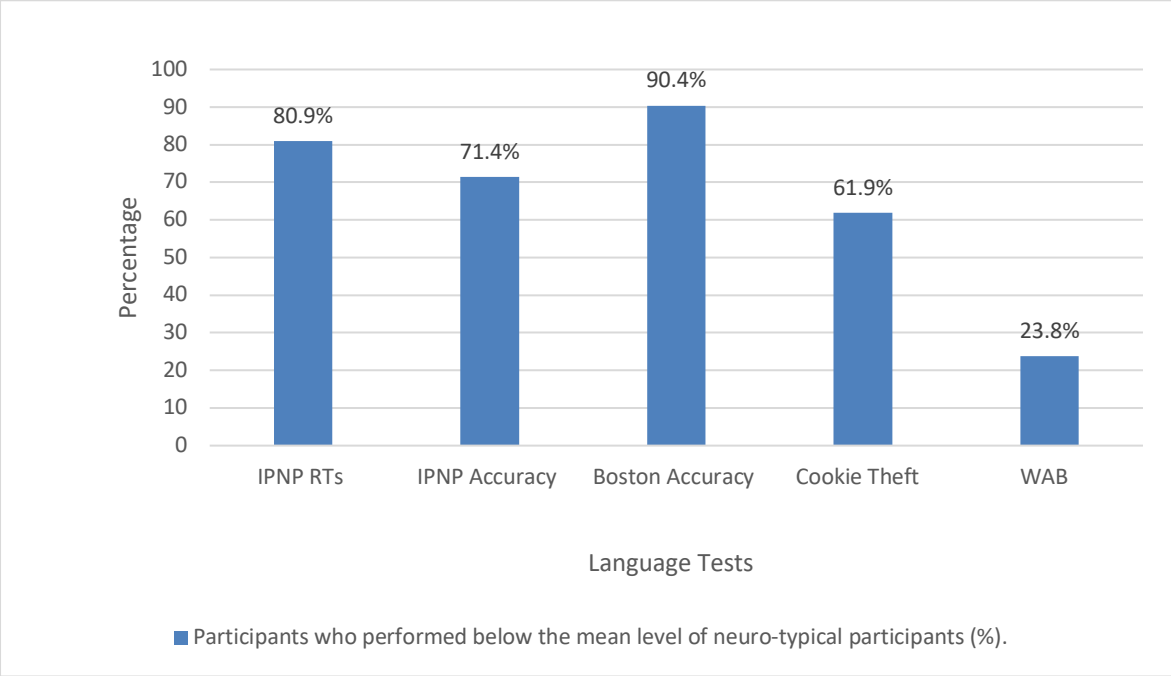


Figure 4. 7 Percentage of MS participants who scored under the mean control score from published data.

As the Western Aphasia Battery (WAB) is an assessment recommended for universal application in order to allow comparison of aphasic symptoms across studies and internationally (Wallace et al., 2018), it is potentially informative to focus specifically on the performance of the participants with MS on this assessment. The mean MS group performance was above the neurotypical mean on various WAB subtests: Spontaneous Speech, Auditory Verbal Comprehension and the Naming subtests, as well as the overall performance in the Aphasia Quotient (See Table 4.12). However, in the Repetition subtest the mean of the group fell slightly below the published normative data mean, but still well below the control range cut off. Figure 4.8 shows WAB subtests individual participants' performance.

Table 4.12. MS group subtests and overall scores in the Western Aphasia Battery.

	Spontaneous speech (20)	Auditory Verbal Comprehension	Repetition (10)	Naming (10)	**Aphasia Quotient (100)**
PwMS Mean (SD)	20 (0)	9.9 (0.1)	9.7 (0.3)	9.85 (0.3)	99.1 (0.9)
Normative/Control Data Mean (SD)	19.9 (0.2)	9.9 (0.2)	9.8 (0.3)	9.5 (0.3)	98.4 (1)
Cut-off	*19.5*	*9.5*	*9.2*	*8.9*	*96.4*

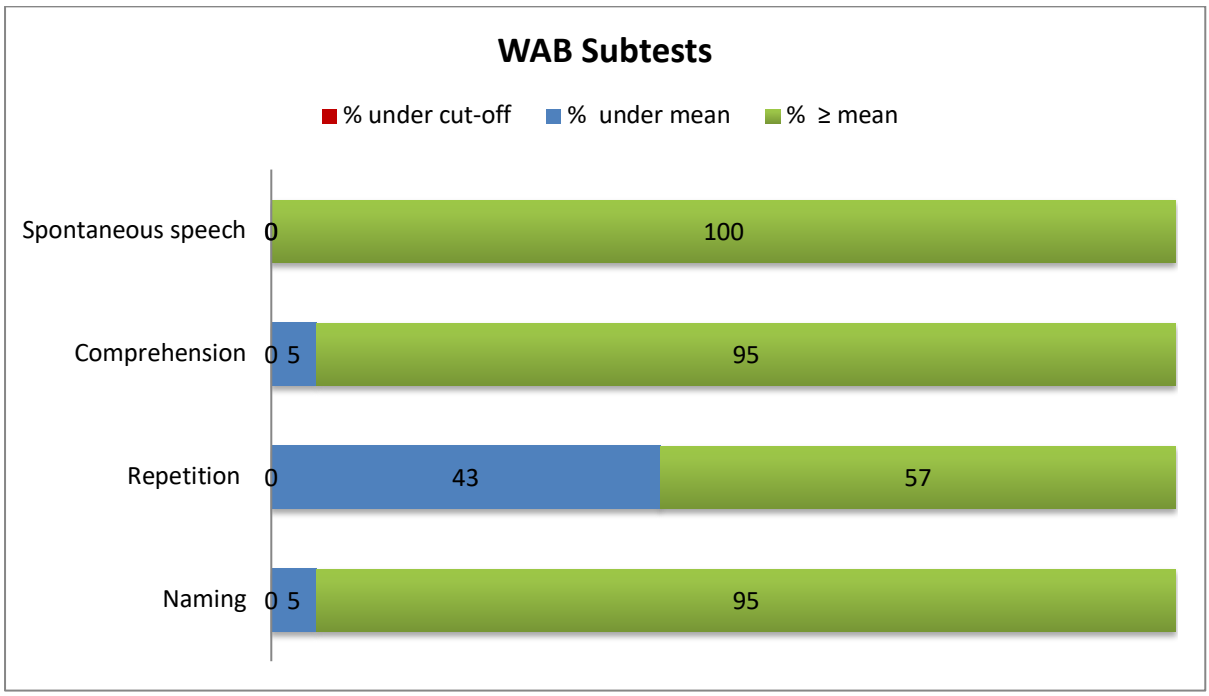


Figure 4. 8 Percentage of PwMS who performed under the published cut-off and mean; and above or equal the mean for published healthy normative data in WAB subtests.

Looking more specifically at naming, in the IPNP (n=55 items), 43% participants performed below the healthy control cut-off score and 81% below the control mean in term of reaction times (Fig. 4.9). On accuracy, 38% of participants fell below the cut-off score and 76% of the participants scored below the healthy control mean (Fig. 4.10).

Similarly, the mean of the MS group on the Boston Naming test in terms of accuracy fell below the lower end of the neuro-typical performance (MS = 47.6, published data cut-off = 47.7). We did not find published data available for healthy control RTs for the Boston Naming test.

Likewise, we did not find published data for the Non-word Repetition task, however most of the participants seem to be at ceiling on this test (mean= 29.1. SD= 1.8).

For the connected speech/descriptive discourse scores for the MS group, elicited by the Cookie Theft Picture Description task, mean performance for participants with MS was similar (and marginally above) the mean for control published data (MS = 47.9, Control published data = 46.6) (Table 4.11). However, again beyond the mean, there was a wide range of performance across the cohort of participants with MS, which translates to a reduced quantity of words and significant facts. (Fig. 4.11)

Overall, when language assessment was based on an internationally-recognised standardised battery (WAB-R), the mean MS performance was at or even better than the control level. However, for specific assessments of lexical retrieval, many people with MS performed below both the control mean and control cut-off levels.

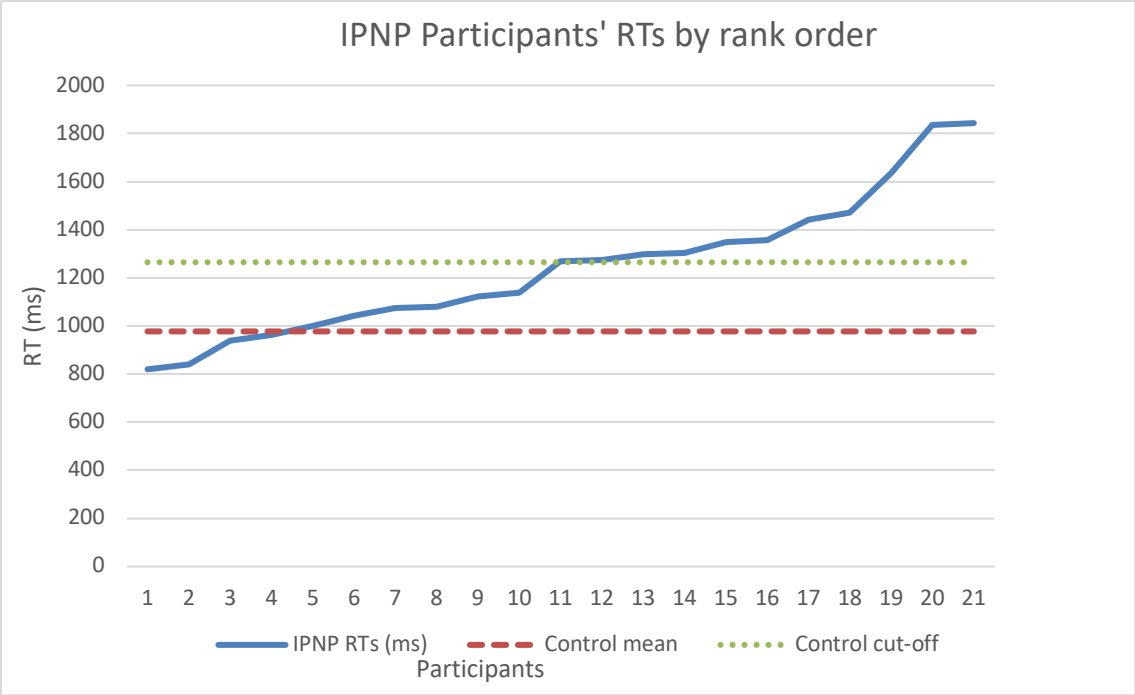


Figure 4. 9. IPNP Naming test reaction times rank order in participants with MS

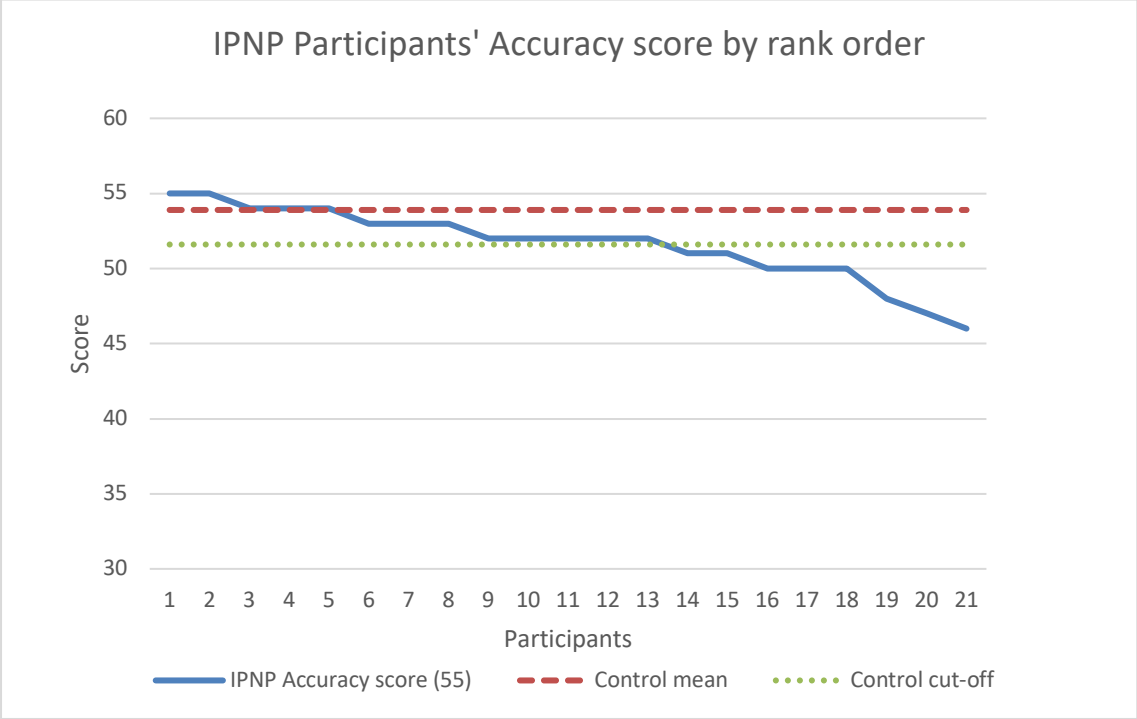


Figure 4. 10. IPNP Naming test accuracy rank order in participants with MS.

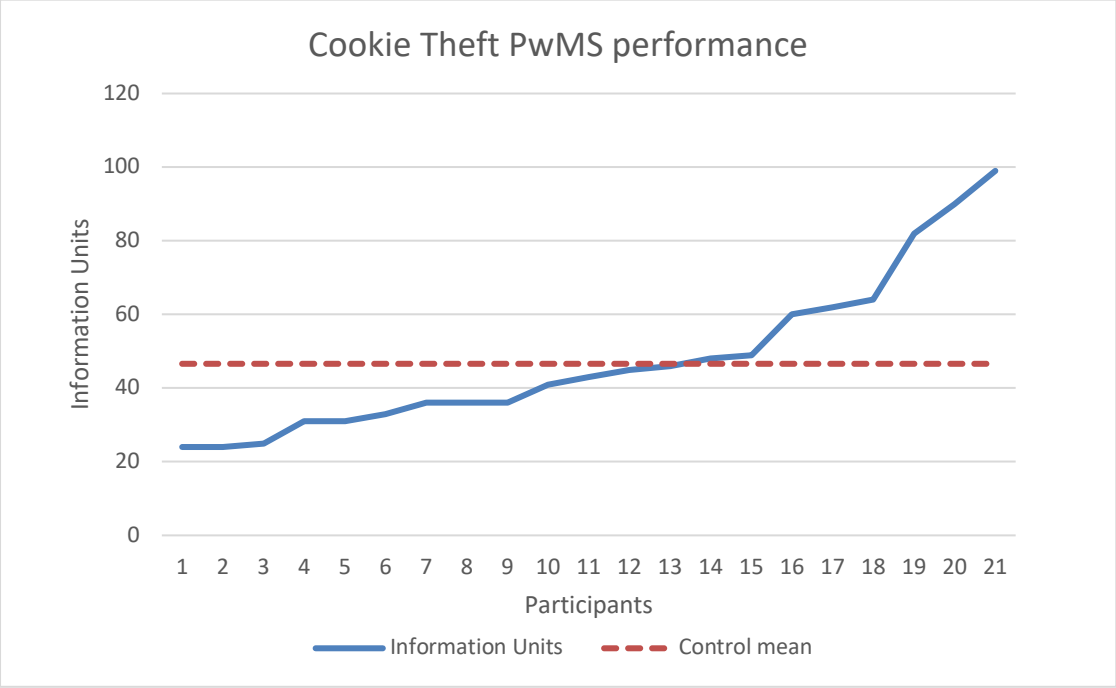


Figure 4. 11. Cookie Theft Picture Description task participants' performance ordered by rank.

Cognitive Assessments data

For the descriptive statistical analyses, cognitive data were divided into four cognitive domains: Visuospatial and Perceptual Skills; Attention and Memory; Executive Functions and Fluency; and Information Processing Speed.

- *Visuospatial and Perceptual Skills.*

The data presented in Table 4.11 show that the MS group scored within the control range for three of four tasks, though within the lower part of that range. For Matrix T-score, Rey Copy and Trail Making Test Motor Speed, the MS group showed marginally poorer performance than the normative mean (% difference 2.2, 1.9 and 3.6 respectively). However, for Trail Making Test Visual Scan, the mean MS group performance was markedly poorer than the control mean and well below the control cut-off with an overall performance difference of nearly 24%. Looking at individual performance, more than half of the participants scored greater than or equal to the healthy normative data on the Trail Making Motor Speed test and the Rey Copy test with 86% and 62% respectively; but for the Matrix Reasoning Test, 62% of the participants performed lower than the normative mean and on the Trail Making Visual Scan Test 71% of the participants fell below the cut-off score for the task (see Figure 4.3.3.6).

This suggests a specific weakness in visual attention, the ability to pay attention to a single item in a busy environment.

Table 4. 13. Visuospatial and Perceptual Organisation skills comparison mean and SD scores between MS group and normative data.

	MS Group ***M (SD)***	**Normative** ***M (SD)***	**Cut-off**	**Difference in %**
Matrix T-score	48.2 (10.9)	50 (10)	30	2%
Rey Copy	34.3 (2.0)	35 (1.4)	32.2	2%
TRAIL MAKING TEST Visual Scan	5.5 (3.5)	10 (1)	8	24%
TRAIL MAKING TEST Motor Speed	9.3 (2.7)	10 (1)	8	4%

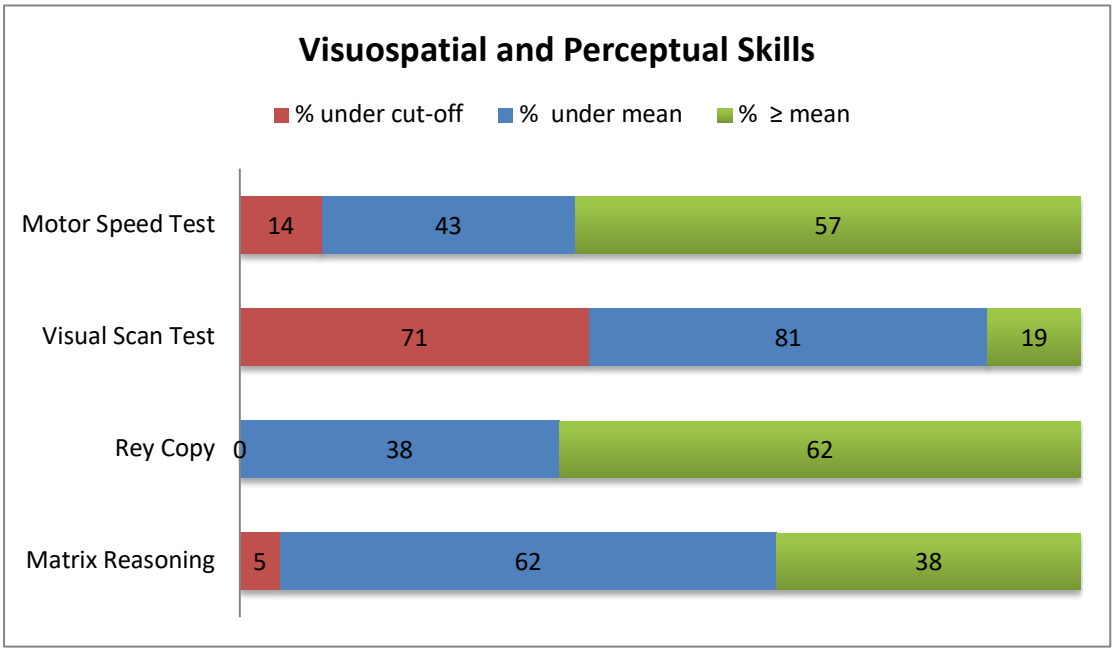


Figure 4. 12. Percentage of participants with MS who performed under the published cut-off and mean; and above the mean for published healthy normative data in the visuospatial and perceptual assessments.

- *Attention and Memory*

Table 4.14 shows that the MS group performance fell under the lower part of the control range on most of the attention and memory tasks, except for the Colour-Word Interference subtest (name+reading) and Rey Memory in which the MS group fell under the lower end of the neuro-typical performance range (MS = 7.5, Cut-off = 8 and MS =26, Cut-off 40 respectively). As shown on Figure 4.13, nearly every participant's individual score was lower than the mean for the published normative data. In fact, 67% of the participants' scores were below the cut-off score on the Colour-Word Interference (name+reading) task, as well as 76% as the participants' scores in the Rey Memory task. This is indicative that attention and memory tasks were more challenging for the PwMS in relative terms, especially selective attention and visual memory.

Table 4. 14. Attention and Memory comparative scores table between MS group and normative data and the difference in percentage between the normative data and the MS group mean.

	MS Group *M (SD)*	Normative *M (SD)*	Cut-off	Difference in %
Digit Span Forward (attention, immediate recall memory)	6.1 (1)	6.8 (0.6)	5.6	9%
Digit Span Backward (working memory)	4.1 (1)	5.6 (1)	3.6	22%
Colour-Word Interference Test (Name + Reading)	7.5 (3.3)	10 (1)	8	13%
Corsi Blocks (Spatial Working Memory)	35.7 (25.4)	55.7 (20.3)	15.1	20%
Rey Memory (Visual Memory)	26.2 (15.2)	45 (2.5)	40	19%

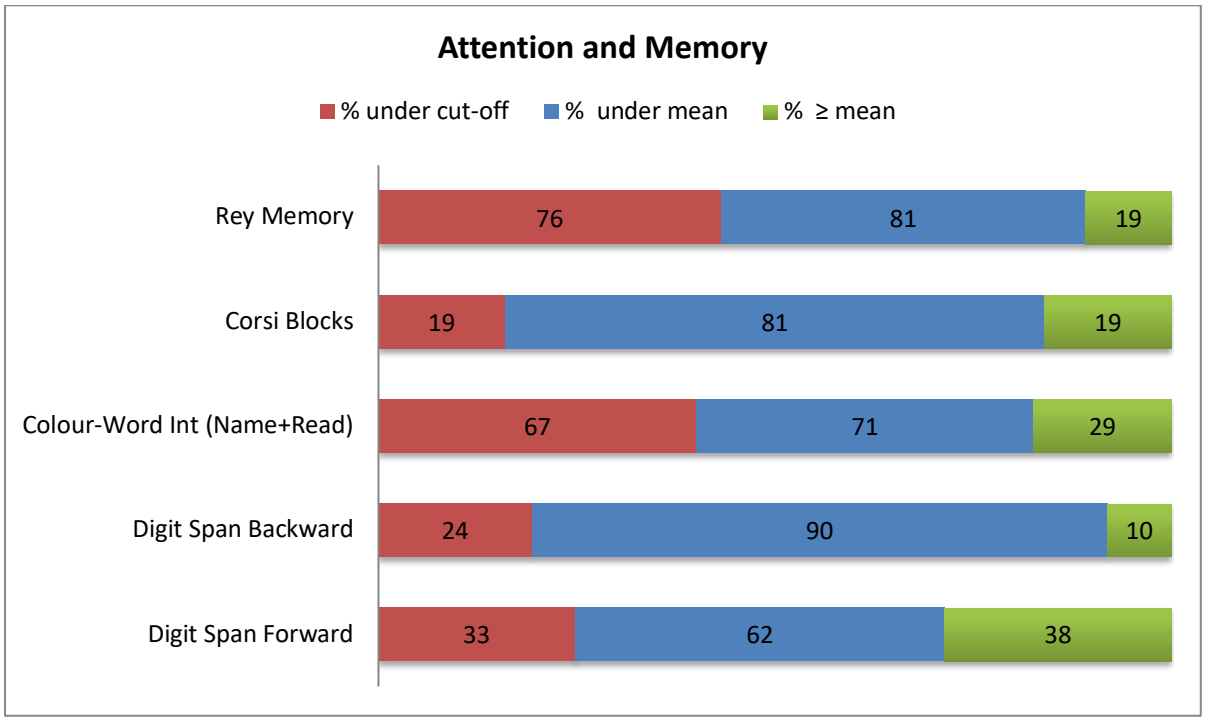


Figure 4. 13. Percentage of participants with MS who performed under the published cut-off and mean; and above the mean for published healthy normative data in the attention and memory assessments.

- *Executive Functions and Fluency*

In terms of executive functions, the MS group showed a poorer performance than the normative mean, falling below the norm on every task as shown in Table 4.15. There is a variable range in performance differences between the MS group and the normative data mean (in %) for each task, from -3% (Design Fluency) to -18% (Number sequencing) (see Table 4.15). In addition, the MS group performance in the number sequencing and letter sequencing trail making tests was distinctly poorer, scoring below the cut-off range (MS = 6.6 vs cut-off = 8, MS = 7 vs cut-off = 8, respectively). 62% of the MS participants scored below the lower end of the neuro-typical performance range for the Trail Making Test Number Sequencing and 57% of the MS participants on the Trail Making Test Letter Sequencing.

On all verbal fluency and semantic tasks, the MS group fell lower than the normative mean as shown in Table 4.15. However, the semantic tasks showed the poorest performance with the

MS group scoring below the control cut-off on the category fluency task (MS = 1.9, Cut-off = 8) and 96-Synonym Judgement (MS = 87.9, Cut-off = 91). This revealed an overall performance difference of 43% and 7% respectively, suggesting that mild deficits in semantic processing (as in comprehension of abstract vocabulary) appeared distinct from more striking deficits in semantic generation, which rely on problem-solving and speed of processing. Looking at individual performances, most of the MS participants scored below the control mean (Figure 4.14). However, on the Category Fluency task a striking 100% of the MS participants fell below the cut-off score and 62% on the 96-Synonym Judgement task.

Table 4. 15. Executive functions and fluency tasks comparative scores table between MS group and normative data and the difference in percentage between the normative data and the MS group mean.

	MS Group *M (SD)*	Normative *M (SD)*	Cut-off	Difference in %
Design Fluency	9.5 (2.1)	10 (3)	8	3%
TRAIL MAKING TEST **Number sequencing**	6.6 (4.1)	10 (1)	8	18%
TRAIL MAKING TEST **Letter sequencing**	7.0 (4.1)	10 (1)	8	16%
TRAIL MAKING TEST **Number-Letter switching**	8.4 (3.6)	10 (1)	8	8%
VERBAL FLUENCY **Letter fluency (Phonemic)**	8.4 (3.4)	10 (1)	8	8%
VERBAL FLUENCY Category fluency (Semantic)	1.9 (1.3)	10 (1)	8	43%
96-Synonym Judgement	87.8 (6.4)	94.5 (1.8)	91	7%

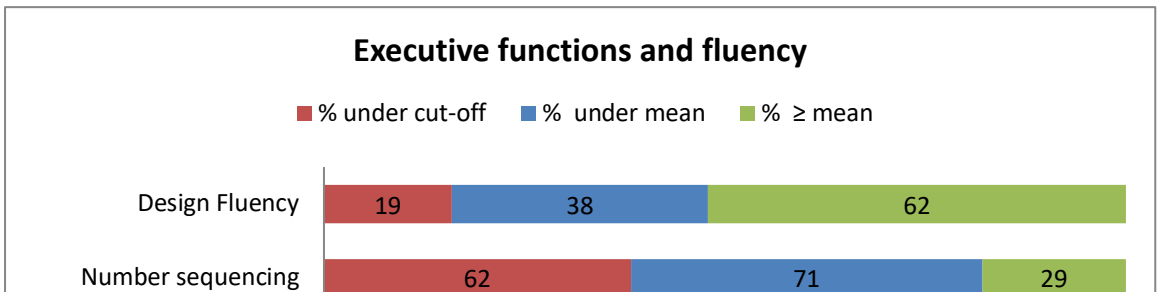


Figure 4. 14. Percentage of participants with MS who performed under the published cut-off and mean; and above the mean for published healthy normative data in the Executive functions and Fluency tests.

- *Information Processing Speed*

In both tasks assessing information processing speed (IPS) - SDMT and Colour-Word Interference Test (inhibition), the MS group performance fell below the normative mean as shown in Table 4.16. The group performance was inferior to the normative mean in both tests, yet the SDMT showed a larger difference in performance compared to the normative data (20% difference). Furthermore, the Colour-Word Interference Test just below the lower end of the neuro-typical performance range (MS = 7.9, cut-off = 8)

Individual performances were also poor with 67% of the participants scoring below the normative mean on the Colour-Word Interference Test (inhibition) and 90% on the SDMT. Likewise, 43% of the MS participants performed under the control cut-off on the Colour-Word Interference Test (inhibition) and 38% on the SDMT (Figure 4.3.3.9).

Impairments on IPS have been widely studied and are among the first cognitive deficits seen in PwMS, more than 50% of the MS population have been found with problems in IPS (Amato et al., 2010; Chiaravalloti & DeLuca, 2008; Rao, Aubin-Faubert, & Leo, 1989). These results might underpin the knowledge about a cognitive slowing in PwMS.

Table 4. 16. Information Processing Speed comparative scores table between MS group and normative data and the difference in percentage between the normative data and the MS group mean.

	MS Group *M (SD)*	Normative *M (SD)*	Cut-off	Difference in %
Symbol Digit Modality Test (SDMT)	36.8 (11.8)	58.6 (12.6)	33.4	20%
Colour-Word Interference Test (Inhibition)	7.9 (3.4)	10 (1)	8	11%

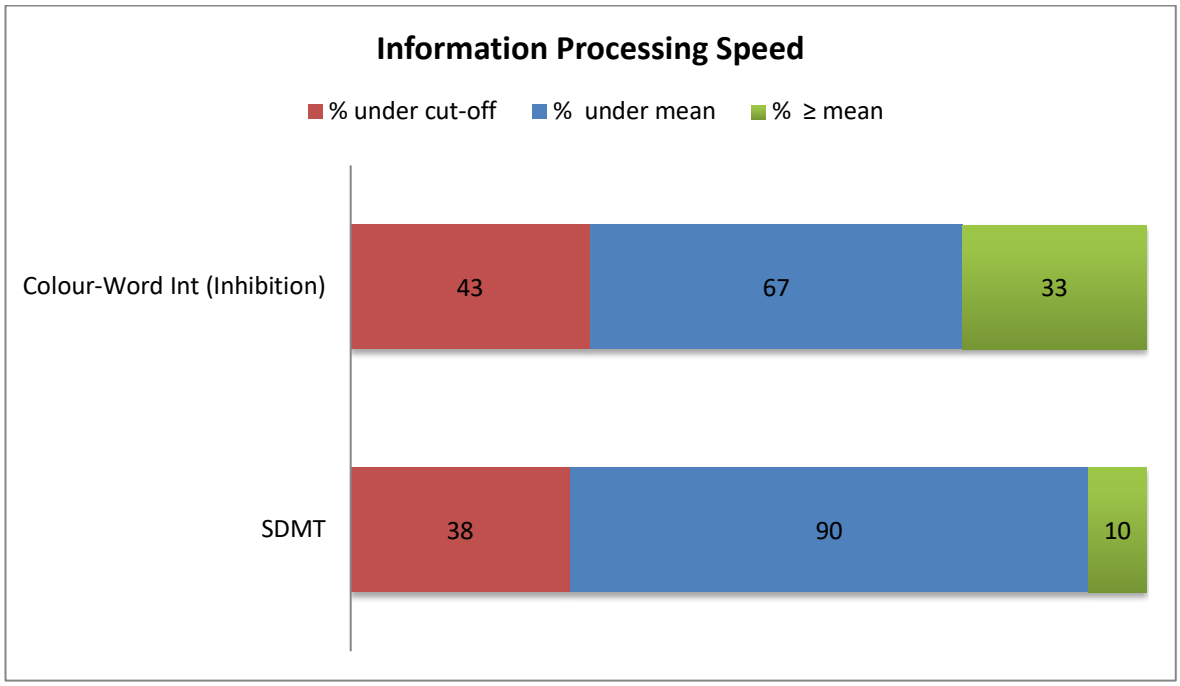


Figure 4. 15. Percentage of participants with MS who performed under the published cut-off and mean; and above the mean for published healthy normative data in the visuospatial and perceptual assessments.

Statistical Analysis

Kendall's Tau correlation analyses were conducted to investigate the association between lexical retrieval skills and broader cognitive-linguistic skills. One assessment was chosen to represent each cognitive domain shown as follows:

- Visual Scan Test = Visuospatial and Perceptual Skills
- REY Memory = Memory and Attention

- Digit Span Backwards = Working Memory
- D-KEFS Number-Letter Switching = Executive Functions
- Verbal Letter Fluency = Phonetic Fluency
- Verbal Category Fluency = Semantic Fluency
- SDMT = Information Processing Speed

For word retrieval the following variables were used: IPNP accuracy and IPNP RT's.

Please see Table 4.17 for full correlation analyses results. There were strong, positive correlations between Rey Memory Test (r_S = .631, N =21, p = .002), Number-Letter Switching Task (r_S = .627, N =21, p = .002) and SDMT (r_S = .677, N =21, p = .001) and naming accuracy (IPNP accuracy). Additionally, correlations were found on Letter Fluency Test (r_S = .501, N =21, p = .021), Category Fluency Test (r_S = .490, N =21, p = .024) and IPNP accuracy. Overall, these results suggested particularly strong associations between accurate naming and memory and attention skills, executive skills and information processing speed. In terms of Naming RT's, there were strong, negative correlations between Rey Memory Test (r_S = .-631, N =21, p = .002), Number-Letter Switching (r_S = -.630, N =21, p = .002), Letter Fluency Test (r_S = -.639, N =21, p = .002), Category Fluency Test (r_S = -.586, N =21, p = .005) and IPNP RT's. There also found correlations between Visual Scan Task (r_S = -.470, N =21, p = .032), SDMT (r_S = -.475, N =21, p = .030) and naming RT's. Overall, the reaction time results indicated particularly strong associations between naming speed and some of the cognitive skills linked to naming accuracy (memory, attention and skills) but also letter and category fluency skills.

Table 4. 17. Kendall's Tau correlation analyses on Naming Accuracy and Naming Reaction Times.

			Visual Scan	Rey	Digit Span Backwards	Number-Letter Switching	Letter Fluency	Category Fluency	SDMT
Spearman's Rho	**Naming Accuracy**	Correlation Coefficient	.423	**.631****	.331	**.627****	.501*	.490*	**.677****
		Sig. (2-tailed)	.056	**.002**	.143	**.002**	.021	.024	**.001**
		N	21	**21**	21	**21**	21	21	**21**

			Visual Scan	Rey	Digit Span Backwards	Number-Letter Switching	Letter Fluency	Category Fluency	SDMT
Spearman's Rho	**Naming RT's**	Correlation Coefficient	-.470*	**-.631****	.122	**-.630****	**-.639****	**-.586****	-.475*
		Sig. (2-tailed)	.032	**.002**	.599	**.002**	**.002**	**.005**	.030
		N	21	**21**	21	**21**	**21**	**21**	21

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Discussion

The current study aimed to investigate the presence and extent of anomia across a sample of people with Rapidly Evolving Severe Relapsing-Remitting Multiple Sclerosis, with varying time since diagnosis, in order to understand the factors that could underlie the anomia symptoms. In achieving this aim, we carried out a replication on the De Dios Perez et al., (2020) that showed that word retrieval speed and accuracy deficits were present in our MS group, with almost 40% of the participants presenting with a clinical performance in word retrieval accuracy and a latency effect of 20% slower naming responses, as well as having a wide range of performance variability between MS participants. This confirms that the presence of anomic symptoms (accuracy or/and retrieval speed) can be common and can vary substantially amongst people with MS.

Cognitive deficits are frequent in MS, ranging from 40% to 70% of prevalence rates (Chiaravalloti & DeLuca, 2008). As expected, MS participants' performance fell toward the end of the cut-off for the normative data range in the cognitive screen. Our results also revealed some degree of semantic impairments in the MS group. We observed that more than half of the naming errors were semantic (semantic paraphasias 44%, semantic description 4%, semantic super-ordinate 3%) and 30% of the MS group showed clinical performance when assessed for semantic processes, even with relatively undemanding semantic matching tasks as found in the Pyramids and Palm trees Test, utilising concrete, imageable concepts only. Previous research in the literature have highlighted semantic deficits in people with MS (Drake, Allegri, & Carra, 2002; Henry & Beatty, 2006; Lethlean & Murdoch, 1994) and clearly semantic impairment can add to naming difficulties; if a person has problems recognising an object, or distinguishing it from related co-ordinates (e.g., strawberry-grape), it will be hard to name it or the process may become inefficient.

The replication study provided results which were markedly similar to the ones reported by De Dios Perez et al., (2020) study, confirming the presence of anomic symptoms in RES-RR MS. As mentioned before, cognitive functions in MS have been widely described; however, the key concern for studying cognitive functions in this research was to identify those cognitive-linguistic deficits leading to language problems such as anomia in PwMS.

The in-depth neuropsychological assessment, which constituted the second part of the present study with results from 21 participants with MS confirmed deficits in attention, memory, speed of information processing, executive functions and verbal fluency. Our results were consistent with the well-recognised cognitive impairment hallmark in MS (Beatty, 2002; Chiaravalloti & DeLuca, 2008; Rao et al., 1991; Zakzanis, 2000).

In particular, when assessed for language skills our findings further confirmed difficulties in word retrieval (accuracy and retrieval speed) in PwMS; 38% of these participants fell below the cut off score of the neuro-typical performance in naming accuracy and 43% were slower on retrieving words compared to the healthy control cut-off score. Furthermore, 62% of the participants produced less quantity of words and a reduction in 'significant facts' when verbally describing a composite (i.e., busy) picture compared to the healthy controls. Our findings supported the reported results from previous literature that found deficits in naming retrieval in PwMS (De Dios Pérez et al., 2020; M. Drake et al., 2002; Friend et al., 1999; Tallberg & Bergendal, 2009). Also, the rates of difficulties in word retrieval were comparable to a study by Lechner-Scott et al. (2010) who assessed MS patients with a neuropsychological screening tool and found that 31% presented deficits in naming tests.

The general positive performance on the WAB, in line with the studies of Gerald et al. (1987) where no aphasic syndrome was identified in our participants with MS, suggests that a diagnosis other than aphasia is most appropriate to people with MS presenting with lexical retrieval inaccuracy and delay. Furthermore, in the present study anomia was not explained by speech deficits since the vast majority of the MS group (90.5%) presented with minimal evidence of dysarthria and essentially neuro-typical motor speech function.

For most cognitive assessments, the MS group mean was lower that the normative mean. However, participants showed marked difficulties on specific cognitive tests. We found that participants were well below the mean cut-off scores on visual scan skills (71% of participants below the cut-off score), attention and visual memory skills (67% and 76% of the participants respectively), semantic verbal fluency (100% of the MS participants) and semantic cognition (62% of the participants). In terms of attention, visual scan and visual memory deficits our results were in line with previous studies which found impairments in these specific areas in PwMS (García, Plasencia, Benito, Gómez, & Marcos, 2009; Gmeindl & Courtney, 2012; Janculjak, Mubrin, Brinar, & Spilich, 2002; Rao et al., 1991). Poor performance in attention,

visual scan tasks and visual short term memory tasks suggested an impairment in the information processing skills, particularly working memory. This could be explained by the Baddeley and Hitch (2000) model of working memory, which indicates that auditory and visual attention systems are part of the ability to maintain information while such information is simultaneously being processed and manipulated by the central executive (Baddeley, 1992; Baddeley & Hitch, 2000). Evidence has suggested that decreased information processing skills is the most basic cognitive deficit experienced by PwMS (Bergendal et al., 2007; Chiaravalloti & DeLuca, 2008), specifically working memory and processing speed (DeLuca et al., 2004; Genova, Lengenfelder, Chiaravalloti, Moore, & DeLuca, 2012). Working memory impairments in MS have been well documented in the literature (D'Esposito et al., 1996; Genova et al., 2012; Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003), for instance Lengenfelder et al. (2003) suggested that the primary working memory deficit in MS is within the central executive system, which controls attention, and receives and filters information, rather than the phonological loop. However, it is unclear whether such deficits are solely due to impairments in working memory alone or if they are conflated by processing speed deficits (DeLuca et al., 2004; Genova et al., 2012).

Our MS participants also produced fewer words on letter (phonemic) verbal fluency tests and displayed a markedly low performance on the category (semantic) fluency tasks compared to neuro-typical data. These results corroborate early research which have found verbal fluency deficits as a common symptom of MS even on the early stages of the disease (Friend et al., 1999; Henry & Beatty, 2006; Lethlean & Murdoch, 1993; Messinis et al., 2013; Renauld et al., 2016; Viterbo, Iaffaldano, & Trojano, 2013). Whereas some studies have found similar impairments on assessments of phonemic and semantic fluency (Beatty, 2002; Henry & Beatty, 2006), others have found semantic fluency more affected (Foong et al., 1997; Zakzanis, 2000). However, studies that found comparable deficits in both verbal fluency tasks, appeared to attribute it to the different clinical features of the MS sub-types (Henry & Beatty, 2006). Our study found semantic fluency more impaired than phonemic fluency in participants along with other semantic cognition tests. Generally, healthy individuals perform better in category fluency than letter fluency (Kavé, 2005), probably because phonemic fluency is more cognitively demanding and may depends more on cognitive control, whilst semantic fluency depends on existing semantic knowledge (Sepulcre et al., 2011; Velázquez-

Cardoso, Marosi-Holczberger, Rodríguez-Agudelo, Yanez-Tellez, & Chávez-Oliveros, 2014). Hence, problems in semantic search and memory might explain the poor performance in semantic cognition tasks in our MS group. Furthermore, Chertkow and Bub (1990) found that difficulties in the generation of category list of words are due to problems in semantic search and the deterioration of the semantic memory store. Our participants seemed to have an adequate performance in speech perception and phonological assembly task (non-word repetition); however, problems in short-term memory and working memory could have been affecting verbal fluency tasks.

Deficits in memory, attention, executive functions and information processing speed seemed to have a strong relationship to lexical retrieval inaccuracy. Similarly, deficits in abstract problem solving (executive functions), attention, visual memory, semantic and phonological fluency and speed of information processing seem to explain the variance in latency of naming responses. Our findings support and are more specific than the reported results from previous literature that suggested that deficits in lexical retrieval correlates with a general cognitive decline in MS (Tallberg & Bergendal, 2009). Phonetic and semantic deficits appear to be affecting speed and word retrieval; these could be explained by a distortion of lexical access and production processes. Yet, Lethlean and Murdoch (1994) analysed naming errors in PwMS and found that the majority of naming errors were semantic paraphasias and they seemed to support an access deficit rather than a semantic deficit.

The present study confirm the findings of previous studies (Friend et al., 1999; Katja Laakso, 2000; Lethlean & Murdoch, 1993, 1994, 1997; Tallberg & Bergendal, 2009) in which subtle language problems were found in PwMS. To our knowledge no other studies have studied the underlying causes of anomia in people with RES RR-MS using an in-depth neuropsychological test administered over several sessions to minimise fatigue in participants and using sensitive speech and language tools.

To conclude, anomia is a common symptom in RES RR-MS but does not resemble the anomic symptoms typical of stroke aphasia in any meaningful way. Neither did anomic symptoms appear to interact substantially with symptoms of motor speech disorder. We suggest that naming errors might be stemming from disruption at the levels of working memory, in particular in the central executive system, and processing speed within the information processing ability, and/or deficits in the semantic access. As well as confirming incidence,

these data robustly demonstrate the underlying cognitive-linguistic essence of anomia in RR-MS. It is underpinned by different underlying impairments in skills such as attention and memory, information processing speed, and executive functions. On this basis, anomia (and other language deficits in MS) appear to stem from what could most accurately be described as a cognitive-communication disorder (as typically reported in cases of traumatic brain injury with diffuse rather than focal brain injury) (Togher, McDonald, Coelho, & Byom, 2014) that than aphasia per se.

Limitations of the study

One obvious limitation of this study is the small number of subjects, which warrants a cautious interpretation of results.

Future research

Although subtle, anomia could affect quality of life in PwMS (Klugman & Ross, 2002) and impact many aspects of daily living, such as reading, socialising, workload management, among others. Given the subtle presentation of these symptoms, this begs the question as to whether anomia warrants clinical treatment in PwMS. On the one hand, the incidence of anomia could be described as moderate and symptom severity of anomia is low in PwMS which suggests low priority for clinical treatment. However, expressive language competence and confidence are central to work and social functioning. Moreover, there is a possibility of facilitate some benefits to other cognitive domains (e.g. information processing speed) by using on the tangible skill of lexical retrieval accuracy and speed. One practical clinical solution could a technology-based therapy designed to increase picture naming accuracy and speed which could support participants' on-going self-management of the anomic symptoms through remote and easy to use software. A longitudinal assessment would allow greater understanding of the role of the progression of the disease in cognitive deficit and language impairment. Finally, a study into subcortical participation using brain imaging techniques of central processes in language, more specific on lexical retrieval in PwMS will expand our knowledge of the nature of anomia in participants with RES RR-MS.

CHAPTER 5

Training Speed and Accuracy of word retrieval in people with relapsing-remitting multiple sclerosis; piloting the application of QuickWord aphasia therapy.

Introduction

Multiple Sclerosis is an chronic inflammatory demyelinating disorder of the central nervous system (CNS) forming widespread lesions or plaques which leads to neurodegeneration (Noseworthy et al., 2000). MS is considered to affect primarily the white matter of the brain, cerebellum and brain-stem, causing axonal degeneration or loss (Lassmann, Brück, & Lucchinetti, 2007). However, studies also show that cortical and subcortical deep grey matter lesions can be present in MS (Fisher, Lee, Nakamura, & Rudick, 2008). MS follow a broad range of symptoms which have been widely studied such as physical disability and cognitive impairment seen even in early stages of the disease (Brassington & Marsh, 1998; Chiaravalloti & DeLuca, 2008).

Language deficits have only recently been studied as a clinical symptom of MS. Prior to this research on communication problems was predominantly focused on speech impairment (Hartelius et al., 2000). According to the Wernicke-Lichtheim-Geschwind model (Geschwind, 1974), cortical grey matter regions were considered to primarily support language processing. As a consequence, language was assumed to be unaffected in MS since the condition mainly affects white matter and subcortical structures. Increasingly, research has shown that language is a complex network and other brain regions outside the classical Wernicke-Lichtheim-Geschwind model are involved, such as white matter and subcortical regions (Ketteler, Kastrau, Vohn, & Huber, 2008; Poeppel & Hickok, 2004; Sanai, Mirzadeh, & Berger, 2008). Hence, researchers such as Lethlean and Murdoch (1997) hypothesised that it would be expected that PwMS with affected cortical and subcortical white matter pathways would be language-impaired. Indeed, a growing body of research evidence suggests that language symptoms are present in different clinical types of MS (De Dios Pérez et al., 2020; Renauld et al., 2016). Selective language deficits such as aphasia have also been found in MS, however, they are rare cases and could be explained as a consequence of cognitive impairment after a long disease course or due to an acute relapse (Lacour et al., 2004; Potagas, Kasselimis, Peppas, Alexandri, & Dellatolas, 2017). The most common language deficits found in the disease affect: verbal fluency, word retrieval, language comprehension and semantic processing (De Dios Pérez et al., 2020; Friend et al., 1999; Henry & Beatty, 2006; Renauld et al., 2016). Nevertheless, other high-level language functions have also been found impaired

in PwMS such as discourse production, comprehension of written information and auditory information (Arrondo, Sepulcre, Duque, Toledo, & Villoslada, 2010; Laakso et al., 2000; Lethlean & Murdoch, 1997).

Language problems have been found irrespective of clinical subtypes, from early stages of the disease (Viterbo et al., 2013) to chronic-progressive forms, yet PwMS perform more poorly in language assessments when they convert from RRMS to SPMS (Friend et al., 1999; Lethlean & Murdoch, 1997; Ntoskou et al., 2018). Studies have shown that even a mild decline in language abilities in PwMS can translate into limitations in communicative participation in everyday activities thereby negatively impacting their quality of life (QoL) (El-Wahsh et al., 2020; Klugman & Ross, 2002; Yorkston et al., 2001). Qualitative research suggests that even if PwMS with subtle language deficits are able to carry on a conversation without motor speech problems, they are often working hard to maintain it in a way that can cause frustration and reduction or disengagement in participation of social activities (Baylor, Burns, Eadie, Britton, & Yorkston, 2011; Baylor, Yorkston, Bamer, Britton, & Amtmann, 2010). Furthermore, El-Wahsh et al., (2020) using an international survey found that 75% of their sample of PwMS self-reported some degree of language impairment, and 65.7% self-reported difficulties with word retrieval. Additionally, De Dios Perez et al., (2020) have demonstrated anomic symptoms in behavioural data of PwMS (RR) when compared to matched neuro-typical peers, with both word accuracy and speed of retrieval affected. Consequently, improving word finding might help relieve frustration and increase participation in communication in PwMS.

Current models of word production suggest that for successful word retrieval the stored semantic and syntactic conceptual representation of the item (lemma) is activated, the phonological form of the selected lemma is retrieved, and then a motor sequence for articulation is created (Dell & O'Seaghdha, 1992; Indefrey, 2011; Levelt et al., 1991). However there are still questions of whether these processes interact (Dell & O'Seaghdha, 1992) or are processed independently (Levelt et al., 1991). Anomia can be the result of difficulties in accessing phonological information, semantic information or in accessing and assembling phonemes (Laine & Martin, 2013).

Anomia treatment, particularly in people with aphasic symptoms after stroke, has typically involved single-item picture naming, which includes presenting the person with a picture of an object along either increasing or decreasing levels of supportive cues (Conroy, Sage, &

Lambon Ralph, 2009a; Nickels, 2002b). Therapy for word retrieval has been demonstrated to improve confrontation naming accuracy in people with language deficits such as aphasia (Conroy et al., 2009b; Conroy, Sotiropoulou Drosopoulou, Humphreys, Halai, & Lambon Ralph, 2018; Nickels, 2002b; Wisenburn & Mahoney, 2009). Different therapies such as the phonological, semantic, semantic feature analysis and mixed therapies showed efficacy for aphasia after stroke, specifically the semantic therapy, which seem to have generalisation to unexposed words (Boyle, 2010). However, these therapies seemed to lack generalisation to connected speech (Wisenburn & Mahoney, 2009). Most naming therapies and even assessments focus solely on accuracy (Crerar, 2004). However, fluent speech requires not only accurate but also a rapid retrieval of words (Levelt, 1993).

Conroy et al., (2018) implemented a novel word retrieval software-based treatment, known as QuickWord, which combined speed and accuracy focused intervention in participants with aphasia. They compared the combined speed and accuracy focused therapy to a standard accuracy focused intervention. Both therapies showed improvements in both naming accuracy and generalisation of the words to connected speech. However, their results also revealed that the speed and accuracy focused treatment achieved greater advances in accuracy, speed and generalisation in connected speech compared to the standard therapy.

Given the relatively subtle presentation of anomia in the participants with MS reported in Chapter 4, this focus on both speed and accuracy of word retrieval appears especially promising and relevant for PwMS. The current study aimed to address the following specific research questions in investigating the application of QuickWord to PwMS:

1. Would QuickWord therapy lead to statistically significant gains in word retrieval accuracy for PwMS across treated and untreated items?
2. Would QuickWord therapy lead to statistically significant gains in word retrieval latency/speed in PwMS across treated and untreated items?
3. If enhanced speed of word retrieval was evident, was this specific to word retrieval or broader measures of information processing as well?
4. What were the perceptions of participants in taking part in this therapy?

Methods

Participants

Eighteen RR MS participants volunteered to take part in the study. Participants were part of the group of 21 individuals in the in-depth neuropsychology study. Although we had aimed to recruit all of the 21 participants from the previous study, ultimately 18 people volunteered to participate in the treatment phase. All participants were previously recruited at the MS Neurology clinic at Salford Royal Hospital Foundation Trust (SRFT) in North West England. The diagnosis of clinically definite or laboratory-supported definite MS was made by the patient's consultant neurologist at the SRFT according to the McDonald criteria (Polman et al., 2011). A total of 13 participants completed the therapy study and the post-therapy assessments (See Table 5.1). Two participants did not complete the therapy study due to health reasons, another participant decided not to continue the therapy programme due to personal reasons, and two more were not able to be tested post-therapy due to the COVID-19 pandemic. These participants were excluded from the study. Of the remaining 13 participants 31% were female and 69% male. Participant demographic information is shown in Table 5.1. The mean (SD) age was 44.7 (10) years, education 14.2 (1.9) years and years since diagnosis 10 (7.6). Participants were assessed at their homes and the therapy treatment was self-administered using their own electronic devices (computer, laptop or tablet) at home. A convenience sample was used in the study where all participants provided written informed consent in the Study 2 Consent Form. Exclusion criteria for this study included participants with native language other than English, presence of severe dysarthria (sufficient to make words produced unintelligible), severe visual impairments, history of other serious neurologic trauma, history of (or current) substance abuse that precluded testing.

Table 5. 1**.** MS Participant demographic information.

Participant	Age	Gender	Education in years	Years since diagnosed (Onset)
1	51	Female	14	7
2	38	Female	12	8
3	40	Male	12	5
4	45	Female	12	4
5	57	Male	16	3
6	51	Male	15	20
7	41	Male	17	17
8	52	Male	12	28
9	65	Male	13	12
10	42	Female	16	7
11	34	Male	15	2
12	32	Male	17	6
13	33	Male	14	11

Therapy methods

Stimuli

To assess and treat word retrieval, 150 black and white noun pictures were selected from the International Picture Naming Project (IPNP) database (Bates et al., 2000), which contains 520 pictures representing objects and provides various psycholinguistic values for these words. Pictures with multiple valid responses and pictures that were already presented to the participants in previous studies (see Chapters 3 and 4) were excluded, which resulted in 300 words.

MATCH software programme (Van Casteren & Davis, 2007) was used on the selected 300 words in order to match three sets of 50 pictures (150 pictures in total). MATCH combines groups of experimental stimuli on as many properties as needed. The three sets were matched according to the following properties: length of the dominant response in phonological syllables, age of acquisition, word frequency and reaction times (in milliseconds). Additionally, t-tests were performed to analyse possible significant differences in words between sets.

One set of 50 pictures each was allocated to the standard picture naming treatment condition. A second set (n= 50 pictures) was allocated to the speeded picture name treatment condition and the remaining set (n= 50 pictures) served as an untreated control. Each participant was allocated in chronological order to one of the three different presentation sets (A, B, C) (i.e. Participant 1 = Set Presentation A; Participant 2 = Set Presentation B: Participant 3 = Set Presentation C…) etc. (Table 5.2).

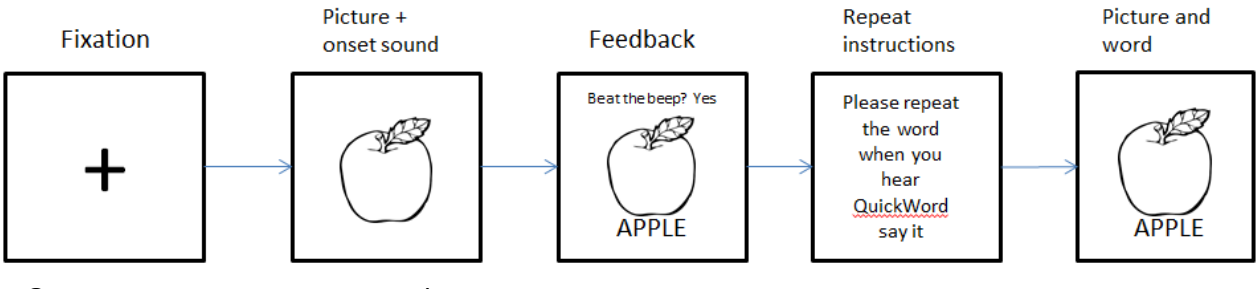
Table 5. 2. Set Presentations

SET Presentation A	
	Set 1 = Standard (n= 50)
	Set 2 = Speeded (n= 50)
	Set 3 = Control (n=50)
SET Presentation B	
	Set 1= Speeded (n=50)
	Set 2= Control (n=50)
	Set 3= Standard (n=50)
SET Presentation C	
	Set 1= Control (n=50)
	Set 2= Standard (n=50)
	Set 3= Speeded (n=50)

Stimuli application: QuickWord

QuickWord is a word retrieval training software programme. The QuickWord application can be accessed on each participant's personal device (computer, laptop, tablet) after accepting a previous invitation email to join in. QuickWord is divided into individual training sessions; each session uses just a single word set. Participants were assigned to two sessions for training: Standard Session (n= 50 pictures) and Speeded Session (n= 50 pictures). Each repetition of all of the words in the word set is called a run. Each presentation of a word is a trial. The participant was instructed to name the picture before a beep occurs. The time between the onset of the picture and the beep is called the naming speed. If a participant names the picture before the beep, the response is said to be 'in time', and automated verbal feedback to confirm this is given. If the beep occurs before the participant names the picture, then the word 'No' is shown, to indicate word production was 'late', i.e. did not occur before the beep. At the end of each trial, each participant was instructed to repeat the word. The instructions on the repeating trial are read aloud while also being presented visually (Figure 5.1). QuickWord automatically detects the participants' vocal response, but does not determine the accuracy of the response, only the time point at which it was produced. Accuracy of production, therefore, needs to be verified by the researcher. At the end of each

session, QuickWord calculates the percentage of 'in-time' responses. The threshold of the naming speed can be decreased (or increased) by the researcher. QuickWord was administered by the researcher and self-administered by the participants. The programme saves data of each training session, such as date and time of the training and reaction time responses, which the researcher has access to.



Baselines assessments

For the *Picture Naming* task, participants were assessed twice by naming (accuracy and reaction times) on the complete set of 150 black and white pictures from the *IPNP* as a mean of stability on their baseline performance in both domains. This testing occurred before the beginning of the therapy across two separate sessions, each session was one week apart one another. Participants were assessed in their homes, in a quiet environment, by the researcher. Pictures were shown each time in random order on a laptop using a PowerPoint presentation. Each picture was presented simultaneously with an auditory cue and stayed on the screen for a maximum of 6 seconds. All answers were audio recorded for later analysis in order to measure naming latencies. Audacity software was used to precisely measure the time taken for each word from the auditory cue to the onset of the participant's correct answer. If no answer was given within the 6 seconds, the reaction time for that trial was treated as a missing data. Pictures were shown in two blocks with 5 minutes rest between blocks to minimise fatigue. Broader assessment of language and cognitive performance were also assessed in the first session.

- The *Dinner Party Narrative* (Mark, Fletcher, & Birt, 1983) was used to assess narrative discourse skills. The task comprises a series of eight black and white pictures which form a sequence of events which form a story. Participants were asked to narrate what was happening in each picture and in the story overall with no time limit for an answer. Answers

were audio recorded, timed and transcribed verbatim for later analysis. Recording was stopped after 10 seconds of silence or when the participant verbally expressed that the task was completed. The following measures (Borovsky, Saygin, Bates, & Dronkers, 2007) were obtained from the narrative discourse sample (Dinner Party): (1) The overall number of words or "tokens". The overall word count has been shown to have good validity in measuring speech fluency (Borovsky et al., 2007; Feyereisen, Pillon, & Partz, 1991). This measure includes nouns, pronouns, adjectives, verbs, adverbs, prepositions, articles, conjunctions, possessives and numerals. Counting began with the first utterance after the instruction and finished on completion of the task. Immediate repetition of the same word was excluded from the count. (2) Type/token ratio (TTR) as a measure of semantic variety of speech (Borovsky et al., 2007). The number of unique or different kinds of words spoken is divided by the overall number of words spoken. (3) Words per minute (WPM) as a measure of speech rate. WPM was calculated by dividing the overall number of words by the length of time of the sample. The start time of the sample began with the first utterance after the instructions and ended when the participant expressed that the task was completed or when the participant was silent for over 10 seconds (silence was not included in the sample time).

- *Verbal Fluency domain in the Addenbrooke's Cognitive Examination-Revised (ACER-R) (Mioshi et al., 2006)* was tested to assess phonological and semantic word list generation. Participants were asked to generate as many words as they could starting with the letter "P" in one minute; after that, they were asked to generate as many words as they could, within a semantic category (animals) in one minute.

To measure working memory and information processing speed abilities the *Symbol Digit Modalities Test (SDMT) (Smith, A., 1982)* was used. The SDMT contains a key with nine different symbols corresponding to the numbers one to nine and a series of the symbols with blank boxes under them to write down the corresponding number. Participants were asked to write down as quickly as possible the correct number for each corresponding symbol in 90 seconds.

Finally, participants were given a *Self-Rating Communication Questionnaire* where they rated their everyday communication by answering two questions ("*How do you rate your verbal communication?"* and *"How do you rate your word finding"*) using a 10-category rating scale where 0 = Very Poor to 10 = Very Good. Additionally, participants were asked to describe if they experienced any difficulties while having a conversation.

Post-therapy assessments

Post-therapy performance on naming the word sets (accuracy and reaction times) was assessed at 1 week after therapy finished and again at 1 month after completing the therapy to establish the longer-term benefits of it. Pictures were presented on a laptop in random order using QuickWord software. Each picture was shown simultaneously with a short auditory cue and stayed on the screen for a maximum of 6 seconds. Again, if no answer was given within the 6 seconds, the reaction time for that trial was treated as missing data. QuickWord automatically picked up the first sound of the participants' answers and then moved on to show the next picture. QuickWord precisely measured the time taken for each word from the auditory cue to the onset of the first answer or sound the participant made. However, all answers were also audio-recorded to analyse word accuracy (as well as latency) as one drawback of QuickWord was that it could take an inaccurate response or random sound as both as valid word response. Audacity was used to get the precise reaction times in those cases. Pictures were shown in two blocks with 5 minutes rest between blocks to minimise fatigue. Finally, a month after therapy completion, the Dinner Party Narrative Task, ACE-R verbal fluency tasks, SDMT and the Self-Rating Communication Questionnaire were used to assess participants.

Treatment Protocol

Treatment was carried on across 6 weeks (Fig 5.2). The first training session was administered by the researcher, where participants were taught how to use QuickWord. Participants could use the training programme as much as they liked with a minimum requirement of two complete training sessions per week within those 6 weeks; previous anomia research has indicated non-significant differences between intensive and non-intensive therapy in the results (Sage, Snell, & Lambon Ralph, 2011). Most of the participants required more than one home visit in the first week to use the therapy software with the researcher. After the second week all participants were able to use QuickWord to train on their own. If there were any question/queries, video calls were used.

Participants were assigned a Set Presentation (A, B or C) which included two sets of words: *Standard* (n= 50) to improve accuracy and *Speeded* (n= 50) to improve accuracy and latency, each one was a session. Participants had to complete the two sessions to be counted as complete training in a given day.

In the *Standard* session, words had a customary time limit to be named (6 seconds). In the Speeded session, the time limit to name the words decreased by one second each week (e.g. 1st week = 6 seconds, 2nd week = 5 seconds, 3rd week = 4 seconds…). This was pre-set as a word speeding protocol, rather than relating directly to individual participant performance.

In both sessions, Standard and Speeded, participants were asked to name the picture presented on the screen. After each naming attempt, written feedback was shown on the screen, followed by another screen asking the participant to repeat the word. Another screen showed the picture, the written word and verbally named the picture (see Fig 5.1). Pictures appeared in random order every time a training set was accessed.

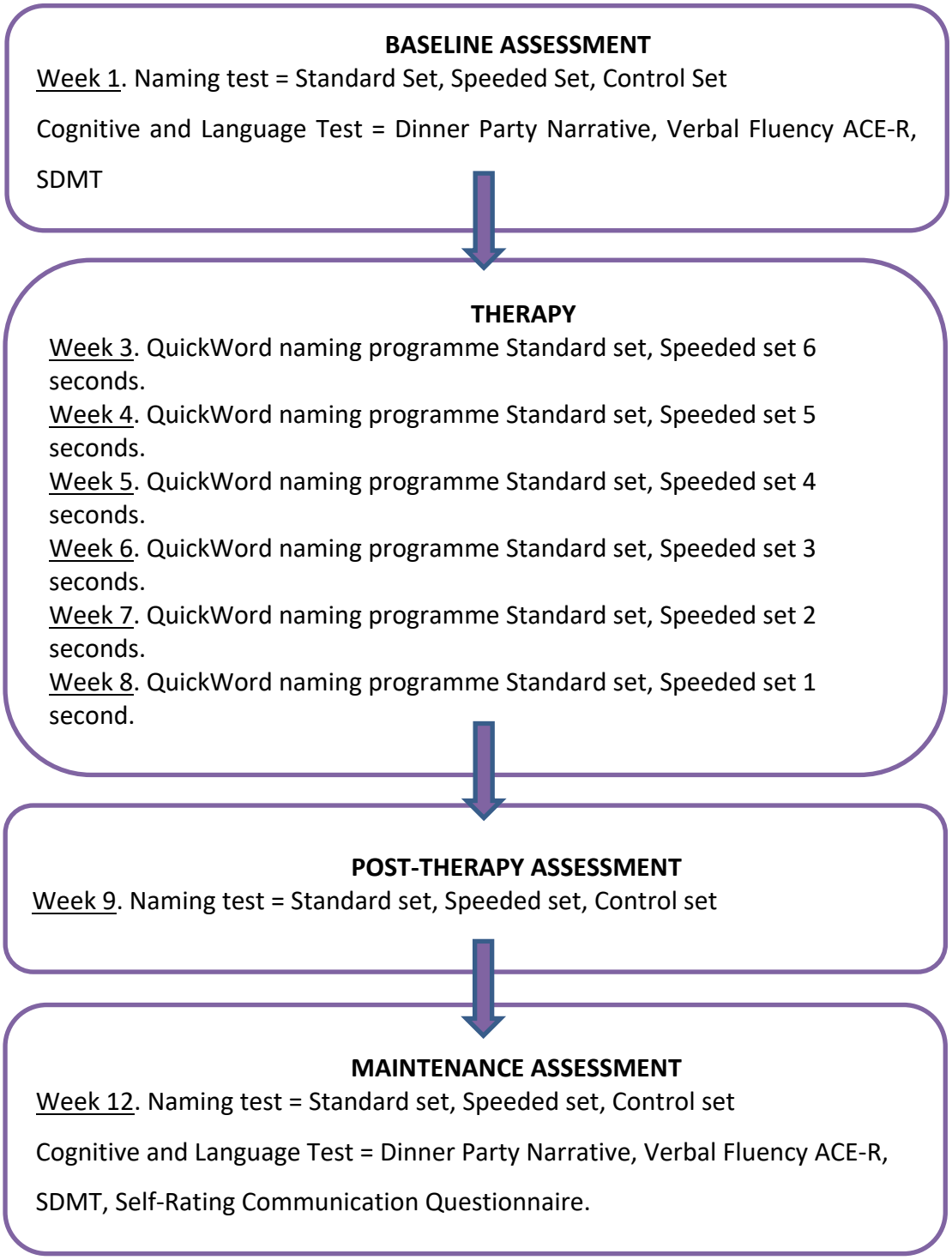


Figure 5. 2 Overview of study design.

Results

Individual scores and descriptive statistics on naming accuracy and reaction times at baseline, post-therapy and maintenance time points on different word sets are presented in Table 5.3 and Table 5.4 respectively. Naming test (accuracy and RTs) baseline scores were the average of the two assessments in week one and two. When looking at differences in naming accuracy while comparing baselines against the post-therapy and maintenance assessment, the largest difference percentage was in the standard word set with 6.8 % immediately post-therapy and 7.2% maintenance assessment respectively, followed by the speeded word set (5.6% and 5.7% respectively) and finally the untreated word set (2.4% and 3.5% respectively) (Table 5.3). It is also important to consider raw scores in this analysis and high baseline performance; the mean baseline performance was 45/50 correctly named items for standard and untreated word sets, and 46/50 for the speeded set. Despite the risk of a ceiling effect limiting accuracy therapy gains, participants were able to increase naming accuracy by approximately 3 items across the treated sets (standard and speeded), and 2 in the untreated set. Beyond these modest numerical differences in naming accuracy between the treated sets, it is evident from Figure 5.3, that naming treatments had a broadly similar benefit for naming accuracy which was stronger than the gain for untreated items, though maintenance was similar across all three conditions.

In terms of naming reaction times, the largest difference when comparing the post-therapy and maintenance assessment with the baseline testing was again for the standard word set (32% and 29% post-therapy and then maintenance assessment respectively), then the speeded word (30% and 25% respectively) and lastly the untreated word set (21% and 23% respectively) (Table 5.4). Again, Figure 5.4 confirms the broader observation that the two treatments generated similarly observable reductions in naming latency. Maintenance of latency reduction was stronger for the untreated condition than the treated ones.

Table 5. 3 Participant performance on naming accuracy for baseline, post-therapy and maintenance on different word sets.

	Participant	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean (SD)	% difference compared to baseline
Standard	Baseline	47	45	44	50	50	42	38	46	50	45	47	42	45	45.5 (3.4)	
word set	Post-therapy	50	48	48	50	49	49	44	48	50	48	50	48	50	48.6 (1.6)	**6.8**
	Maintenance	49	49	49	50	50	50	45	48	50	49	48	48	50	48.8 (1.3)	**7.2**
Speeded	Baseline	49	46	46	49	50	46	37	48	48	46	49	43	46	46.4 (3.3)	
word set	Post-therapy	50	49	50	50	49	49	46	48	50	47	50	49	50	49.0 (1.2)	**5.6**
	Maintenance	50	49	50	50	49	50	47	49	49	46	50	49	50	49.1 (1.2)	**5.8**
Untreated	Baseline	46	45	45	48	50	44	36	47	48	42	45	45	49	45.4 (3.4)	
word set	Post-therapy	46	43	45	50	50	48	38	48	47	45	47	48	50	46.5 (3.2)	**2.4**
	Maintenance	50	47	47	50	50	49	38	47	48	43	45	47	50	47.0 (3.3)	**3.5**

Table 5. 4. Participant performance on naming speed for baseline, post-therapy and maintenance on different word sets.

	Participant	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean	% difference compared to baseline
Standard	Baseline	1554.6	1717.9	965.9	1444.6	2239.9	1365.8	2027.4	764.1	780.1	1370.0	946.2	1716.5	1230.1	**1394.1 (460)**	
word set	Post-therapy	984.8	998.4	682.7	993.9	1081.8	1285.2	1422.4	614.1	656.0	820.5	657.4	909.5	1287.9	**953.4 (266)**	**32**
	Maintenance	1085.4	1267.2	520.5	1342.1	1139.9	1271.6	1384.6	514.1	624.5	853.2	818.4	1053.3	1189.1	**1004.9 (307.8)**	**29**
Speeded	Baseline	1463.6	1516.6	1037.7	1353.5	2495.3	1642.3	1861.9	810.9	682.6	1268.7	870.9	1349.9	1349.9	**1361.8 (439.8)**	
word set	Post-therapy	1038.0	946.0	708.3	1127.7	1118.4	1264.7	1321.4	570.9	632.3	707.8	610.6	870.8	1368.2	**945 (307.2)**	**30**
	Maintenance	1040.4	1140.0	523.4	1437.9	1207.4	1245.3	1458.7	511.6	639.4	876.8	733.5	1212.2	1252.9	**1021.5 (333.5)**	**25**
Untreated	Baseline	1604.8	1710.2	1031.2	1504.2	2278.7	1813.2	1731.0	831.6	819.5	1366.5	842.4	1505.9	1496.1	**1425.8**	
word set	Post-therapy	1156.2	1421.8	854.6	1002.5	1292.9	1326.6	1641.1	748.3	750.1	961.3	731.9	1285.5	1486.6	**1127.6**	**21**
	Maintenance	1257.4	1437.1	651.9	1292.3	1240.9	1202.7	1617.3	614.3	748.4	788.7	769.0	1308.7	1325.7	**1096.5**	**23**

For statistical analyses of these results of naming speed and accuracy, a 3*3 ANOVA was conducted where treatment set and time were within subject factors. Each factor had three levels; in the treatment set were standard, speeded and untreated, and in the time points were baseline, post-therapy and maintenance assessment.

In relation to accuracy, the 3*3 repeated measures ANOVA demonstrated that the main effect of treatment set was significant: $F(2,24) = 8.65$, $p = 0.001$, there was also a main effect of time: $F(2,24) = 17.9$, $p = 0.001$ and a significant interaction between treatment set and the assessment time: $F(4,48) = 3.5$, $p = 0.01$ (See Fig 5.3).

Post hoc analyses were carried out to compare if the standard, speeded and untreated treatment sets had significant changes between the three time points (baseline, post-therapy and maintenance assessment) in terms of naming accuracy. The results indicate that for the *standard treatment set*, there was a statistically significant difference between the baseline and the post-therapy assessment ($z = 2.86$ $p = .004$ $r = 0.79$) and the baseline and maintenance assessment ($z = 2.81$ $p = .005$ $r = 0.78$). In the *speeded set*, the baseline and post-therapy assessment ($z = 2.85$ $p = .004$ $r = 0.79$) and baseline and maintenance assessment ($z = 2.83$ $p = .005$ $r = 0.79$) presented a significant difference. Lastly, in the *untreated set* there was also a significant difference between the baseline and post-therapy assessment ($z = 2.06$ $p = .040$ $r = 0.72$) and the baseline and maintenance assessment ($z = 2.862.72$ $p = .007$ $r = 0.75$). However, no statistical difference was found between any of the post-therapy and the maintenance treatment sets in any of the time points. Positive changes effects in word accuracy, therefore, were only observed after all the treatment sets (standard, speed, untreated) when we compared the baseline tests and the post-therapy assessments, and the baseline sets and the maintenance assessments.

With regard to latency, the 3*3 ANOVA showed a main effect on the treatment set: $F(2,24) = 14.61$, $p = 0.001$, a main effect on time: $F(2,24) = 19.52$, $p = 0.005$ and a significant interaction between treatment and time point: $F(4,48) = 2.5$, $p = 0.05$ (See Fig 5.4). The standard, speeded and untreated treatment sets with the three time points (baseline, post-therapy and maintenance assessment) were compared by performing post hoc analyses using Wilcoxon Signed Rank Tests on reaction times. The results demonstrated that in the *standard treatment set*, there was a statistically significant difference between the baseline and post-therapy assessment ($z = 3.11$ $p = .002$ $r = 0.86$) and between baseline and maintenance assessment ($z = 3.18$ $p = .001$ $r = 0.88$). In the *speeded set*, there was also a significant

difference between the baseline and post-therapy assessment (z = 3.11 p = .002 r = 0.86) and between the baseline and maintenance assessment (z = 3.04 p = .002 r = 0.84). In the *untreated set*, again there was a statistically significant difference between the baseline and post-therapy assessment (z = 3.18 p = .001 r = 0.88) and between the baseline and maintenance assessment (z = 3.18 p = .001 r = 0.88). These analyses show a significant reduction in reaction times in the different time points after each treatment sets compared to the baseline assessments.

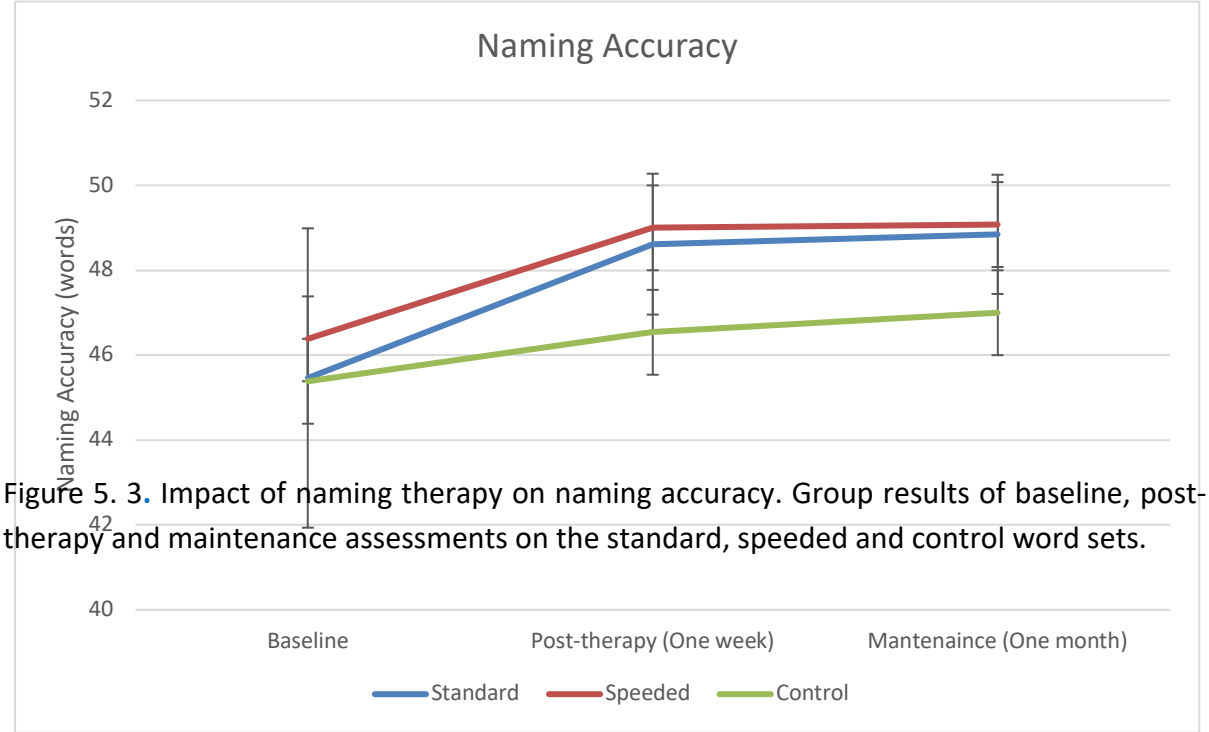


Figure 5. 3. Impact of naming therapy on naming accuracy. Group results of baseline, post-therapy and maintenance assessments on the standard, speeded and control word sets.

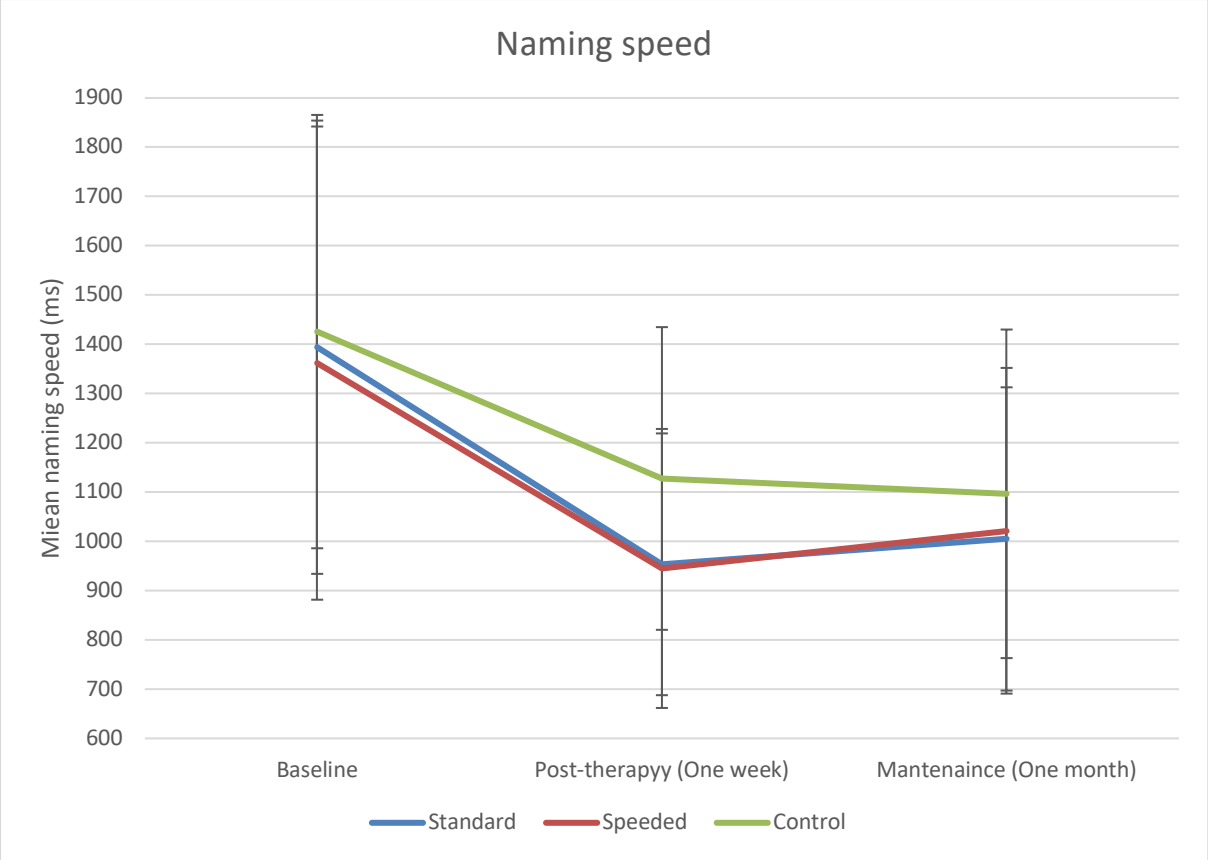


Figure 5. 4. Impact of naming therapy on naming reaction times. Group results of baseline, post-therapy and maintenance assessments on the standard, speeded and control word sets.

Beyond the group mean performance across the three therapy conditions, we next examined individual participant performance with respect to naming accuracy and latency. Figures 5.5 (a,b,c) show individual performance across the discreet conditions and clearly demonstrate relatively narrow divergence across the cohort from the group mean (Standard baseline group mean 45.5, SD 3.4; Speeded baseline mean 46.4, SD 3.3). Only participant 7 had a baseline accuracy score which fell below 40 in any condition, and despite having high baseline scores,

there was no ceiling effect which restricted evidence of some progress in naming accuracy. In contrast, latency individual performance (Figures 5.6 a,b,c) did show more individual participant variability across the treatment conditions. For example, participant 5 showed mean baseline naming performance of >2000ms in all conditions, in contrast to participant 8 for whom baseline latency performance was <1000ms in all conditions. The mean group performance for naming latency had, therefore, a more substantial standard deviation given greater variability in both baseline starting points and responses to treatment.

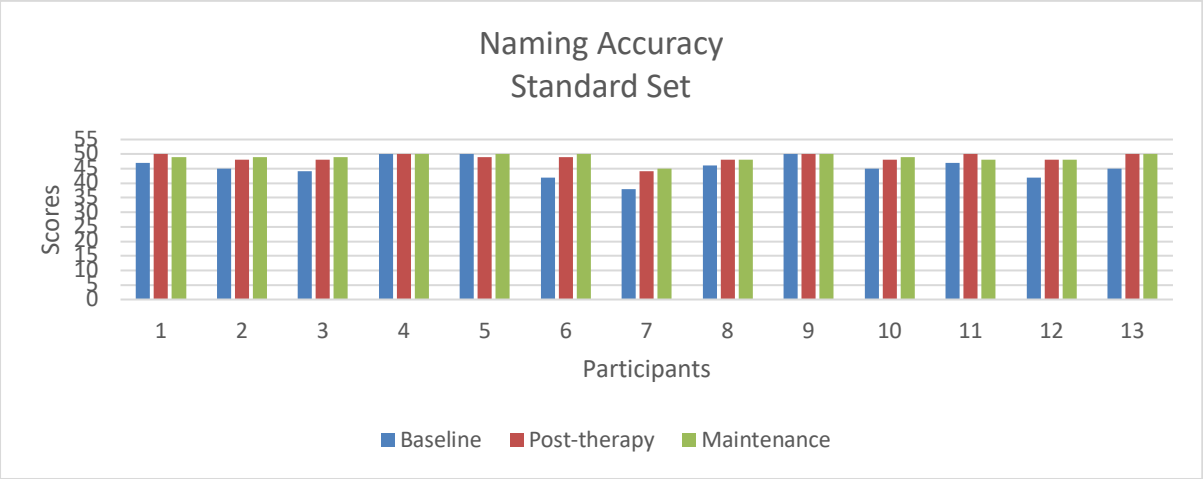


Figure 5.5a

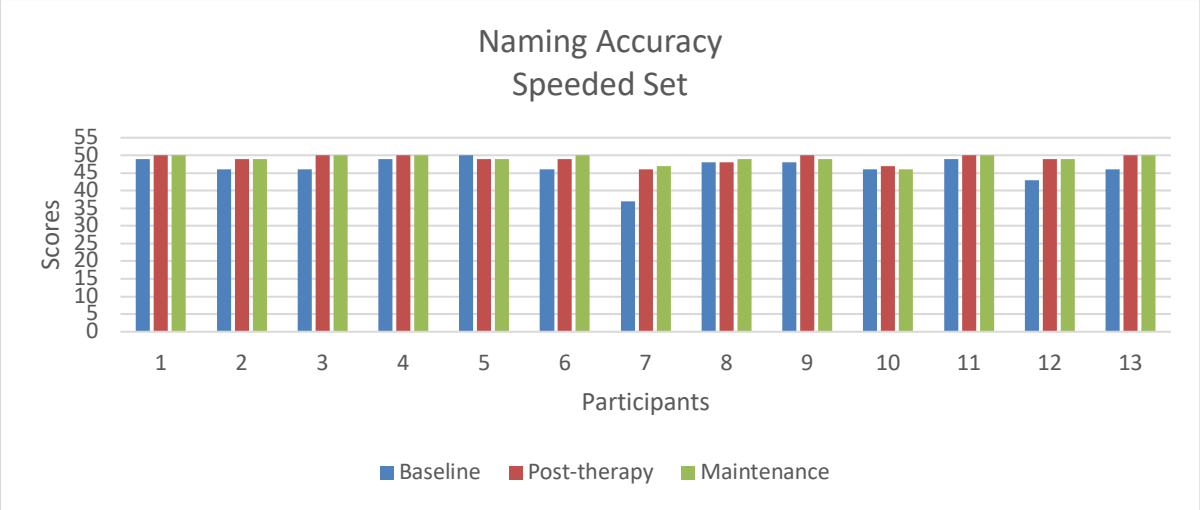


Figure 5.5b

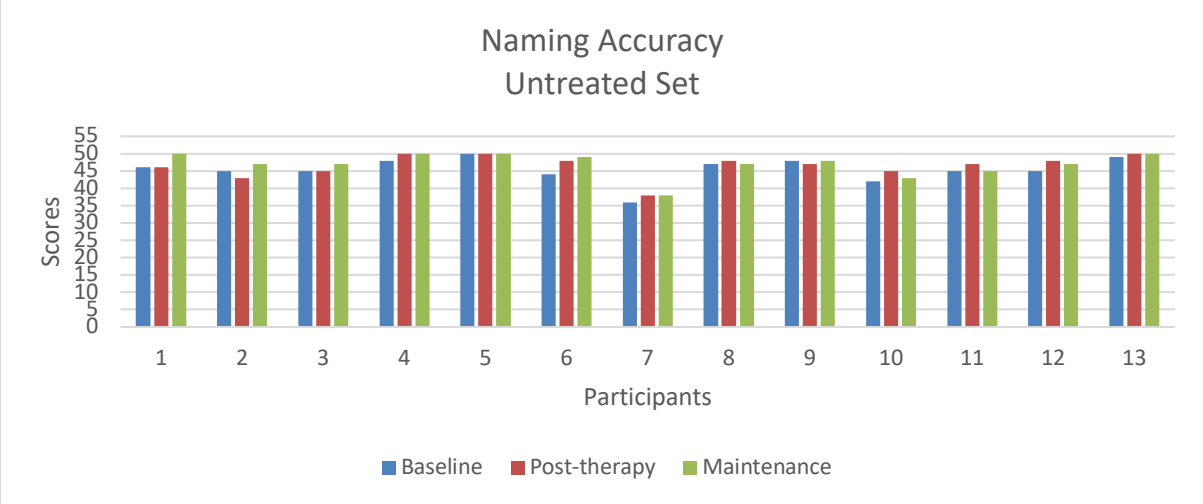


Figure 5.5c

Figures 5. 5 (a, b, c). Individual performance on naming accuracy in Standard (a), Speeded (b) and untreated set (c).

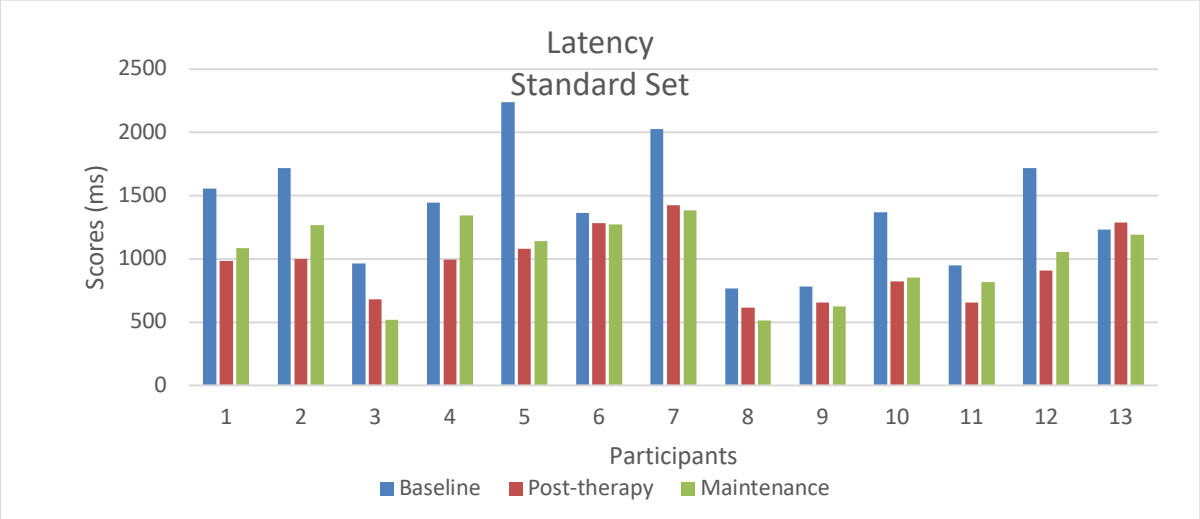


Figure 5.6a

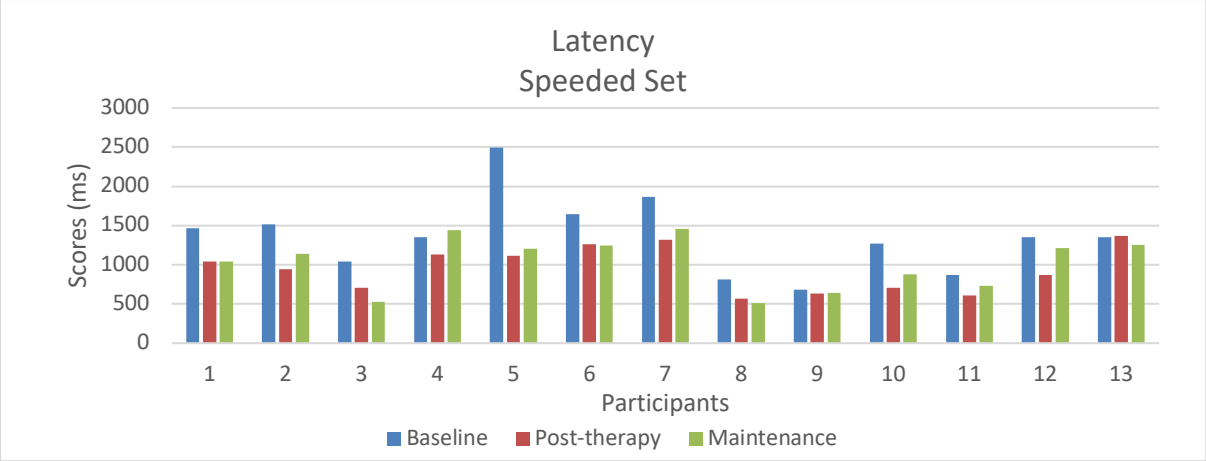


Figure 5.6b

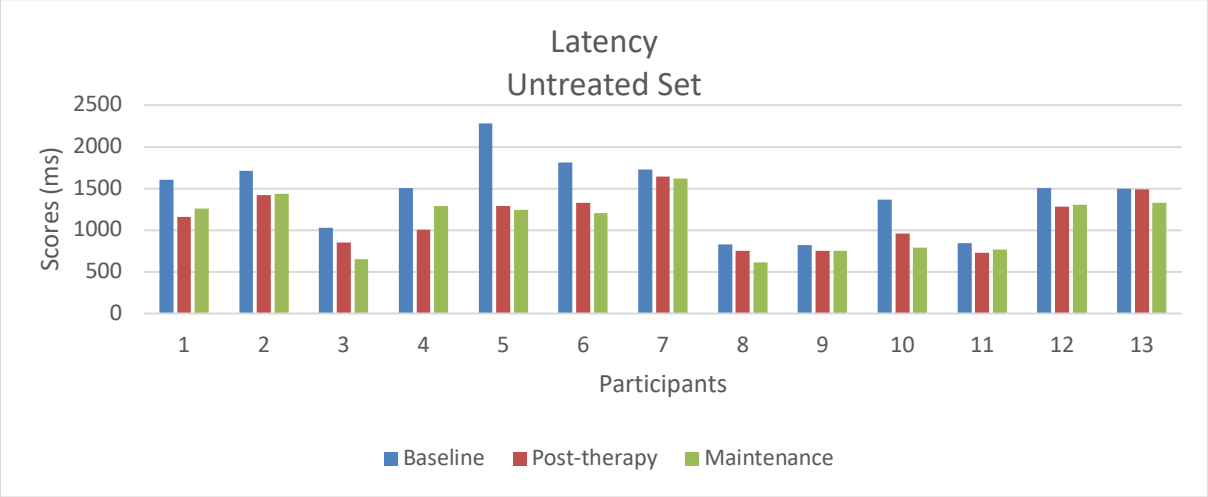


Figure 5.6c

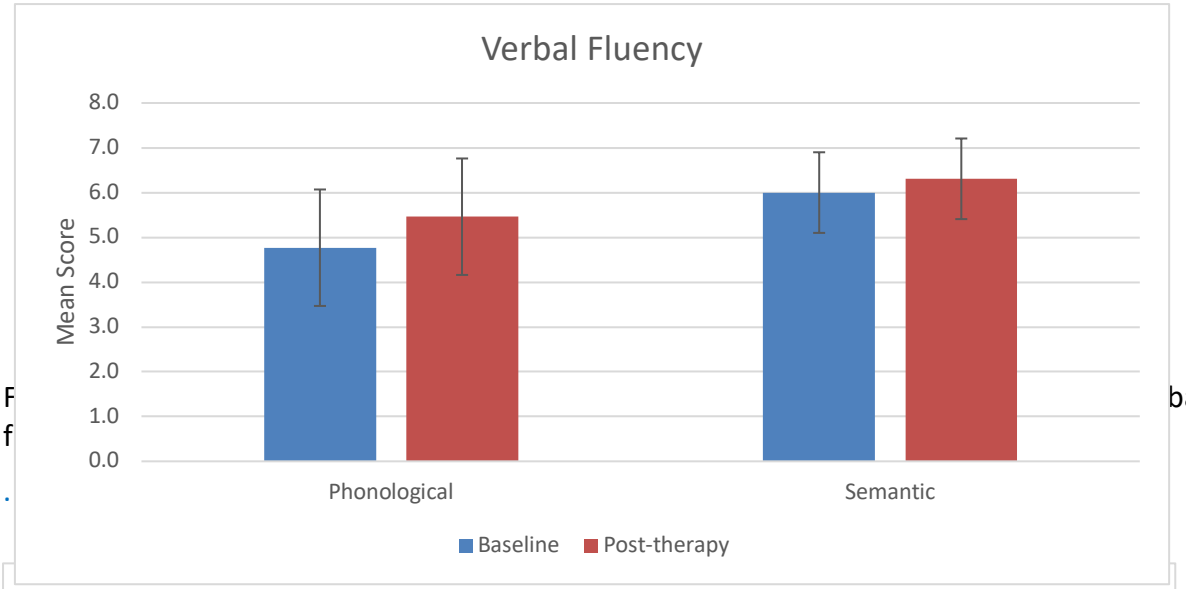
Figures 5. 6 (a, b, c). Individual naming latency performance on Standard (a), Speeded (b) and untreated sets (c).

Next, we examined whether there were significant differences in language and cognitive assessment scores after treatment (Table 5.5). Verbal Fluency (phonological task) showed the largest difference in percentage between baselines and post-therapy mean scores (12.7%) and the Wilcoxon Signed rank test indicated a statistically significant difference between them (z = 2.26 p = .024 r = 0.63) (Fig 5.7). For Verbal Fluency, (the semantic task) there was no significant difference between baseline and post-therapy scores (Fig 5.7) with a percentage change of (4.8%). SDMT, with a difference between baseline and post-therapy assessment scores of 6.6%, had a significant difference between assessments (z = 2.14 p = .030 r = 0.5) (Fig 5.8). The Dinner Party narrative task assessing the speech rate in words per minute had a difference of 8.7% between the baseline and post-therapy assessments (z = 2.76 p = .006 r = 0.77) (Fig 5.9) but no significant difference. Also, the overall number of words (tokens) in the Dinner Party task showed a post-therapy decrease of 4.3%, though this did not

reach statistical significance (Fig 5.9). The type/token ratio did not present any changes between baseline and post-therapy assessments with a stable group performance of 0% change (Group mean baseline and post-therapy 0.5, SD 0.1) (Fig 5.10).

Table 5. 5**.** Cognitive and verbal assessments scores before and after a month of the picture naming therapy.

Assessment	Verbal Fluency Phonological	Verbal Fluency Semantic	SDMT	Dinner Party (Token)	Dinner Party (WMP)	Dinner Party (TTR)
Baseline mean (SD)	4.8 (1.3)	6 (0.9)	42.2 (11.1)	257.6 (82.9)	112.8 (14.7)	0.5 (0.1)
Post-therapy mean (SD)	5.5 (1.3)	6.3 (0.9)	45.2 (12.2)	246.5 (91.8)	123.5 (16.3)	0.5 (0.1)
Difference between scores	0.7	0.3	3	-11.1	10.7	0
Difference in %	12.7	4.8	6.6	- 4.3	8.7	0



F bal
f
.

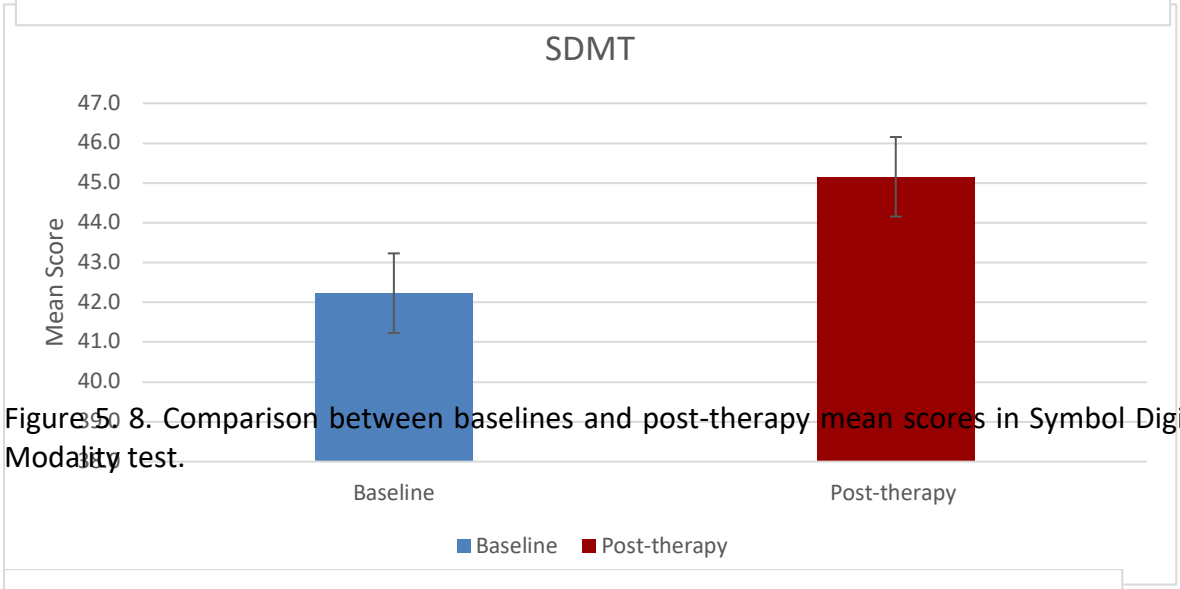


Figure 5. 8. Comparison between baselines and post-therapy mean scores in Symbol Digits Modality test.

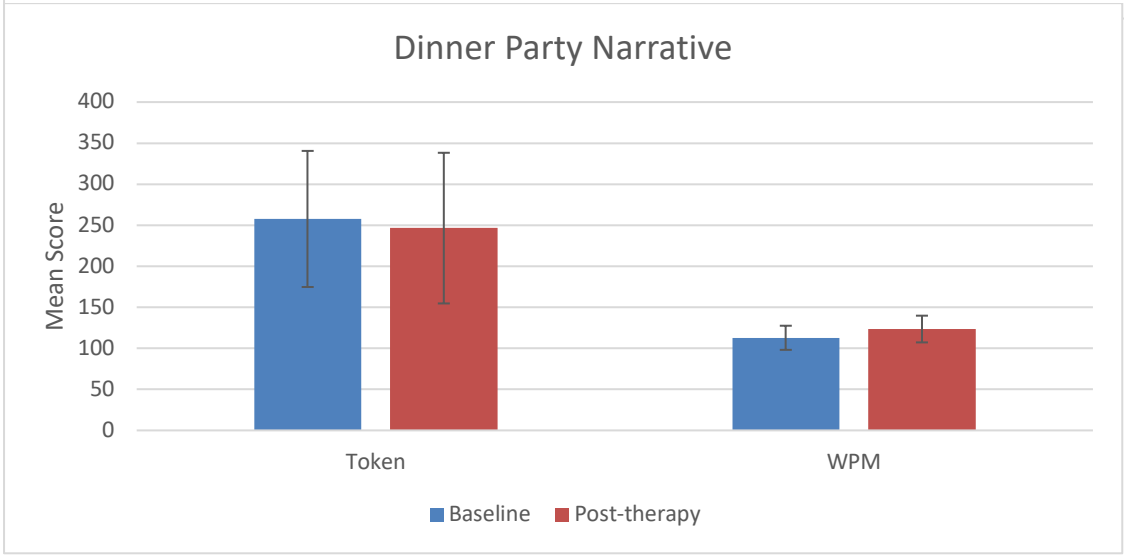


Figure 5. 9**.** Comparison between baselines and post-therapy assessments in the Dinner Party narrative tasks.

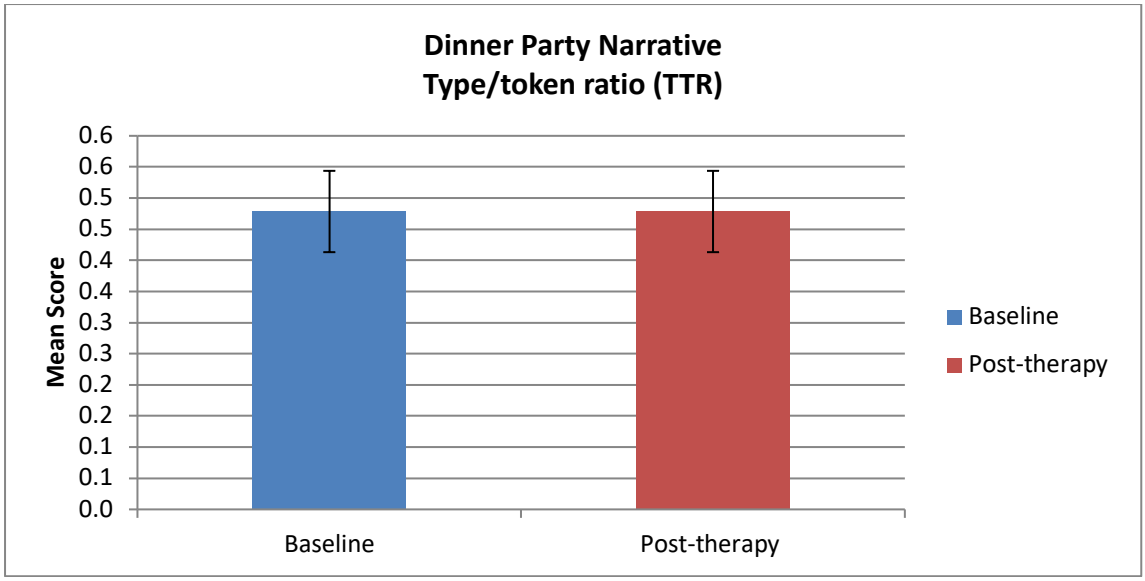
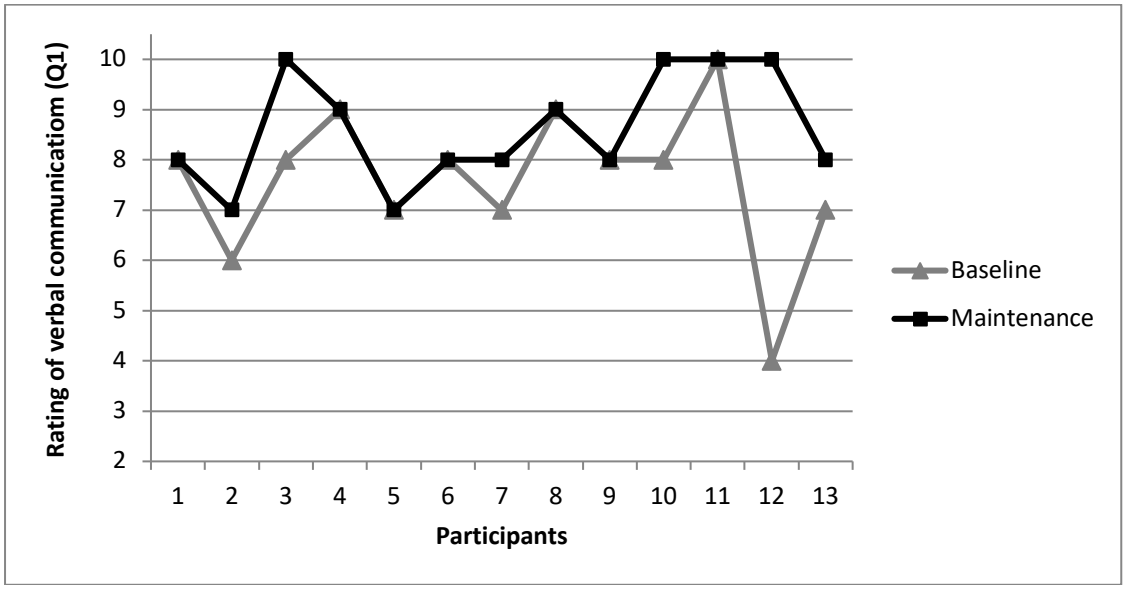


Figure 5. 10**.** Comparison between baselines and post-therapy assessments in the Dinner Party narrative TTR.

In terms of self-reported perceptions of communication, the participants with MS had a pre-treatment group mean (SD) rating for question 1 (*How do you rate your verbal communication?) of* 7.6 (1.5); a month after treatment, this scored had increased to 8.6 (1.1) indicating a positive change of one point in this rating. Most participants perceived slightly better verbal communication at maintenance period; only participant 12 had a 6 points positive difference in perception (Fig. 5.11a). On question 2 (*How do you rate your word finding?),* the participants with MS had a pre-treatment mean of 6.3 (1.6) points and a post-treatment mean rate of 7.3 (1.8), again suggesting a modest but discernible benefit for word retrieval specifically. This was the case for most of the participants with MS, except participant 7, who discerned slightly poorer word finding at post-treatment maintenance (1 point) (Fig. 5.11b). In response to the question *Do you experience any difficulties while having a conversation?,* 85% of MS participants answered YES before treatment versus 62% month after treatment (Fig 5.12). When questioned at baseline, participants also described certain difficulties they perceived while having a conversation: 100% of the participants perceived word finding difficulties, 38% detected becoming tired when speaking, 23% responded that they go off topic when speaking and 7% described difficulties initiating a conversation. When

questioned again at maintenance, 69% of the participants still perceived word finding difficulties, however they described it as *"occasionally* or *minimal"* and 23% reported becoming tired when speaking. Difficulties such as going off topic when speaking and initiating a conversation were not mentioned at maintenance.

a.



b.

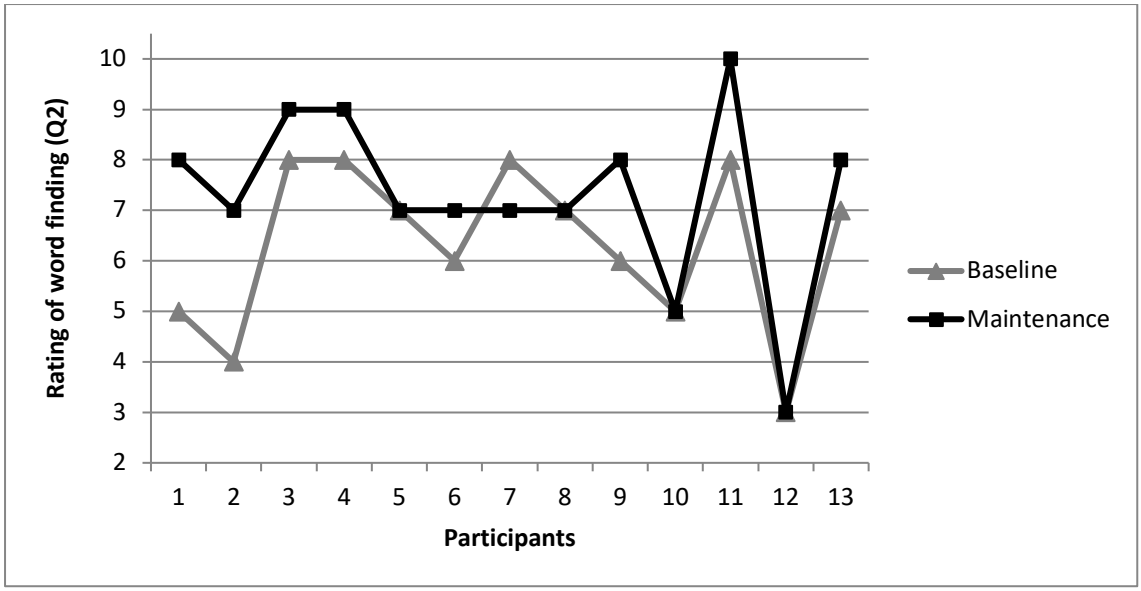


Figure 5. 11 (a & b). Self-rating Communication Questionnaire participants' ratings for **a)** Q1 *How do you rate your verbal communication?* And **b)** Q2 *How do you rate your word finding?* In a 0 (Very poor) to 10 (Very good) scale.

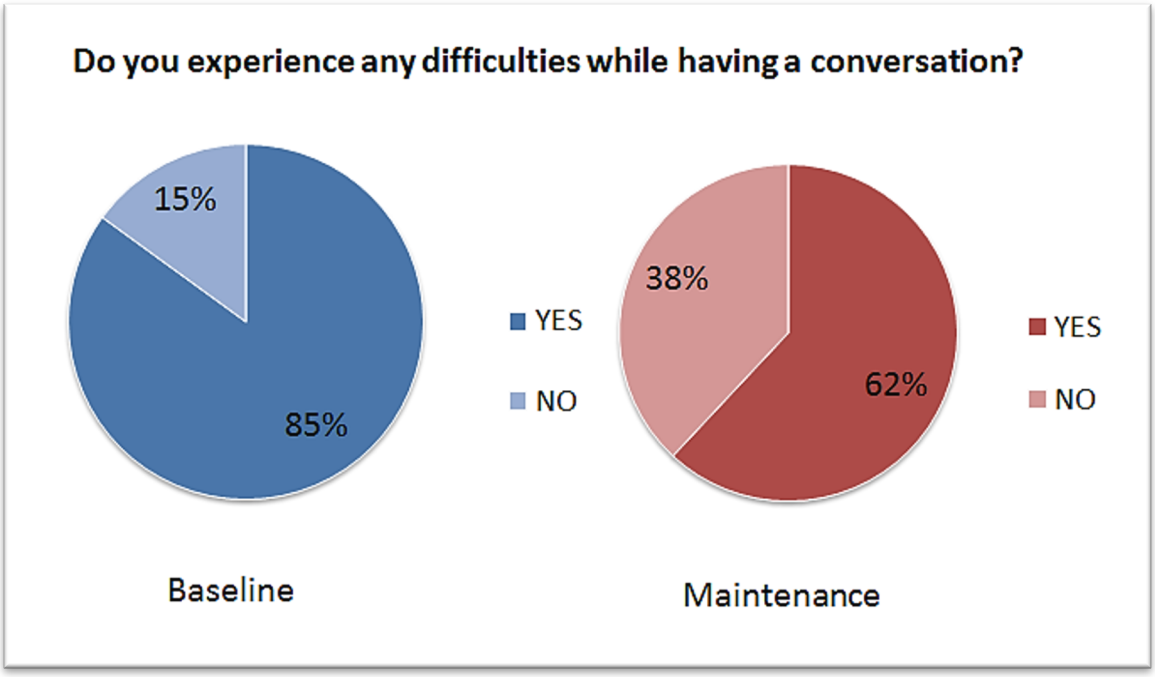


Figure 5. 12**.** Participants' self-reported difficulties while having a conversation (Yes, No) before and a month after naming therapy.

Discussion

Anomia is one of the most common language deficits in MS not only reported in the literature (Brandstadter et al., 2020; De Dios Pérez et al., 2020; Renauld et al., 2016) but also self-reported by people with MS (Brandstadter et al., 2020; El-Wahsh et al., 2020; Johansson et al., 2020). Even mild word retrieval difficulties may lead to a negative impact on self-confidence and quality of life (Klugman & Ross, 2002). Consequently, there is a need to investigate and develop effective interventions to improve word retrieval skills which may enhance verbal communication more broadly.

This study therefore aimed to explore the effects of one treatment method focusing on accuracy and speed of word retrieval, including consideration of possible direct naming benefits as well as wider indirect benefits to broader cognitive-linguistic skills. Given that we had previously observed from the De Dios et al. (2020) study and our replication study (Chapter 3) that anomia in MS not only affects naming accuracy but also latency, a key goal was to evaluate a novel treatment that focused on speeding up naming responses using a self-managed word-retrieval programme (QuickWord). Conroy et al. (2018) implemented QuickWord on participants with post-stroke aphasia, showing improvements to both naming and generalisation of the trained words to connected speech. Furthermore, the study showed that when the treatment conditions were closely matched for psycholinguistic variables, the speeded therapy was significantly better than the standard therapy (word cueing without time pressure) for naming accuracy, naming latency and deployment of trained words in connected speech. Given these robust findings with a comparable clinical population, we hypothesised that, with MS participants, the use of standard word-cueing and speeded treatment would generate improvements in confrontation naming, but also that greater improvements in accuracy and latency would be observed using the speeded therapy. We also investigated indirect cognitive-linguistic effects of the interventions.

As hypothesised, both treatments (standard and speeded) increased picture naming accuracy a week after treatment and improvement was maintained a month after the completion of the intervention without any additional practice. Statistically significant accuracy gains were evident, despite the risk of ceiling effects with relatively high accuracy scores at baseline. The untreated items also showed a modest significant increase in naming accuracy a week and a month after the treatment. The same pattern was observed in naming

latency, where standard and speeded treatments significantly decreased the naming reaction times a week after treatment and these were maintained a month later, with also discreet but significant improvement in control items latency for both treatments. Unlike the findings from Conroy et al. (2018) in which the speeded therapy showed better improvements in naming accuracy and latency than the standard, the two treatments (standard and speeded) in our study generated similar gains in naming accuracy and reductions in naming latency. That said, the speeded therapy did not give an added bonus for improving confrontational naming. A possible reason for this might be that the participants with MS in this study presented with much milder anomia compared to the post-stroke participants in the Conroy et al. (2018) study. Therefore, although high baseline performance did not eliminate significant treatment effects, there was less scope to observe the hypothesised potential specific effects of speeded treatment with respect to naming accuracy and latency. When focusing on individual participants for example, the only participant that was not at ceiling at baseline showed a higher improvement on confrontational naming (accuracy) in the speeded therapy than in the standard one. Also, Conroy et al (2018) noted that participants with stroke aphasia with the poorest phonological skills showed a better benefit from the speeded therapy. Our MS group overall, had shown more semantic deficits (See Chapter 4) than phonological ones, which may explain why there was no greater benefit in the speeded intervention compared to the standard one. This is also consistent with the findings from Best et al. (2013) meta-analysis in participants with aphasia that showed better treatment response in naming when they presented greater phonological than semantic deficits.

As discussed in Chapter 4, people with RR-MS presenting with anomia cannot reasonably be described as having aphasia, in terms of type or severity of symptoms. Also, in terms of neural networks underpinning anomic symptoms, in RR-MS this appeared to derive from a more general cognitive-linguistic disorder (Mackenzie & Green, 2009). With respect to indirect effects from therapy outcomes, we observed differences in language and cognitive assessments after the picture naming therapy. There seemed to be a general improvement in speed reactions, such as information processing speed, verbal phonological fluency as well as speech production (words produced per minute in discourse). The fact that we did not observe improvement in semantic verbal fluency test might be tied with our results in Chapter 3 where MS participants showed marked difficulties on the semantic verbal fluency tasks. Seemingly, phonological fluency tends to be more dependent on executive abilities such as

information processing speed and working memory, whilst semantic fluency on semantic processes such as access, storage and retrieval (Henry & Beatty, 2006; Henry & Crawford, 2004a; Zakzanis, 2000). Hence, the intervention on this study might be mainly affecting speeding and working memory as participants showed improvement on information processing speed, verbal phonological fluency and speech production tasks. Also, in line with this, Conroy et al. (2018) found a better gain on phonological deficits using the speeded therapy. However, a recent study focused on semantic feature analysis treatment on PwMS with mild anomia, also failed to improve naming accuracy and latency and connected speech (Kristensson et al., 2021).

Our findings were consistent with previous studies (Conroy et al., 2009b; Conroy et al., 2018) in that picture-naming therapy produced gains in naming accuracy and latency and these may generalise to connected speech tasks. Although various outcomes achieved statistical significance, this does not necessarily mean that these benefits were in any way meaningful to these participants, in terms of their functional communication skills and any daily challenges they face in practical communication domains. Although different naming therapies (including speeded) have proven to have benefit for people with aphasia, people with RR-MS, as mentioned before, did not show signs of aphasia in our previous studies (See Chapter 4), and probably therapy gains in people with MS might not be as prominent as in people with other neurological disorders (e.g. stroke aphasia, traumatic brain injury). Nevertheless, therapy seemed to be beneficial for speed processing speed, which is one of the most common cognitive deficits in MS. This could be accounted for with respect to the more focal and localised neurological damage in people with stroke aphasia, whereas those with MS have more diffuse axonal and tissue injury (De Stefano et al., 2002). However, while acknowledging the limitation of the same researcher carrying out both the treatment and assessments, we did obtain some evidence in the self-reported measures that people with MS perceived better verbal communication and functional word retrieval skills after treatment.

In summary, people with RR-MS presenting with even subtle anomic symptoms are at risk of communication problems that may restrict their daily activities and quality of life. Targeted early intervention could help to improve or maintain language abilities in people with RR-MS and sustain quality of life. In this small-group study, we demonstrated that, using self-management, naming therapy was relatively straight-forward to implement, had direct and

indirect benefits, where participants were able to engage successfully with limited guidance. Participants seemed to value the experience of treatment which could motivate them to continue to use technology in guided self-management of language and cognitive symptoms in MS.

Limitations of the study

One obvious limitation of this study is the small number of subjects. Also, the same researcher carried out both, the assessments and the treatments.

Future research

As well as focusing on increases in performance (gains in accuracy/reductions in latency), further research could also investigate the potential of this therapeutic approach in maintenance of lexical retrieval skills over time, in the face of progressive neurological deterioration in all forms of MS. Furthermore, an attention control comparison could be usefully included in order to distinguish specific communication benefits from anomia therapy in people with RR-MS, as opposed to more generic communication encouragement/treatment engagement benefits within a randomised controlled trial. In the light of the results, future research could also explore a therapy focused on semantic processes in PwMS.

CHAPTER 6

Neural correlates of verbal fluency performance in Relapsing Remitting Multiple Sclerosis.

Introduction

Multiple sclerosis is a complex autoimmune disease in which the incidence and prevalence is increasing around the world (Browne et al., 2014). The characteristic pathological hallmark of MS is an inflammatory demyelination causing widespread lesions or plaques in the brain and spinal cord (Chiaravalloti & DeLuca, 2008), as the disease progresses, it leads to irreversible axonal damage (Trapp et al., 1998). Due to the widespread lesions in the central nervous system, MS results in motor, neuropsychiatric, cognitive and language deficits (Brassington & Marsh, 1998; Ntoskou et al., 2018). Cognitive impairment can be present in any phase of the disease, the most common symptoms are deficits in speed information processing, executive functioning, attention and memory (Chiaravalloti & DeLuca, 2008).

Previously, MS was seen as a white matter disorder resulting in focal demyelinating lesions, yet it is currently known that grey matter areas are also affected and grey matter involvement appears to be widespread in MS (Calabrese et al., 2012; Vercellino et al., 2005). Reduction in GM volume could be the final outcome of pathological processes that exert an influence in both grey and white matter in MS (Geurts, Calabrese, Fisher, & Rudick, 2012). According to Chard et al. (2002), atrophy in GM progresses faster than atrophy in WM and it predominates in early stages of the disease. These GM changes are also functionally relevant as imaging studies on markers of brain atrophy have shown that cognitive impairment is more closely related to grey matter (GM) pathology than white matter (WM) lesion burden (Amato et al., 2004; Benedict et al., 2004; Calabrese et al., 2009). Atrophy can be involved with cortical thinning, especially in the temporal and frontal regions (Calabrese et al., 2010; Narayana et al., 2013).

Cognitive deficits in MS have been widely studied, unlike language deficits which have until recently been relatively overlooked, possibly because language had been mainly associated with cortical lesions (Geschwind, 1974) and MS was linked with WM and subcortical pathology (Browne et al., 2014). However, as mentioned before, MS has been related to grey matter pathology and mounting research demonstrates the role of white matter 'disconnection' in the emergence of language deficits (Ketteler et al., 2008; Poeppel & Hickok, 2004). Furthermore, language deficits in MS may be more subtle and less frequent than other general cognitive deficits (Renauld et al., 2016). Research into language processing in MS has

begun to accumulate and deficits in language comprehension, semantic processing and even in high-level language functions such as discourse production have been reported specially in the progressive forms of the disease (Arrondo et al., 2010; Friend et al., 1999; Laakso et al., 2000; Lethlean & Murdoch, 1993). Symptoms affecting word retrieval in confrontation naming and in verbal fluency tasks appear to be the most commonly identified symptoms experienced by people with MS (Brandstadter et al., 2020; De Dios Pérez et al., 2020; Henry & Beatty, 2006; Renauld et al., 2016), and these can be present even in the early stages of the disease (Brandstadter et al., 2020; Viterbo et al., 2013).

Verbal fluency tests are frequently used to measure language processing such as access to the mental lexicon and lexical retrieval (Shao et al., 2014), executive control (Henry & Crawford, 2004b), processing speed and attention (Elgamal et al., 2011). These tasks are usually divided in two categories: semantic and phonemic fluency (Lezak et al., 2012) and have also been found to provide brief and sensitive measures of cognitive decline in people with MS (Henry & Beatty, 2006). Whilst both measures of verbal fluency seem to be impaired in MS, some authors report greater deficits in semantic fluency (Foong et al., 1997) and others in phonemic fluency (Nocentini et al., 2001). Abilities associated with verbal fluency performance in healthy individuals seem to be multifactorial and can differ across the different fluency variants (Kraan et al., 2013). Both verbal fluency tasks demand comparable capacities such as sustained attention, strategic search and processing speed (Elgamal et al., 2011; Salthouse et al., 2003); however each type of verbal fluency also measures individual cognitive abilities (Henry & Crawford, 2004a). Semantic verbal fluency has been associated specifically with lexical access (Kraan et al., 2013) and semantic memory, as it relies on the integrity of the storage of conceptual knowledge (Henry & Crawford, 2004a; Rosser & Hodges, 1994). Nonetheless, phonemic fluency has been linked to attention and executive functions as there appear to be more engagement of working memory processes in the selection of words based on the orthographic cues (Bryan & Luszcz, 2000; Shao et al., 2014). Corresponding with clinical observations, functional imaging studies on healthy participants have shown that verbal fluency depends on a network of regions primarily in the left hemisphere. Furthermore, there is evidence from lesion studies that the left frontal lobe plays an important role in both semantic and phonemic fluency (G. Robinson, T. Shallice, M. Bozzali, & L. Cipolotti, 2012), more specifically the left inferior frontal gyrus (Katzev, Tüscher, Hennig, Weiller, & Kaller, 2013).

Phonemic and semantic verbal fluency have shared, but also unique, brain structural underpinnings (Shao et al., 2014). A meta-analysis by Henry and Crawford (2004) observed that while both types of verbal fluency can be impaired in people following frontal lesions, those with predominantly frontal lobe lesions are more likely to show phonemic fluency problems, whereas those with temporal lobe lesions more frequently show semantic fluency problems. Moreover, fMRI studies found that semantic fluency was associated with activation in occipital cortex, fusiform gyrus and left middle frontal gyrus (Birn et al., 2010); whereas phonemic fluency had a greater activation in the precentral and inferior frontal gyrus, ventral occipito-temporal cortex bilaterally and superior parietal cortex bilaterally (Birn et al., 2010). In people with RR MS, verbal fluency has been linked to executive dysfunction and thinning in the left anterior cingulate cortex (Geisseler et al., 2016).

To the best of our knowledge, few studies have examined whether deficits in verbal fluency are associated with regional brain volumes in people with MS. Hence, this study is aimed to improve our characterisation and understanding of the brain structural correlates of verbal fluency tasks among people with MS and to provide a valuable insight on the mechanisms through which MS disrupts semantic and phonemic fluency. We expect to see changes in volumes in both frontal and temporal cortex.

Methods

Participants

One hundred and five participants with a diagnosis of clinically definite RRMS were recruited through the Helen Durham Centre for Neuroinflammation at the University Hospital of Wales. Seventy-two females and 33 males with a mean age and SD of 43.7 (9.8) and a disease duration of 12.3 (7.6) years. Patients had no history of other serious neurologic trauma or psychiatric disease, were relapse free and had had no change to their medical (neurological) treatment for 3 months prior to undergoing the MRI scan. Twenty-seven healthy controls (HC) were used to directly compare with MS participants and were recruited from the community. These were 15 females and 12 males. All participants were aged between 18 and 60 years, were right-handed and had no contraindications for MR scanning. All participants underwent MRI scanning and assessment of clinical and cognitive function. The study was approved by the NHS SouthWest Ethics and the Cardiff and Vale University Health Board R&D committees,

and all participants provided written informed consent to participate in the study. Access to these data (MRI scans and cognitive test sores) was facilitated by Dr Nils Muhlert, who took over as co-supervisor to the PhD in 2020, and had been involved in the development of this database while based previously at Cardiff University.

Neuropsychological assessment of Verbal Fluency

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao, 1990) was administered to all participants to assess cognitive functions. The BRB-N is a normative test battery and has been shown to have a high sensitivity and specificity in discriminating cognitive impairment in PwMS (Bever Jr, Grattan, Panitch, & Johnson, 1995; Boringa et al., 2001). The battery consists of five tests including the 10/36 Spatial Recall Test to assess visual memory; the Selective Reminding Test to assess verbal memory; the Symbol Digit Modalities Test (SDMD) to assess attention, information processing speed and executive function; the Paced Auditory Serial Addition Task (PASAT) to assess sustained and divided attention and information processing speed; and the Word List Generation (WLG) to assess semantic and phonemic verbal fluency (Rao, 1990). The test can be administered in 20-30 minutes. For the purposes of this study, we only focused on the WLG scores to investigate verbal fluency. Participants' scores were converted to Z scores based on means and standard deviations from the 27 HCs. Participants were considered cognitively impaired (CI) if they scored ≥1.5 standard deviations below the control mean, i.e. $Z \leq -1.5$, on two or more tests. All other participants were considered cognitively preserved (CP).

MRI data acquisition protocol

All images were acquired with a 3T clinical MR imaging unit (HDX; General Electric Medical System, Milwaukee, Wisc., USA) using a dedicated eight channel receive-only head RF coil. All participants were asked to close their eyes and stay calm during the fMRI acquisition. The sequences acquired in each subject included a high-resolution 3D T1-weighted (3DT1) structural scan (Rao, 1990 matrix = 256x256x172, FOV = 256 x 256 mm, flip angle = 20). A T2/proton-density (PD)-weighted sequence (voxel size = 0.94x0.94x4.5 mm, TE = 9.0/80.6 ms, TR = 3000 ms, FOV = 240 x 240 mm, 36 slices) and a fluid-attenuated inversion recovery

(FLAIR) sequence (voxel size = 0.86x0.86x4.5 mm, TE = 122.3 ms, TR = 9502 ms, FOV = 220 x 220 mm, 36 slices) was also acquired to identify T2-hyperintense multiple sclerosis lesions. A T2* weighted gradient-echo echo-planar (GE-EPI) imaging sequence (voxel resolution = 3.4x3.4x3 mm, TE = 35 ms, TR = 3000 ms, FOV = 220 x 220 mm, 100 volumes, 46 axial slices each in an interleaved order was used to get the resting state fMRI. For the dMRI acquisition, a twice refocused diffusion-weighted spin echo echo-planar (SEEPI) sequence was acquired with 6 volumes with no diffusion weighting and 40 volumes with diffusion gradients applied in uniformly distributed directions (Camino 40), b = 1200 s/mm2, voxel size=1.8x1.8x2.4 mm, TE = 94.5 ms, TR = 16000 ms, FOV = 230 x 230 mm, 57 slices. QUIPSS II cut-off at 700 ms obtained 16 tag-control pairs each for short inversion times, TI (400, 500, 600, 700 ms) and 8 tag-control pairs for long TI (1100, 1400, 1700 and 2000 ms). Finally, the equilibrium magnetization of cerebrospinal fluid, needed for the quantification of CBF was obtained by calibration (M0) image. To correct for coil inhomogeneities, a minimal contrast image was obtained with TE=11ms, TR=2000 ms.

Pre-processing of structural data and image registration

MRI images were analysed using Statistical Parametric Mapping software version 12 (SPM 12) (Wellcome Dept. of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) (Friston, 2003), running under MATLAB R2020a (MathWorks, Natick, MA). T1-weighted (T1w) hypointense lesions were filled in order to reduce the impact of WM lesions on brain tissue segmentations (Chard, Jackson, Miller, & Wheeler-Kingshott, 2010).

An optimised method of voxel-based morphometry (VBM) was used for grey and white matter pre-processing and for the creation of templates. Firstly, different tissue types were identified within the images and scalp, skull and dural venous sinus voxels were removed. The original MRI images (in native space) were segmented into GM and WM partitions in native space. Then anatomical template was created for all the participants (MS and HC). In order to create a more accurate inter-subject alignment, an algorithm for diffeomorphic image registration (DARTEL) was used (Ashburner, 2007), which generated a template using all participants' (N=160) GM tissue segmentations. Each grey matter image was smoothed, spatially normalised and Jacobian scaled in Montreal Neurological Institute (MNI) space also using DARTEL. The size of the Gaussian full width at half maximum (FWHM) was specified at

8 mm for smoothing the pre-processed data. All registrations were reviewed by the student and supervisor to confirm their accuracy. Finally total intracranial volume was calculated.

Statistical Analysis

Lesion Volumes

In order to interpret any differences among the pre-processed data a basic model was set up. The normalised, smoothed and segmented data were analysed using VBM and the analysis was carried out in SPM12. People with MS were compared to healthy controls to examine any significantly affected specific regions in PwMS. An analysis of multiple regression was used to compare volumetry measurements among the two groups. Gender, age and total intracranial volume (TIV) were incorporated as covariates. A significance level of 0.05 was considered as statistically significant (family wise error (FWE) corrected) for voxel-wise VBM comparison between groups and for voxel-wise LPM a significance level of 0.001 (uncorrected) was used.

Associations of Verbal Fluency with GM atrophy

In order to explore the associations between GM and measures of verbal fluency in PwMS, statistical analysis tools from SPM12 were used to set up a multiple regression model. Age, sex, TIV and verbal scores were used as covariates. Comparisons were corrected for voxel-wise VBM comparisons at the voxel level at $p<0.05$ threshold, with the family wise error correction method and a significance of 0.001 (uncorrected) for voxel-wise LPM.

Results

One hundred and five participants with RR MS and 27 healthy controls were studied. Demographics and verbal fluency scores are presented in Table 6.1.

Table 6. 1**.** Demographic and Clinical Characteristics of people with RR MS and healthy controls.

	RR MS	**HC**
Age (y) *SD*	43.7 *(9.8)*	38.1 *(11)*
Sex (F:M)	33:72	15:12
Disease duration (y) *SD*	12.3 *(7.6)*	
Word List Generation scores *SD*	26.8 *(6.8)*	28.9 (*7.5)*

Grey Matter Atrophy

The total intracranial volume did not differ between the HC and the RR MS participants (p = .068). Compared to HC, reduced GM volume was found in participants with RR MS, including predominantly bilateral in deep GM structures such as thalamus and putamen. Furthermore, significant reductions in GM volume (p<0.05 FWE corrected) were found in the right hippocampus and corpus callosum and in a few small regions in the putamen, precuneus and gyrus rectus in people with RR MS compared to HC (Table 6.2 and Figure 6.1).

Associations with GM atrophy and clinical verbal fluency parameters

RR MS participants performed worse than HC in the verbal fluency test, but no statistically significant differences were found (p>0.05).

Verbal fluency in participants with RR MS was significant correlated with reductions in GM volume within the left precentral gyrus, and right thalamus (Table 6.3 and Figure 6.2; FWE-corrected). Similarly, in the a priori defined ROI analysis in the anterior cingulate showed a small but significant GM volume reduction in the left side associated with poorer verbal fluency performance (p>0.01 non-corrected).

Table 6. 2**.** Regions of significant grey matter loss in patients with Relapsing Remitting Multiple Sclerosis compared to healthy volunteers.*

Cluster Voxel	Region	Side	Peak T value	Coordinates, mm[a]		
				x	y	z
868	Thalamus	Left	5.59	-17	-17	8
946	Thalamus	Right	5.41	20	-29	3
361	Putamen	Left	5.37	-30	11	-3
18	Hippocampus	Right	5.07	21	-5	-18
177	Putamen	Right	5.06	30	8	-8
6	Precuneus	Right	4.86	11	-48	8
1	Gyrus Rectus	Left	4.84	-3	35	-21

*P<.05 FWE corrected.

[a]Data were obtained using statistical parametric mapping. The values refer to Montreal Neurologic Institute space coordinates.

Table 6. 3 Regions with increased lesion probability associated with poorer performance in verbal fluency tests in people with Relapsing Remitting Multiple Sclerosis.

Cluster Voxel	Region	Side	Peak T value	Coordinates, mm[a]		
				x	y	z
50	Precentral gyrus	Left	5.13	-33	-18	47
13	Thalamus	Right	5.41	-44	3	33
**8	Anterior Cingulate	Left	3.37	-41	-74	30

P<.05 FWE corrected.

[a]Data were obtained using statistical parametric mapping. The values refer to Montreal Neurologic Institute space coordinates.

**Region of interest (ROI), P<0.01 non-corrected.

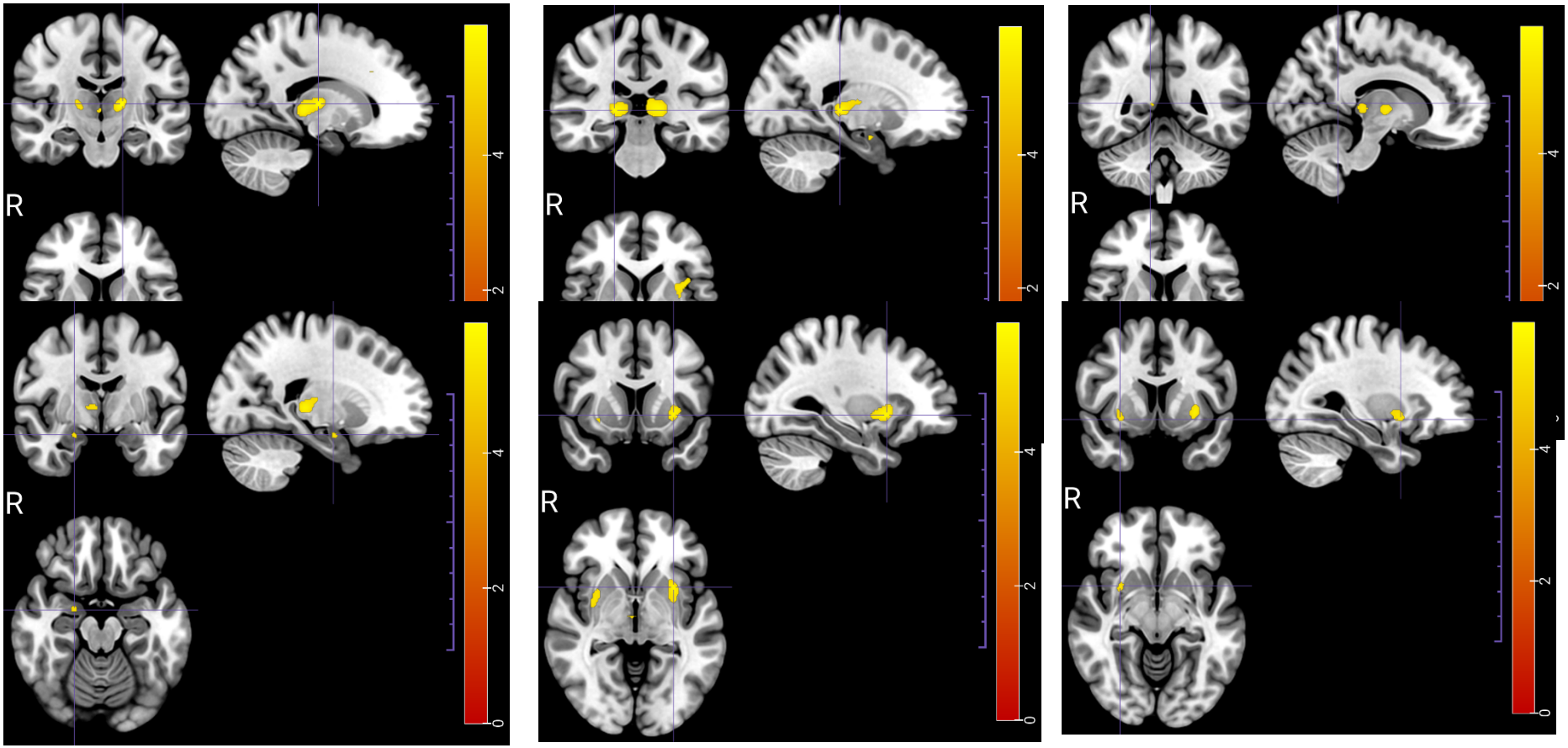


Figure 6. 1. Regions of significant grey matter volume reduction in patients with Relapsing Remitting Multiple Sclerosis compared to healthy volunteers (thalamus, putamen, hippocampus, precuneus, gyrus rectus)

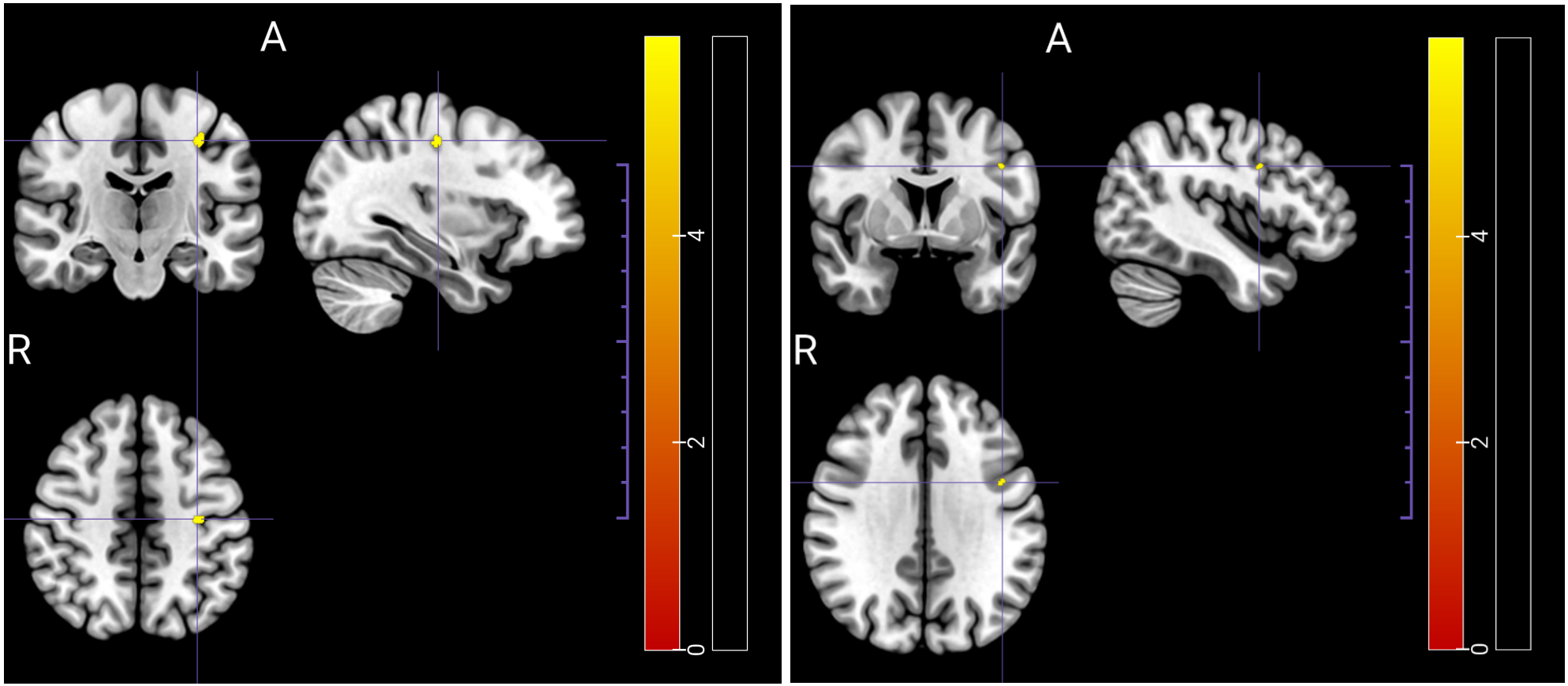


Figure 6. 2. Regions with increased lesion probability associated with poorer performance in verbal fluency tests in people with Relapsing Remitting Multiple Sclerosis (precentral gyrus).

Discussion

Multiple sclerosis is primarily regarded as a white matter disease, in which a T-cell inflammatory process is correlated with the loss of myelin sheaths. However there is also an occurrence of demyelinating lesions in grey matter (Vercellino et al., 2005). Generally, atrophy in GM has been seen to relate more to cognitive impairment than WM atrophy (Chard et al., 2002; Rudick, Lee, Nakamura, & Fisher, 2009). Measures of cortical GM may provide important information on the presence of tissue loss in normal appearing brains as it can be more sensitive to changes (Fisher et al., 2008; Valsasina et al., 2005). The present study assessed the GM volumes of participants with RR MS compared to healthy individuals and their relationship with verbal fluency test outcomes using an optimised VBM method. We also aimed at achieving a better understanding of the nature of MS related verbal fluency impairment.

Our results did not show a significant reduction in the total GM volume concentrations in participants with RR MS compared to HC. However, regional subcortical atrophy was seen in specific regions such as the thalamus and putamen bilaterally and the right hippocampus, right precuneus and left gyrus rectus. When examining the correlation between worse verbal fluency and GM volume, we found associations with reduced GM concentrations in the left precentral gyrus and the right thalamus. We also saw a small association with the anterior cingulate within the region of interest.

Mounting studies have shown GM volume loss starting at the clinically isolated syndrome (CIS) and following throughout the different stages of the disease, with secondary-progressive (SP) MS patients showing the greater GM atrophy and the CI appearing with the least volume loss (Chard et al., 2002; Geurts et al., 2012; Giorgio, Battaglini, Smith, & De Stefano, 2008; Roosendaal et al., 2011).

Our studies are in line with previous findings demonstrating significant GM volume reduction in the thalamus not only in people with RR MS (Kern et al., 2015; Wylezinska et al., 2003) but also in other forms of the disease, from CIS to secondary progressive forms (Azevedo et al., 2018; Minagar et al., 2013; Rocca et al., 2010; Štecková et al., 2014). In addition to the thalamus, other GM-rich structures such as the hippocampus and other structures of the basal ganglia including the putamen have been shown atrophy in patients with RRMS in previous studies (Batista et al., 2012; Hulst & Geurts, 2011; Krämer et al., 2015; Popescu &

Lucchinetti, 2012) also consistent with our results. It is of interest that the GM volume loss in our participants does not seem to be entirely lateralised or confined in one specific area of the brain. We observed bilateral atrophy in parts of the forebrain including thalamus and putamen. As mentioned before, thalamic atrophy occurs early and consistently through the duration of the disease and a number of clinical observations and neuroimaging studies have clearly demonstrated the relation between the thalamus and cognitive decline (Kern et al., 2015), specifically thalamic volume has been observed as a strong predictor of cognitive performance (Batista et al., 2012; Nygaard, Langeskov-Christensen, Dalgas, & Eskildsen, 2021; Papathanasiou et al., 2015). Cortical and hippocampal GM loss has also been related with cognitive deficits, particularly the hippocampus is associated with memory impairment in PwMS (Sicotte et al., 2008).

Although verbal fluency tests scores were no statistically different when compared to the HC, our group of RRMS participants performed slightly poorer. However, our results showed an association between poorer cognitive performance in verbal fluency tests and volume change in some brain structures such as the right thalamus and the left precentral gyrus in the RRMS group.

The anterior cingulate was analysed as a ROI seeing that studies had associated dorsal anterior cingulate activation in verbal fluency tests (Fu et al., 2002), furthermore Geisseler et al. (2016) found a strong correlation of cortical thinning in the left anterior cingulate and verbal fluency scores, which predicted patients with RR MS verbal fluency performance. Our study found evidence in line with the predictions of Geisseler et al. (2016), however we did not find a strong association, hence a replication in a larger sample might be needed.

Although we do not have specific phonemic and semantic verbal scores, atrophy in parts of the temporal lobe and frontal lobe might suggest that both abilities could be affected in our RR MS group, as Henry and Crawford's (2004) meta-analysis found that lesions in temporal lobe are disposed to affect semantic fluency and lesions in frontal lobe are seem to affect mainly phonemic fluency. Moreover, fMRI studies showed that phonemic fluency was associated with activation in the precentral gyrus among others (Birn et al., 2010) and semantic fluency with the activation of the hippocampal formation (Pihlajamäki et al., 2000), both showing atrophy in our study.

Verbal fluency tests have often conceptualised as a measure of verbal ability and executive function in different neurological diseases such as Alzheimer disease (Melrose et al., 2009;

Shao et al., 2014; Whiteside et al., 2016). In fact, Melrose et al. (2009) examined the neural processes associated with confrontation naming and word retrieval in AD and found that temporal regions are involved in processing information within the semantic knowledge network, and frontal regions are involved in the controlled verbal retrieval. Verbal fluency tasks also demands attention and information processing speed. Our results showed an atrophy in thalamus and putamen in our MS group and an association of thalamus GM volume reduction and poorer verbal fluency scores which are in accordance with Batista et al. (2012) findings of thalamus and putamen atrophy which in turn predicted slow information processing speed in PwMS. This might suggest that verbal fluency deficits in MS indicates a more general decline in information processing speed rather than an executive function impairment. Henry and Beatty (2006) according to their findings also suggested that MS might not be particularly associated with executive impairment but with a slow processing speed on tests of verbal fluency.

In conclusion, we found GM volume reduction in our RR MS group in parts of frontal, temporal, parietal and forebrain of the brain, which might suggest an association of both semantic and phonemic verbal fluency deficit. Moreover, the specific atrophy in the thalamus and putamen might suggest a slowing of information processing speed on verbal fluency measures.

Limitations of the study

One limitation of this study is that the neuroimaging data was not collected by the main researcher of this thesis and the participants who volunteered were not the same group as the one that we have been using throughout all the studies. Using the same participants would help to relate even stronger the results of our previous studies to the present one.

Future research

One of most common symptoms in people with MS appears to be difficulties in word retrieval showing in verbal fluency tests and confrontation naming tests. It would be conducive to explore separately phonemic and semantic verbal fluency and GM atrophy to better understand its neural correlates. Also, careful analysis of the words produced during the verbal tasks may have added clinical value. Anomia has been shown to be present from the early stages of the disease throughout the progressive forms. Hence future studies in larger

cohorts and longitudinal follow- up or a comparison study between the different forms of the disease and GM volume loss are needed to investigate functional significance and identify predictors of anomia in people with MS.

CHAPTER 7

General Discussion

Summary of thesis findings.

Chapter 2 consisted of a literature review which critically described previous research available relating to communication problems in people suffering with MS, with a particular focus on anomia. Initially a background of MS was provided, which included pathology, epidemiology, courses, progression, symptoms and general treatments of the disease. Then communication disorders (both speech and language disorders) in MS were explored. The literature review noted that the main focus in MS clinical research has been on symptoms of physical disability (fatigue, limb weakness, mobility limitations etc.), reflecting their obviousness in terms of both physical signs as well as directly limiting effects in people's lives. Cognitive impairments then followed and, more recently, research has turned to communication disorders. Rao (1986) argued that the reason because language impairments in MS were not reported in the literature might had been that symptoms were very subtle or there were maybe underdiagnosed. Yet, Hartelius et al. (2000) contended that approximately 50% of the MS population suffer from some kind of communication disorder. However, 75% of people with MS self-reported some degree of language impairments in a recent international survey (El-Wahsh et al., 2020). The literature review revealed that language disorders have been reported from early stages of the disease to secondary-progressive forms. Moreover, qualitative research with PwMS has found that even a mild decline in language skills can cause reduction or disengagement in participation in everyday activities, diminishing quality of lives (Klugman & Ross, 2002; Yorkson et al., 2001). Word retrieval has been found as one of the most common language deficits in PwMS (De Dios Perez et al., 2019, Renauld et al., 2016). The relationship between language and cognition in MS is not fully understood. Some studies have found impairments in lexical access, verbal reasoning, comprehension and even a few cases of aphasia, whilst others associate language impairments with other cognitive deficits such as slow processing speed and impairments on executive functions. However, a growing body of literature in the past decade suggests that language and cognition impairments can coincide in PwMS. Hence, the need for comprehensive assessment tests sensitive enough to detect subtle language deficits and simple and engaging treatments to reduce the severity of word retrieval even in the first stages of the disease. To understand anomia in PwMS, an effective assessment of word-finding ability is essential and the most frequent and reliable tools used to assess it are picture

naming tasks. However, in order to fully investigate mechanisms of anomia, other assessments should also be accompanied with naming tests such as language and cognition tasks. Literature has shown that therapies for anomia are widely used in people with neurological impairments such as aphasia proving to be quite successful, although they might not always translate to significant improvements in everyday communication. It is suggested that in order to achieve better results and generalisation on a naming therapy, word retrieval needs to be quick and accurate, and therapies should be short termed and highly intensive. The understanding of the nature and extent of language deficits in MS such as anomia is relevant to lead better treatment, hence a better quality of life. Consequently, ***Chapter 3*** examined communication deficits in people with RR MS, with a focus on word retrieval impairments through implementing a communication screen with a relatively large cross-section of participants with RR MS (n=100) with different lengths of time in their diagnosis and different degree of physical disabilities. The data from PwMS has been obtained through a previous and separate study, eventually reported by De Dios et al. (2020). Publication of this study required collation and direct statistical comparison with a sufficient sample of control participants (n=40), which was achieved within this PhD study. This communication screen examined the accuracy and speed of naming responses across the participants from the MS and control sub-groups in the context of data obtained from speech, language and cognitive screening tools. The key outcomes in this study revealed difficulties in word retrieval for people with RR MS presented as both inaccuracy and slow naming latency in the naming tests with an overwhelming dominance of semantic errors and/or 'no responses'. The RR MS group also presented with some degree of cognitive impairment in more than one domain, such as attention, orientation, language, verbal fluency and memory, and some level of semantic processing deficits. In terms of speech functions, the study found less frequent and very mildly symptoms of dysarthria, and did not found evidence for the presence of severe dysarthria when reading isolated words. However, in some cases, dysarthria may have had a negative effect on word retrieval, as we also found a large variability in the performance of the RR MS group.

The findings of this study are important as they confirmed the presence of anomic symptoms as clearly shown by word retrieval inaccuracy and slow naming latency in a specific course of the disease, as we focused solely on RR MS in a robust statistical sample of individuals. The results were in line with previous findings that aimed to explore the extent of naming deficits

specifically in individuals with RR MS (Kambanaros, Messinis, Nasios, Nousia, & Papathanasopoulos, 2017) and in PwMS in general (Lethlean & Murdoch, 1994; Renauld et al., 2016). At the time of submitting this study for publishing (De Dios et al., 2020) there were just a few papers focused exclusively on anomia in MS, however to date more research have confirmed our initial results (Bauer & Saldert, 2020; Brandstadter et al., 2020; Kristensson et al., 2021). Our findings are also consistent with Beatty and Monson (1989) and Lethlean and Murdoch (1994), both of whom found a predominance of semantic errors on naming tests in PwMS. A further analysis of the findings suggested that deficits in semantic processing skills were strongly related to anomic symptoms which, could be explained by a partial semantic processing deficit for lexical access rather than an impairment of the lexical pool (Lethlean & Murdoch, 1994; Sepulcre et al., 2011). Moreover, the non-responses in the confrontation naming task could suggest slowed lexical processing, especially in the semantic and/or executive search strategy domain (Sepulcre et al., 2011). In conclusion, *Chapter 3* helped us confirm that anomia is a common symptom in RR MS and it can be manifested by both, inaccuracy and slow naming latency, as well as it gave us an insight of the probable nature of it.

Chapter 4 described a study which aimed to explore the incidence and severity of anomic symptoms across a sample of people with RR MS (n=51) and to understand the cognitive-linguistic-motor factors involved in word retrieval deficits (n=21). In achieving those aims the study was divided in two parts. Firstly, we carried out a replication of *Chapter 3* in a new group of RR MS participants recruited in the same clinical setting and with comparable demographic characteristics from the previous study RR MS group. Secondly, an in-depth neuropsychological and communication assessment in a group selected across the cohort from *Chapter 3* study (n=9), and the new replication group (n=12), in total (n=21). In light of the findings in *Chapter 3*, it was expected to see a degree of anomic symptoms in the new cohort. The outcomes in the replication study were strikingly similar from the De Dios et al. (2020), confirming the presence of word retrieval difficulties also presenting inaccuracy and slow latency in people with RR MS. Again, there was a wide variation in the performance of each participant suggesting that anomic symptoms are common and can vary within a specific stage of the disease. The findings also showed semantic impairments in both cohorts, when assessed for semantic processes and in naming errors, with more than half of the errors being of semantic nature. RR MS participants in this study also presented some degree of cognitive

impairment in the screening test, with attention, orientation, verbal fluency and language falling towards the control cut-off score. In the second part of the study, we found the presence of anomic symptoms with both deficits in accuracy and retrieval speed. In addition, participants with RR MS produced less quantity of words and reduced significant facts in a picture description task. However, the RR MS group presented minimal evidence of dysarthria which suggested that word retrieval deficits cannot be fully explained by speech deficits. Equally, no participants presented with a typical aphasia syndrome. The outcomes of the in-depth neuropsychological assessment revealed low scores for most cognitive trials, however there were marked impairments on specific tests. The most pronounced deficit we found was on semantic fluency in which all participants performed under the neurotypical cut-off score, followed by visual memory skills, visual scan skills, attention and semantic cognition (all well below the neurotypical cut-off scores). Poor performance on visual attention domains, visual scans and visual memory might suggest an impairment in the information processes ability, especially in working memory (Baddeley, 1992; Baddeley, 2003, 2010), which have been well documented in PwMS (D'Esposito et al., 1996; Genova et al., 2012; Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003). In fact, it is suggested that the central executive system (which controls attention, and receives and filters information) within the working memory is the main deficit in PwMS (Lengenfelder, 2003). We also found impairments in semantic cognition and semantic fluency, which corresponded with results in *Chapter 3,* which might be caused by problems in semantic search and a deterioration of the semantic memory store. Regarding phonological verbal fluency, it seemed that participants had an adequate performance in speech perception and phonological assembly task (non-word repetition); however, problems in short-term memory and working memory could also have affected verbal fluency task performance. Deficits in memory, attention, executive functions and information processing speed seemed to have a strong relationship to lexical retrieval inaccuracy. Similarly, deficits in abstract problem solving (executive functions), attention, visual memory, semantic and phonological fluency and speed of information processing seemed to explain the variance in latency of naming responses. Our findings suggest that difficulties in naming retrieval in individuals with RR MS stemmed from disruption in both systems of the information processes ability, working memory and information processing speed and/or deficits in the semantic access, search or memory store. On this basis, anomia

in people with RR MS could be described as a cognitive-communication disorder rather than aphasia per se.

As reported in *Chapters 3* and *4,* word retrieval deficits are common in PwMS and even subtle problems may negatively impact people's overall communication. Hence, ***Chapter 5*** examined the efficacy of a computer-based and self-managed naming therapy called QuickWord in a sample of people (n=13) selected across the group from *Chapter 4*. QuickWord used a combined speed- and accuracy-focused intervention (encouraging increasingly speed production across repetitions) and a standard accuracy-focused intervention (standard naming method) and compared the efficacy between them. Each participant was also evaluated for naming, connected speech and self-rated communication outcomes in order to explore cognitive and self-perceived communication profiles at baseline, post-therapy (a week after the treatment) and maintenance (a month after the treatment). Despite the near ceiling effects for accuracy at baseline for most of the participants, the study found that both treatments (standard and speeded) increased accuracy in picture naming at post-therapy and maintenance testing. This was also true for the control items that also showed a small significant increase in naming accuracy a week and a month after treatment. In terms of naming latency, the naming reaction times were significantly reduced when tested post-therapy and these were maintained a month later. A modest significant latency improvement was also observed in the untreated items for both treatments. However, our data did not support our hypothesis that speeded therapy would show better improvements in naming accuracy and latency compared to the standard one as in Conroy et al. (2018). The speeded therapy did not show an advantage for improving confrontational naming over the standard intervention. In fact, the standard word set had the largest differences in both naming accuracy and latency in the post-therapy and maintenance assessment compared to the speeded word set. A possible explanation might be that unlike the post-stroke participants in the Conroy et al. (2018), our participants presented with mild anomia and high ceilings at baseline, which could affect the opportunity to see specific effects of the speeded intervention. For instance, the single participant who did not show ceiling effects benefited more from the speeded therapy on naming accuracy that the standard one. Moreover, as showed in *Chapters 3* & *4* our participants consistently presented with semantic deficits rather that phonological ones, which set this study apart from Conroy et al. (2018) in which the participants with the highest phonological deficits obtained a greater benefit from the

speeded therapy. This elucidation is consistent with the Best et al. (2013) meta-analysis in which aphasic participants showed a better treatment benefit when they presented greater phonological deficits rather than semantic.

Our findings also showed improvement when assessed for information processing speed, verbal phonological fluency and speech production. Yet, we did not find any improvement in semantic verbal fluency. Perhaps, QuickWord therapy might be mainly enhancing executive abilities such as information processing speed and working memory. These observations are in line with Conroy et al. (2018), who found greater benefits in participants with phonological deficits compared to semantic ones when using speeded therapy in participants with aphasia. Whereas in the MS literature, phonological fluency tends to be more dependent on executive abilities such as the speed of information processing and working memory, whereas semantic fluency seems to depend more on semantic memory (Henry & Beatty, 2006; Zakzanis, 2000). Our findings obtained with a self-reported questionnaire showed a better perceived verbal communication and functional word retrieval skills after the use of QuickWord in people with RR MS.

Chapter 6 reported the final study in the thesis, which aimed at achieving a better understanding of the neural nature of MS related verbal fluency impairment by assessing the grey matter (GM) volumes of participants with RR MS (n=105) compared to healthy individuals (n=27) and their relationship with verbal fluency test outcomes using an optimised VBM method. Participants with RR MS did not show a significant reduction in the total GM volume concentrations compared to healthy controls. Yet, specific regions presented regional subcortical atrophy such as the right hippocampus, right precuneus and left gyrus rectus. Furthermore, associations with reduced GM volumes in the left precentral gyrus and the right thalamus were found when examining the correlation between worse verbal fluency and GM concentrations, as well as a small association with the anterior cingulate within the ROI. RR MS participants did not seem to present with GM volume loss entirely lateralised or confined in one specific area of the brain, probably because of the focal inflammatory nature of the disease. Bilateral atrophy in the thalamus and putamen was also observed, which was in line with previous findings showing thalamic atrophy from early stages (CIS) and consistently through the progressive forms of the disease forms (Azevedo et al., 2018; Kern et al., 2015; Minagar et al., 2013; Rocca et al., 2010; Štecková et al., 2014; Wylezinska et al., 2003). Volume loss in parts of the temporal lobe and frontal lobe might affect semantic

fluency and phonemic fluency respectively, corresponding to Henry and Crawford's (2004) meta-analysis. Other authors have found that that temporal regions, along with thalamus and putamen atrophy, might be involved in deficits in information processing within the semantic knowledge network, and frontal regions are involved in the controlled retrieval information in people with neurodegenerative disorders (Batista et al., 2012; Melrose et al., 2009). This suggested that low scores on verbal fluency indicated a more general decline in processing information.

Theoretical and clinical implications

Anomia as a common symptom in RR MS

Historically, language disorders were not usually associated with MS, as studies on symptoms in the disease had generally been focused on physical and cognitive conditions. With growing awareness of the cognitive sequelae of MS, some limited findings related to language deficits emerged. The first studies on language disorders in MS did not find conclusive results as some authors found subtle deficits, whilst others did not find any (Herderschee, Stam, & Derix, 1987). This reflected the fact that symptoms are perceived as uncommon, underdiagnosed or overlooked (Rao, 1986). However, increasingly clinical research has now been focusing on communication disorders in people with MS, including speech impairments and in particular verbal fluency. However, fluency is usually been considered as a general cognitive deficit rather than a simple language impairment. Two systematic reviews on speech and language disorders revealed that communication deficits are present in MS even in the earliest stages of MS, and that word retrieval and fluency problems are frequent (De Dios Perez, 2007; Renauld et al., 2016). Moreover, over 70% of people with MS reported language difficulties (El-Wahsh et al., 2020; Klugman & Ross, 2002). Although previous studies have mentioned anomic symptoms in MS, they did not provide clear and convincing accounts as to the nature and extent of anomia in people with MS. People with MS have reported that even subtle changes in word retrieval may change the way they relate to other people, leading to a negative impact in their quality of life. The cognitive-linguistic screening and assessment data reported in this thesis (Chapters 3 and 4) examined the presence and extent of anomia and its interaction with dysarthria and cognitive impairments. Participants with RR MS were assessed with cognitive, language and speech tests, since cognition and language impairments might coincide in the disease, and dysarthria may affect the speed of the verbal responses. Our findings showed a high prevalence of cognitive impairment, with more than half of the participants presenting with at least mild cognitive deficits. Regarding word retrieval, competent naming abilities require both accuracy and speed in word production, thus measuring latency along with accuracy could be more useful and sensitive in characterising retrieval deficits, as found in a study in people with anomic aphasia by Galletta and Goral (2018). Therefore, the use of a bespoke picture naming test was developed, in which both accuracy and response latency were measured. The replication of the De Dios et

al. (2020) study constituted extending a sample size providing a stronger statistical sample (n=150). The language assessment results in the study in Chapter 3, its replication and subsequent use (Chapter 4) were strikingly similar and confirmed that anomia symptoms are present in RR MS population, as indicated by slow response latency and word retrieval inaccuracy. As a group, participants performed at the lower end of the control range, however there was a large variability within the PwMS in the two groups, suggesting that anomia can vary within the relapsing- remitting form of the disease. In order to get an indication about the types of processes (semantic and/or lexical) involved in the naming impairments an analysis of errors in the naming task was used. Such analysis revealed a predominance of semantic errors, particularly semantic paraphasias and no-responses. Semantic deficits were also evident in the semantic processing test. According to Dell's (1986) model of word retrieval, there are 3 levels of representation through which language is produced (lexical, semantic and phonological), anomia might occur when one or more levels of representation are disrupted. Semantic deficits in our MS groups suggested a problem in the access of semantic knowledge which in turn increases word retrieval deficits. In addition, Sepulcre et al. (2011) noted that no responses in naming tests might suggest a slow lexical processing in the semantic domain and/or executive search process. The prevalence of anomic symptoms is not the only important finding, but also the decrease of speed in which objects are named affecting the flow of the communication process, adding on the impact in their everyday life. According to our observations, measureable anomic symptoms were present in the majority of people diagnosed with RR MS, which is the most common form of the disease (Alonso, Jick, Olek, & Hernan, 2007). However, there was a large variation in presentation from very subtle to severe anomic impairments and this variation does not seem to have a correlation with the duration of the disease. The more subtle presentations could make it difficult to detect anomia with routine cognitive tests in clinical practice, causing the symptoms to be overlooked and underestimated. The presence of dysarthria in a small part of our cohort did not seem to account for the anomic deficits. On the other hand, underlying semantic problems and slow lexical processing seem to be the largest contribution to anomic deficits. The early detection and treatment of anomic symptoms is important before it limits their capacity to relate normally with their community, in consequence affecting their quality of life.

Anomia in RR MS as a cognitive communication disorder

Although the cohort of participants was large (n=151), the use of a quick screen into language and cognition offered only a limited insight into the nature of anomia in people with RR MS, in which underlying semantic problems and slow lexical processing seem to be contributing to anomia. A more extensive neuropsychological battery, plus language and speech assessments were utilised in order to explore the character of word retrieval deficits. Participants were selected on the basis of their performance in the naming test in both accuracy and latency (from mild to severe). It was important to use a formal rating scale assessment for dysarthria (to obtain detailed information about the existence of any motor speech disorders) and a proper evaluation of aphasia (to assess the primary aspects of language) along with the large array of cognitive of tests in order to understand the features contributing to anomia specifically in RR MS participants.

Most participants presented with normal speech function, only two showed mild problems with respiration, mild difficulties on lips and tongue movement and mild laryngeal phonation. The same happened when assessed for aphasia; overall, the MS group performed above the neurotypical mean. However, on the lexical retrieval subtest, 43% of the MS group fell slightly below the published normative data mean. This suggests that our MS participants did not present any aphasic syndrome and anomia was not explained by motor speech deficits. In terms of cognition, the RR MS group performed lower than the normative mean in most cognitive assessments; these findings were expected as cognitive deficits can be present in up to 70% of PwMS at any stage of the disease (Amato et al., 2001; Rao et al., 1991). Nevertheless, most participants were particularly impaired in specific functions such as attention, visual scan skills, visual memory skills, semantic cognition and verbal fluency, in particular semantic fluency. Poor performance in some of those skills could be impairing working memory in PwMS, which is controlled by the executive system (Baddeley, 1992). According to the Baddeley and Hitch's (2000) model of working memory, audition, visual attention and memory systems among others, are required to efficiently maintain information whilst it is simultaneously being processed and manipulated by the central executive. Deficits in working memory in MS disease are very common, for instance Lengenfelder et al. (2003) suggested that working memory deficit in PwMS is caused by damage in the executive system rather than the auditory. Our participants also performed

poorly on semantic cognition tasks and verbal fluency tests, especially in semantic fluency. In fact, it was surprising that every single participant performed below the mean cut-off scores in the category fluency task, as the semantic fluency task (D-KEFS) has been standardised and widely used in neurological conditions and neurodegenerative diseases such as MS without being considered overly difficult (Lebkuecher, Chiaravalloti, & Strober, 2021; Strong, Tiesma, & Donders, 2010). Moreover, healthy individuals tend to perform better in semantic fluency rather than in phonemic fluency (Kave, 2005). Verbal fluency tests have been considered to be measures of executive function rather than pure language (Henry & Crawford, 2004a, 2004b; Whiteside et al., 2016), whilst phonemic depends more on cognitive control, semantic hang on existing semantic knowledge and memory (Kave, 2005; Sepulcre et al., 2011; Velázquez-Cardoso et al., 2014). Hence, difficulties in semantic search and in the semantic memory store could be affecting category fluency tests and semantic cognition tasks, whilst problems in information processes in the working memory, could be influencing phonemic fluency tasks. This is in line with our study (Chapter 6) in which we explore GM volume concentrations in people with RR MS and their relationship with verbal fluency tests performance and found GM volume atrophy in parts of frontal, temporal, parietal and forebrain of the brain. Atrophy in those areas suggested a possible deficit in both semantic and phonemic skills. According to Henry and Crawford's (2004) meta-analysis, lesions in temporal lobe tend to affect semantic fluency while lesions in the frontal lobe are more likely to affect mainly phonemic fluency. More specifically, studies using fMRI observed that there was an association with activation in the precentral gyrus amongst others and phonemic fluency and the activation of the hippocampal formation and semantic fluency, both structures showing GM volume reduction in our study (Birn et al., 2010; Pihlajamäki et al., 2000). We also found an association between thalamus MG volume reduction and poorer performance in verbal fluency scores, which along with putamen atrophy showed in our RR MS participants, suggested that verbal fluency deficits denote a more general decline in speed of information processing, as showed in Batista et al. (2012) findings in which atrophy in the thalamus and putamen (Lebkuecher et al., 2021) led to an association in which vocabulary and processing speed tests predicted performance in letter fluency and vocabulary tests predicted category fluency performance in people with MS.

Various and numerous neuropsychological tests were used to measure cognitive functions in the RR MS. However, the most representative test for each cognitive domain was used to

correlate with naming retrieval performance in both accuracy and speed. We found a strong relationship between difficulties in attention, memory, executive functions and information processing speed to word retrieval inaccuracy. Likewise, deficits in attention, visual memory, verbal fluency tasks problem solving and speed of information seemed to associate with the variance in latency of naming responses.

Language problems, such as word retrieval impairments, have become to attract more research attention. Previously, they had typically been overlooked, possibly because of being too subtle. However, we have observed that anomia is a common symptom of MS. It has also been debated as to whether language deficits were part of a general cognitive decline experienced by a large number of PwSM. Our findings suggest that difficulties in word retrieval in people with RR MS could be explained by a disturbance at the level of working memory and a slow processing of information in the central executive system and a deficit in the semantic access and/or semantic memory. Features of aphasia were not found in the RR MS, and symptoms of dysarthria did not seem to interact with the anomic symptoms. On this basis it was suggested that anomia in RR MS cannot be considered a pure language deficit or simply part of a general cognitive decline, but as a cognitive-communication disorder. Exploring the underlying cognitive-linguistic essence of anomia could enable us to tailor more effective communication therapies, focused to help people in their everyday general communication, ultimately improving each individual's quality of life.

The nature of the therapeutic effect: generalisation to connected speech after self-managed anomia therapy (QuickWord) in MS

Word retrieval difficulties are one of the most common language deficits in MS and the most self-reported (De Dios Pérez et al., 2020; El-Wahsh et al., 2020; Klugman & Ross, 2002). Changes in language and cognitive-linguistic skills are often perceived as the most significant feature in reduction in quality of life, where even subtle communication deficits negatively impact on individuals and families, (LaPointe, 1999). Communication deficits in MS are evident at the earliest stages of the disease and inevitably worsen as the disease progresses, due to the degenerative nature of MS (Friend et al., 1999). Therefore, the development of early effective interventions focused on improving word retrieval skills is important, which may optimise verbal communication in people with MS.

A word retrieval treatment was carried on our MS participants across 6 weeks.This therapy not only focused on word accuracy as per traditional word retrieval treatments, but also targeted latency (word cueing with time pressure). Our novel treatment method (QuickWord) was a self-administered word retrieval training software programme which, after signing up, could be accessed on line by MS participants to train on their own time. Participants were taught how to use the programme by the researcher, whom personally guided them until they were confident of using QuickWord on their own. The adherence of participants to therapies could be benefited by online training, as in regular clinical settings the individual has to travel to a rehabilitation centre, or receive home visits from a therapist at a specific time, which may put an extra demand on rehabilitation resources. The use of such online resources in clinical settings is growing more than ever. The recent COVID-19 pandemic changed people's lifestyles with growing office work, doctor appointments and even friends and family reunions required to be done via video-chat. QuickWord could be an efficient way to continue therapy when patients cannot travel or decide not to leave home.

QuickWord was previously used by Conroy et al. (2018) on participants with post-stroke aphasia, observing gains on both naming and generalisation of the trained words to connected speech. They also showed greater improvements using the speeded treatment in accuracy and speed of word retrieval. Although our MS participants presented relatively high scores at baseline, they still showed significant improvement on picture naming accuracy and decreased naming reaction times following both treatment methods, the standard and

speeded treatments, as measured a week after the intervention with maintained improvement a month after therapy. Untreated items also showed gains in naming accuracy and decreased naming reaction times in both treatments a week after treatment and maintained a month later. Nonetheless, the speeded therapy did not show an added advantage for improving word retrieval as seen in Conroy et al. (2018). Although participants with post-stroke aphasia are somewhat a comparable clinical population with our RR MS participants, there are important differences that could explain the contrasting outcomes on the speeded therapy. The mean severity on post-stroke participants was much marked on both accuracy and latency, for instance the mean baseline accuracy on confrontation naming tests in Conroy et al. (2018) was 35.3 (max=80) against 45.7 (max=50) in MS participants, and the mean baseline reaction times in post-stroke participants was 2.6 ms versus 1.3 ms in MS participants (control performance ~<1 second). Although significant treatments effects were observed regardless high baselines performance in MS participants in both interventions, there could have been less leeway for higher gains in accuracy and latency when training. This could be seen in RR MS participant 7 (naming accuracy) and RR MS participants 5 and 7 (reaction times) in Chapter 5, which were not at baseline ceilings and showed greater improvements in both therapies. Another important difference between therapy outcomes in the two populations was that stroke aphasia participants with the greatest phonological deficits were the ones that showed better gains with the therapy intervention whilst our MS group showed more semantic deficits that phonologic ones. According to Best et al. (2013), aphasia participants who presented with greater phonological deficits showed better response in confrontational naming intervention compared to semantic. In terms of indirect cognitive-linguistic effects of therapy, we found a general improvement on information processing speed test (SDMT), verbal phonological fluency, as well as a gain on words produced per minute in discourse. Yet, we did not find improvements in the semantic verbal fluency task, which might be linked with our suggestions that MS anomic symptoms can be explained by a disruption at the level of information processing in the working memory and a deficit in access into the semantic knowledge and/or memory, hence, the improvement in information processing speed and speech production over semantic skills using QuickWord intervention.

Perhaps therapy gains in people with RR MS might not be as striking as in other neurological and/or neurodegenerative disorders such as stroke or dementia. However, QuickWord could

be more beneficial in later stages of the disease (Primary Progressive, Secondary Progressive MS), in which participants present with poorer performance in cognitive communication measures (Friend et al. 1999). Nevertheless, our MS group self-reported better verbal communication and functional word retrieval skills after treatment. Even when presenting with subtle symptoms of anomia in RR MS, we would argue that people should be encouraged to engage in self-management to try to enhance their speed and reliability of vocabulary production.

Novel contributions

Within one research project, we have presented a relatively large-scale screening study with over 150 PwMS, derived from a large specialist neuroscience centre serving a geographically, socially and linguistically diverse Greater Manchester and North West England population (Jivraj & Finney, 2013). We moved from a broad-shallow data mining approach to a narrow-deep one, for in-depth cognitive-linguistic-motor assessment and a treatment study with a more modest and feasible number of participants. Utilising a different imaging data-base, some understanding of the likely neural basis of category fluency deficits in RR MS was achieved. To our knowledge, achieving this comprehensive cycle of research enquiry in relation to anomia in RR MS, moving from screening to assessment, diagnosis, treatment and imaging, within one research project is a unique contribution to this evolving field. Furthermore, given the parallel methods used across these studies and several which focused on stroke aphasia, informative and close comparisons were able to be readily made between the nature and treatability of anomia in MS relative to stroke aphasia.

We focused on and explored language symptoms in one specific group MS group (RR MS) and used a tailored novel and relatively sensitive assessment (IPNP) in a large cohort, which included the feature of naming latency measure to explore subtle word retrieval deficits. Furthermore, a novel self-administered software programme was used for the first time beyond stroke aphasia, and in one of the first reported attempts at early interventions for anomia in MS.

Limitations of the thesis

The findings of this thesis have to be seen in light of some limitations. Although in the initial screening we used a relatively large cohort, a larger sample size in the in-depth cognitive-language assessment and treatment could have generated more informative results.

Another limitation was the complexity of recruiting for the in-depth assessments and sus-sequent treatment. It was challenging to retain participants to take part in these studies, compared to the screening as they had to commit to a greater time commitment. Furthermore, the large number of speech, language and cognitive tests used meant that participants offered substantial time periods for assessment. Although we broke the assessments into 3 – 4 different sessions, each session was between 1-1.5 hrs, which due to the nature of the disease, could have caused fatigue in our participants. Participants were assessed in their homes, which also put time pressure on the researcher. The need to travel long distances to visit each participant meant the researcher could see a limited number of participants a day, leading to long gaps of time between sessions.

QuickWord is a novel software programme that was developed along and for our therapy study. However, being so novel meant technical glitches were discovered along the way. That made data collection slower and needed extra trial and error practices.

Furthermore, we did not succeed into obtaining financial resources for a MRI scan of each participant recruited for the in-depth assessment. Imaging in the same cohort could have given us more precise information about the relation to both, the behavioural and the structural imaging data.

The same researcher collected all the data in the in-depth tests and naming intervention, which could affect the objectivity of assessments, with some risk of bias given lack of blindedness to time points of assessment. Lastly, COVID-19 restrictions made it challenging to collect data from the Self-rating Communication Questionnaire, as some participants were not familiarised with video-chats. We also lost a couple of participants due not being able visit them for assessments.

Directions for future research

Progress has been made into recognising cognitive-language symptoms in RR MS. However, future studies with larger participant numbers and longitudinal follow-up could be designed to investigate the functional and prognostic significance of the anomic symptoms observed. Further studies researching these symptoms should also be made in other clinical courses of the disease, especially the progressive courses. Anomia and other cognitive-communication symptoms could be subtle and underdiagnosed in MS, thus the need for a more complex and comprehensive assessment, sensitive enough to detect subtle language deficits.

Although atrophy in GM is directly associated with cognition deficits, it is also important to direct future research into the study of white matter tracts. For instance, analyses with Diffusion Tensor MRI tractography (DTI) could help identify the underlying white matter neurobiology of anomic symptoms and the ways in which cognitive subsystems interact over the course of the disease. This could lead to the identification of neurobiological markers for risk of cognitive-linguistic deficits related to MS which could be screened for on diagnostic MRI scanning.

It has now been observed that therapy for word-retrieval and production disorders can be effective. However, our findings in the therapy study did not show the effect that we expected regarding the speeded factor in the training. Given the nature of cognitive-communication disorder in MS, it would be beneficial to investigate further into adding a semantic feature into therapy. However, a recent study which evaluated treatment effects of semantic feature analysis (SFA) on mild anomia in PwMS, found no robust effects on confrontation naming abilities, connected speech or self-reported communicative participation. These researchers concluded that SFA as an only element of treatment may not be enough to observe treatment effects on subtle anomia in MS (Kristensson et al., 2021). Therefore, future research could also usefully explore semantic therapy with more demanding and high-level processing semantic association tasks as well as integrating a time pressure.

REFERENCES

Achiron, A., Ziv, I., Djaldetti, R., Goldberg, H., Kuritzky, A., & Melamed, E. (1992). Aphasia in multiple sclerosis Clinical and radiologie correlations. *Neurology, 42*(11), 2195-2195.

Almaghyuli, A., Thompson, H., Lambon Ralph, M. A., & Jefferies, E. (2012). Deficits of semantic control produce absent or reverse frequency effects in comprehension: Evidence from neuropsychology and dual task methodology. *Neuropsychologia, 50*(8), 1968-1979. doi:https://doi.org/10.1016/j.neuropsychologia.2012.04.022

Alonso, A., Jick, S. S., Olek, M. J., & Hernan, M. A. (2007). Incidence of multiple sclerosis in the United Kingdom. *Journal of Neurology, 254*(12), 1736-1741.

Amato, M., Bartolozzi, M., Zipoli, V., Portaccio, E., Mortilla, M., Guidi, L., . . . De Stefano, N. (2004). Neocortical volume decrease in relapsing–remitting MS patients with mild cognitive impairment. *Neurology, 63*(1), 89-93.

Amato, M., Portaccio, E., Goretti, B., Zipoli, V., Battaglini, M., Bartolozzi, M. L., . . . Sorbi, S. (2007). Association of neocortical volume changes with cognitive deterioration in relapsing-remitting multiple sclerosis. *Archives of neurology, 64*(8), 1157-1161.

Amato, M. P., Ponziani, G., Pracucci, G., Bracco, L., Siracusa, G., & Amaducci, L. (1995). Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. *Archives of neurology, 52*(2), 168-172.

Amato, M. P., Ponziani, G., Siracusa, G., & Sorbi, S. (2001). Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Archives of neurology, 58*(10), 1602-1606.

Amato, M. P., Portaccio, E., Goretti, B., Zipoli, V., Hakiki, B., Giannini, M., . . . Razzolini, L. (2010). Cognitive impairment in early stages of multiple sclerosis. *Neurol Sci, 31*(Suppl 2), S211-214. doi:10.1007/s10072-010-0376-4

Amato, M. P., Zipoli, V., & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *J Neurol Sci, 245*(1-2), 41-46.

Anlar, O. (2009). Treatment of Multiple Sclerosis. *CNS & Neurological Disorders - Drug Targets- CNS & Neurological Disorders), 8*(3), 167-174. doi:10.2174/187152709788680670

Arrondo, G., Sepulcre, J., Duque, B., Toledo, J., & Villoslada, P. (2010). Narrative speech is impaired in multiple sclerosis. *The European Neurological Journal, 2*(1), 1.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage, 38*(1), 95-113.

Azevedo, C. J., Cen, S. Y., Khadka, S., Liu, S., Kornak, J., Shi, Y., . . . Pelletier, D. (2018). Thalamic atrophy in multiple sclerosis: A magnetic resonance imaging marker of neurodegeneration throughout disease. *Annals of neurology, 83*(2), 223-234. doi:https://doi.org/10.1002/ana.25150

Baddeley, A. (1992). Working memory. *Science, 255*(5044), 556-559. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-0026554483&partnerID=40&md5=9a71c31e4a3b92dd39606cb4e4388c61

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in cognitive sciences, 4*(11), 417-423.

Baddeley, A. (2003). Working memory and language: An overview. *Journal of communication disorders, 36*(3), 189-208.

Baddeley, A. (2010). Working memory. *Current biology, 20*(4), R136-R140.

Baddeley, A., & Hitch, G. (2000). Development of working memory: Should the Pascual-Leone and the Baddeley and Hitch models be merged? *Journal of experimental child psychology, 77*(2), 128-137.

Bagert, B., Camplair, P., & Bourdette, D. (2002). Cognitive dysfunction in multiple sclerosis. *CNS drugs, 16*(7), 445-455.

Baldo, J. V., Shimamura, A. P., Delis, D. C., Kramer, J., & Kaplan, E. (2001). Verbal and design fluency in patients with frontal lobe lesions. *Journal of the International Neuropsychological Society, 7*(05), 586-596.

Barkhof, F. (2002). The clinico-radiological paradox in multiple sclerosis revisited. *Current opinion in neurology, 15*(3), 239-245.

Barthel, G., Meinzer, M., Djundja, D., & Rockstroh, B. (2008). Intensive language therapy in chronic aphasia: Which aspects contribute most? *Aphasiology, 22*(4), 408-421.

Basso, A. (1993). Therapy for aphasia in Italy. In *Aphasia Treatment* (pp. 1-23): Springer.

Bates, E., Andonova, E., D'amico, S., Jacobsen, T., Kohnert, K., Lu, C., . . . Herron, D. (2000). Introducing the CRL international picture-naming project (CRL-IPNP). *Center for Research in Language Newsletter, 12*(1), 12-11.

Bates, E., D'Amico, S., Jacobsen, T., Szekely, A., Andonova, E., Devescovi, A., . . . Tzeng, O. (2003). Timed picture naming in seven languages. *Psychon Bull Rev, 10*(2), 344-380.

Batista, S., Zivadinov, R., Hoogs, M., Bergsland, N., Heininen-Brown, M., Dwyer, M. G., . . . Benedict, R. H. (2012). Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. *Journal of Neurology, 259*(1), 139-146.

Bauer, M., & Saldert, C. (2020). Complex oral semantic verbal fluency in non-brain-damaged adults and individuals with multiple sclerosis and subjective anomia. *Aphasiology, 34*(12), 1471-1486. doi:10.1080/02687038.2019.1676393

Baylor, C., Burns, M., Eadie, T., Britton, D., & Yorkston, K. (2011). A qualitative study of interference with communicative participation across communication disorders in adults. *American Journal of Speech-Language Pathology*.

Baylor, C., Yorkston, K., Bamer, A., Britton, D., & Amtmann, D. (2010). Variables associated with communicative participation in people with multiple sclerosis: A regression analysis. *American Journal of Speech-Language Pathology*.

Beatty, W. (2002). Fluency in multiple sclerosis: which measure is best? *Multiple Sclerosis Journal, 8*(3), 261-264.

Beatty, W. W., & Monson, N. (1989). Lexical processing in Parkinson's disease and multiple sclerosis. *Topics in geriatrics, 2*(3), 145-152.

Beatty, W. W., & Monson, N. (1990). Semantic priming in multiple sclerosis. *Bulletin of the Psychonomic Society, 28*(5), 397-400. doi:10.3758/bf03334049

Benedict, R. H., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., Bobholz, J., . . . Caruso, L. (2002). Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol, 16*(3), 381-397.

Benedict, R. H., Morrow, S. A., Rodgers, J., Hojnacki, D., Bucello, M. A., Zivadinov, R., & Weinstock-Guttman, B. (2014). Characterizing cognitive function during relapse in multiple sclerosis. *Multiple Sclerosis Journal, 20*(13), 1745-1752.

Benedict, R. H., Weinstock-Guttman, B., Fishman, I., Sharma, J., Tjoa, C. W., & Bakshi, R. (2004). Prediction of Neuropsychological Impairment in Multiple Sclerosis: Comparison of Conventional Magnetic Resonance Imaging Measures of Atrophy and Lesion Burden. *Archives of neurology, 61*(2), 226-230. doi:10.1001/archneur.61.2.226

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., De Leon, C. F. M., Arnold, S. E., . . . Bienias, J. L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology, 60*(12), 1909-1915.

Bergendal, G., Fredrikson, S., & Almkvist, O. (2007). Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. *Eur Neurol, 57*(4), 193-202. doi:10.1159/000099158

Berndt, R. S. (2013). Symptom co-occurrence and dissociation in the interpretation of agrammatism. *The Cognitive Neuropsychology of Language (Psychology Revivals)*, 221.

Best, W., Greenwood, A., Grassly, J., Herbert, R., Hickin, J., & Howard, D. (2013). Aphasia rehabilitation: Does generalisation from anomia therapy occur and is it predictable? A case series study. *Cortex, 49*(9), 2345-2357.

Bever Jr, C., Grattan, L., Panitch, H., & Johnson, K. (1995). The brief repeatable battery of neuropsychological tests for multiple sclerosis: a preliminary serial study. *Multiple Sclerosis Journal, 1*(3), 165-169.

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., & Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. *NeuroImage, 49*(1), 1099-1107.

Boringa, J. B., Lazeron, R. H., Reuling, I. E., Adèr, H. J., Pfennings, L. E., Lindeboom, J., . . . Polman, C. H. (2001). The Brief Repeatable Battery of Neuropsychological Tests: normative values allow application in multiple sclerosis clinical practice. *Multiple Sclerosis Journal, 7*(4), 263-267. doi:10.1177/135245850100700409

Borovsky, A., Saygin, A. P., Bates, E., & Dronkers, N. (2007). Lesion correlates of conversational speech production deficits. *Neuropsychologia, 45*(11), 2525-2533.

Boyle, M. (2010). Semantic feature analysis treatment for aphasic word retrieval impairments: What's in a name? *Topics in Stroke Rehabilitation, 17*(6), 411-422.

Brandstadter, R., Fabian, M., Leavitt, V. M., Krieger, S., Yeshokumar, A., Katz Sand, I., . . . Sumowski, J. F. (2020). Word-finding difficulty is a prevalent disease-related deficit in early multiple sclerosis. *Multiple Sclerosis Journal, 26*(13), 1752-1764. doi:10.1177/1352458519881760

Brassington, J. C., & Marsh, N. V. (1998). Neuropsychological aspects of multiple sclerosis. *Neuropsychology review, 8*(2), 43-77.

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., . . . Haeusler, K. G. (2017). Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *The Lancet, 389*(10078), 1528-1538.

Bright, P., Jaldow, E. L. I., & Kopelman, M. D. (2002). The National Adult Reading Test as a measure of premorbid intelligence: A comparison with estimates derived from demographic variables. *Journal of the International Neuropsychological Society, 8*(6), 847-854. doi:10.1017/S1355617702860131

Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B. V., & Thompson, A. J. (2014). Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology, 83*(11), 1022-1024.

Bryan, J., & Luszcz, M. A. (2000). Measurement of executive function: Considerations for detecting adult age differences. *Journal of clinical and experimental neuropsychology, 22*(1), 40-55.

Butler, M., Retzlaff, P. D., & Vanderploeg, R. (1991). Neuropsychological test usage. *Professional psychology: Research and practice, 22*(6), 510.

Butters, N., Granholm, E., Salmon, D. P., Grant, I., & Wolfe, J. (1987). Episodic and semantic memory: A comparison of amnesic and demented patients. *Journal of clinical and experimental Neuropsychology, 9*(5), 479-497.

Caine, D., & Hodges, J. R. (2001). Heterogeneity of semantic and visuospatial deficits in early Alzheimer's disease. *Neuropsychology, 15*(2), 155.

Calabrese, M., Agosta, F., Rinaldi, F., Mattisi, I., Grossi, P., Favaretto, A., . . . Rinaldi, L. (2009). Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. *Archives of neurology, 66*(9), 1144-1150.

Calabrese, M., Poretto, V., Favaretto, A., Alessio, S., Bernardi, V., Romualdi, C., . . . Gallo, P. (2012). Cortical lesion load associates with progression of disability in multiple sclerosis. *Brain, 135*(10), 2952-2961.

Calabrese, M., Rinaldi, F., Mattisi, I., Grossi, P., Favaretto, A., Atzori, M., . . . Rinaldi, L. (2010). Widespread cortical thinning characterizes patients with MS with mild cognitive impairment. *Neurology, 74*(4), 321-328.

Calabrese, P. (2006). Neuropsychology of multiple sclerosis. *Journal of Neurology, 253*, i10-i15.

Caramazza, A., & Hillis, A. E. (1990). Where Do Semantic Errors Come From? *Cortex, 26*(1), 95-122. doi:https://doi.org/10.1016/S0010-9452(13)80077-9

Carotenuto, A., Arcara, G., Orefice, G., Cerillo, I., Giannino, V., Rasulo, M., . . . Bambini, V. (2018). Communication in multiple sclerosis: pragmatic deficit and its relation with cognition and social cognition. *Archives of Clinical Neuropsychology, 33*(2), 194-205.

Carragher, M., Conroy, P., Sage, K., & Wilkinson, R. (2012). Can impairment-focused therapy change the everyday conversations of people with aphasia? A review of the literature and future directions. *Aphasiology, 26*(7), 895-916.

Channon, S., Baker, J., & Robertson, M. M. (1993). Working memory in clinical depression: An experimental study. *Psychological Medicine, 23*(1), 87-91. doi:10.1017/S0033291700038873

Charcot, J. M. (1877). Lectures on the diseases of the nervous system delivered at la salpetriere (trans. G. Sigerson)(pp. 194-195). *London: The New Sydenham Society*.

Chard, D. T., Griffin, C. M., Parker, G. J. M., Kapoor, R., Thompson, A. J., & Miller, D. H. (2002). Brain atrophy in clinically early relapsing–remitting multiple sclerosis. *Brain, 125*(2), 327-337.

Chard, D. T., Jackson, J. S., Miller, D. H., & Wheeler-Kingshott, C. A. M. (2010). Reducing the impact of white matter lesions on automated measures of brain gray and white matter volumes. *Journal of magnetic resonance imaging, 32*(1), 223-228.

Chenery, H. J. (1993). The dissolution of language in Alzheimer's dementia.

Cherktow, H., & Bub, D. (1990). Semantic memory loss in dementia of the Alzheimer's type. *Brain, 113*, 397-417.

Chiaravalloti, N. D., & DeLuca, J. (2002). Self-generation as a means of maximizing learning in multiple sclerosis: An application of the generation effect. *Arch Phys Med Rehabil, 83*(8), 1070-1079. doi:10.1053/apmr.2002.33729

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology, 7*(12), 1139-1151.

Cockburn, J., Keene, J., Hope, T., & Smith, P. (2000). Progressive decline in NART score with increasing dementia severity. *Journal of clinical and experimental Neuropsychology, 22*(4), 508-517.

Cohen, J. A., & Rae-Grant, A. (2012). Disease-Modifying Therapy. In *Handbook of Multiple Sclerosis* (pp. 35-59). Tarporley: Springer Healthcare Ltd.

Confavreux, C., & Vukusic, S. (2006). Natural history of multiple sclerosis: a unifying concept. *Brain, 129*(Pt 3), 606-616. doi:10.1093/brain/awl007

Connick, P., Chandran, S., & Bak, T. H. (2013). Patterns of cognitive dysfunction in progressive MS. *Behav Neurol, 27*(3), 259-265. doi:10.3233/ben-120286

Conroy, P., Sage, K., & Lambon Ralph, M. A. (2009a). The effects of decreasing and increasing cue therapy on improving naming speed and accuracy for verbs and nouns in aphasia. *Aphasiology, 23*(6), 707-730.

Conroy, P., Sage, K., & Lambon Ralph, M. A. (2009b). Improved vocabulary production after naming therapy in aphasia: can gains in picture naming generalise to connected speech? *International Journal of Language & Communication Disorders, 44*(6), 1036-1062.

Conroy, P., Sotiropoulou Drosopoulou, C., Humphreys, G. F., Halai, A. D., & Lambon Ralph, M. A. (2018). Time for a quick word? The striking benefits of training speed and accuracy of word retrieval in post-stroke aphasia. *Brain, 141*(6), 1815-1827.

Crawford, J. R., Parker, D. M., & Besson, J. A. (1988). Estimation of premorbid intelligence in organic conditions. *The British Journal of Psychiatry, 153*(2), 178-181.

Crayton, H. J., & Rossman, H. S. (2006). Managing the symptoms of multiple sclerosis: a multimodal approach. *Clinical therapeutics, 28*(4), 445-460.

Crerar, M. A. (2004). Aphasia rehabilitation and the strange neglect of speed. *Neuropsychological Rehabilitation, 14*(1-2), 173-206.

D'Esposito, M., Onishi, K., Thompson, H., Robinson, K., Armstrong, C., & Grossman, M. (1996). Working memory impairments in multiple sclerosis: Evidence from a dual-task paradigm. *Neuropsychology, 10*(1), 51.

Darley, F. L., Aronson, A. E., & Brown, J. R. (1969). Clusters of deviant speech dimensions in the dysarthrias. *J Speech Hear Res, 12*(3), 462-496.

Darley, F. L., Brown, J. R., & Goldstein, N. P. (1972). Dysarthria in multiple sclerosis. *J Speech Hear Res, 15*(2), 229-245.

Davies, D. R., Jones, D. M., & Taylor, A. (1984). Selective-and sustained-attention tasks: Individual and group differences. *Varieties of attention*, 395-447.

De Dios Pérez, B., Cordova Luna, E., Cloutman, L., Rog, D., Preston, E., & Conroy, P. (2020). Anomia in people with rapidly evolving severe relapsing-remitting multiple sclerosis: both word retrieval inaccuracy and delay are common symptoms. *Aphasiology, 34*(2), 195-213. doi:10.1080/02687038.2019.1642999

De Stefano, N., Narayanan, S., Francis, S. J., Smith, S., Mortilla, M., Tartaglia, M. C., . . . Arnold, D. L. (2002). Diffuse Axonal and Tissue Injury in Patients With Multiple Sclerosis With Low Cerebral Lesion Load and No Disability. *Archives of neurology, 59*(10), 1565-1571. doi:10.1001/archneur.59.10.1565

Delis, D. C., Kaplan, E., Kramer, J. H., Delis, D., & Kramer, J. (2001). Delis-Kaplan executive function system (D-KEFS). Examiner's manual.

Dell, G. S., & O'Seaghdha, P. G. (1992). Stages of lexical access in language production. *Cognition, 42*(1-3), 287-314.

DeLuca, G. C., Yates, R. L., Beale, H., & Morrow, S. A. (2015). Cognitive impairment in multiple sclerosis: clinical, radiologic and pathologic insights. *Brain Pathol, 25*(1), 79-98. doi:10.1111/bpa.12220

DeLuca, J., Barbieri-Berger, S., & Johnson, S. K. (1994). The nature of memory impairments in multiple sclerosis: acquisition versus retrieval. *Journal of clinical and experimental Neuropsychology, 16*(2), 183-189.

DeLuca, J., Chelune, G. J., Tulsky, D. S., Lengenfelder, J., & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of clinical and experimental Neuropsychology, 26*(4), 550-562. doi:10.1080/13803390490496641

DeLuca, J., Gaudino, E. A., Diamond, B. J., Christodoulou, C., & Engel, R. A. (1998). Acquisition and storage deficits in multiple sclerosis. *Journal of clinical and experimental Neuropsychology, 20*(3), 376-390.

DeLuca, J., Genova, H. M., Hillary, F. G., & Wylie, G. (2008). Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *J Neurol Sci, 270*(1), 28-39.

Demirkiran, M., Özeren, A., Sönmezler, A., & Bozdemir, H. (2006). Crossed aphasia in multiple sclerosis. *Multiple Sclerosis Journal, 12*(1), 116-119.

Denney, D. R., Lynch, S. G., Parmenter, B. A., & Horne, N. (2004). Cognitive impairment in relapsing and primary progressive multiple sclerosis: mostly a matter of speed. *Journal of the International Neuropsychological Society, 10*(07), 948-956.

Dimitrov, I., Kirkova, V., Kaprelyan, A., Ivanov, B., Usheva, N., Grudkova, M., . . . Deleva, N. (2015). Application of the Rey-Osterrieth complex figure test for assessment of cognitive impairment in multiple sclerosis. *Scripta Scientifica Medica, 47*(3), 59-64.

Drake, M., Allegri, R., & Carra, A. (2002). Language abnormalities in patients with multiple sclerosis. *Neurologia (Barcelona, Spain), 17*(1), 12-16.

Drake, M. A., Allegri, R. F., & Carrá, A. (2002). [Language abnormalities in patients with multiple sclerosis]. *Neurologia, 17*(1), 12-16.

Drew, M., Tippett, L. J., Starkey, N. J., & Isler, R. B. (2008). Executive dysfunction and cognitive impairment in a large community-based sample with Multiple Sclerosis from New Zealand: a descriptive study. *Archives of clinical neuropsychology, 23*(1), 1-19.

Duffy, J. R. (2013). *Motor speech disorders: Substrates, differential diagnosis, and management*: Elsevier Health Sciences.

El-Wahsh, S., Ballard, K., Kumfor, F., & Bogaardt, H. (2020). Prevalence of self-reported language impairment in multiple sclerosis and the association with health-related quality of life: An international survey study. *Multiple sclerosis and related disorders, 39*, 101896.

Elgamal, S. A., Roy, E. A., & Sharratt, M. T. (2011). Age and verbal fluency: the mediating effect of speed of processing. *Canadian geriatrics journal: CGJ, 14*(3), 66.

Enderby, P., John, A., & Petheram, B. (2013). *Therapy outcome measures for rehabilitation professionals: speech and language therapy, physiotherapy, occupational therapy* (2nd ed. ed.). Chichester, UK: John Wiley & Sons.

European Medicines Agency. (2014). Gilenya: International non-proprietary name: FINGOLIMOD. Secondary Gilenya: International non-proprietary name: FINGOLIMOD. Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002202/WC500169449.pdf

Feuillet, L., Reuter, F., Audoin, B., Malikova, I., Barrau, K., Cherif, A. A., & Pelletier, J. (2007). Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Multiple Sclerosis Journal, 13*(1), 124-127.

Feyereisen, P., Pillon, A., & Partz, M.-P. d. (1991). On the measures of fluency in the assessment of spontaneous speech production by aphasic subjects. *Aphasiology, 5*(1), 1-21. doi:10.1080/02687039108248516

Fillingham, J. K., Sage, K., & Lambon Ralph, M. A. (2006). The treatment of anomia using errorless learning. *Neuropsychological rehabilitation, 16*(2), 129-154.

Finkelsztejn, A. (2014). Multiple sclerosis: overview of disease-modifying agents. *Perspectives in medicinal chemistry, 6*, PMC. S13213.

Fisher, E., Lee, J. C., Nakamura, K., & Rudick, R. A. (2008). Gray matter atrophy in multiple sclerosis: a longitudinal study. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 64*(3), 255-265.

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., . . . Ron, M. A. (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain, 120*(1), 15-26.

Fridriksson, J., Kjartansson, O., Morgan, P. S., Hjaltason, H., Magnusdottir, S., Bonilha, L., & Rorden, C. (2010). Impaired speech repetition and left parietal lobe damage. *Journal of Neuroscience, 30*(33), 11057-11061.

Friedman, J. H., Brem, H., & Mayeux, R. (1983). Global aphasia in multiple sclerosis. *Ann Neurol, 13*(2), 222-223.

Friend, K. B., & Grattan, L. (1998). Use of the North American Adult Reading Test to Estimate Premorbid Intellectual Function in Patients with Multiple Sclerosis. *Journal of clinical and experimental Neuropsychology, 20*(6), 846-851. doi:10.1076/jcen.20.6.846.1110

Friend, K. B., Rabin, B. M., Groninger, L., Deluty, R. H., Bever, C., & Grattan, L. (1999). Language functions in patients with multiple sclerosis. *Clin Neuropsychol, 13*(1), 78-94. doi:10.1076/clin.13.1.78.1979

Friston, K. J. (2003). Statistical parametric mapping. In *Neuroscience databases* (pp. 237-250): Springer.

Fromm, D., Holland, A. L., Nebes, R. D., & Oakley, M. A. (1991). A longitudinal study of word-reading ability in Alzheimer's disease: Evidence from the National Adult Reading Test. *Cortex, 27*(3), 367-376.

Fu, C. H., Morgan, K., Suckling, J., Williams, S. C., Andrew, C., Vythelingum, G. N., & McGuire, P. K. (2002). A functional magnetic resonance imaging study of overt letter verbal fluency using a clustered acquisition sequence: greater anterior cingulate activation with increased task demand. *Neuroimage, 17*(2), 871-879.

García, M. C., Plasencia, P. M., Benito, Y., Gómez, J. J., & Marcos, A. R. (2009). Executive function and memory in patients with relapsing-remitting multiple sclerosis. *Psicothema, 21*(3), 416-420.

Gay Snodgrass, J. (1984). Concepts and their surface representations. *Journal of Verbal Learning and Verbal Behavior, 23*(1), 3-22. doi:http://dx.doi.org/10.1016/S0022-5371(84)90479-1

Geisseler, O., Pflugshaupt, T., Bezzola, L., Reuter, K., Weller, D., Schuknecht, B., . . . Linnebank, M. (2016). Cortical thinning in the anterior cingulate cortex predicts multiple sclerosis patients' fluency performance in a lateralised manner. *NeuroImage: Clinical, 10*, 89-95.

Genova, H. M., Lengenfelder, J., Chiaravalloti, N. D., Moore, N. B., & DeLuca, J. (2012). Processing speed versus working memory: Contributions to an information-processing task in multiple sclerosis. *Applied Neuropsychology: Adult, 19*(2), 132-140.

Gerald, F. J. F., Murdoch, B. E., & Chenery, H. J. (1987). Multiple Sclerosis: Associated Speech and Language Disorders. *Australian Journal of Human Communication Disorders, 15*(2), 15-35. doi:10.3109/asl2.1987.15.issue-2.02

Geschwind, N. (1974). The organization of language and the brain. In *Selected papers on language and the brain* (pp. 452-466): Springer.

Geurts, J. J., Calabrese, M., Fisher, E., & Rudick, R. A. (2012). Measurement and clinical effect of grey matter pathology in multiple sclerosis. *The Lancet Neurology, 11*(12), 1082-1092.

Ghaffar, O., & Feinstein, A. (2007). The neuropsychiatry of multiple sclerosis: a review of recent developments. *Curr Opin Psychiatry, 20*(3), 278-285. doi:10.1097/YCO.0b013e3280eb10d7

Giles, E., Patterson, K., & Hodges, J. R. (1996). Performance on the Boston Cookie Theft picture description task in patients with early dementia of the Alzheimer's type: missing information. *Aphasiology, 10*(4), 395-408.

Giorgio, A., Battaglini, M., Smith, S. M., & De Stefano, N. (2008). Brain atrophy assessment in multiple sclerosis: importance and limitations. *Neuroimaging clinics of North America, 18*(4), 675-686.

Gmeindl, L., & Courtney, S. M. (2012). Deconstructing spatial working memory and attention deficits in multiple sclerosis. *Neuropsychology, 26*(1), 57-70. doi:10.1037/a0026213

Goodglass, H., & Kaplan, E. (1972). The assessment of aphasia and related disorders. Philadelphia: Lea, Febiger Görres S, Meier-Baumgartner HP (1990). Stationäre Patienten und Tagesklinikpatienten in der geriatrischen Rehabilitation: Ein Vergleich. *Z Geriatrie, 3*, 10-16.

Goodglass, H., Kaplan, E., & Barresi, B. (2001). *The assessment of aphasia and related disorders*: Lippincott Williams & Wilkins.

Gordon, P. A., Lewis, M. D., & Wong, D. (1994). Multiple sclerosis: Strategies for rehabilitation counselors. *Journal of Rehabilitation, 60*(3), 34.

Grafman, J., Rao, S. M., & Litvan, I. (1990). Disorders of memory. *Neurobehavioral aspects of multiple sclerosis, 4*, 102-117.

Hamilton, F., Rochester, L., Paul, L., Rafferty, D., O'Leary, C. P., & Evans, J. J. (2009). Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler, 15*(10), 1215-1227. doi:10.1177/1352458509106712

Hartelius, L., Runmarker, B., & Andersen, O. (2000). Prevalence and characteristics of dysarthria in a multiple-sclerosis incidence cohort: relation to neurological data. *Folia Phoniatr Logop, 52*(4), 160-177. doi:21531

Henry, J. D., & Beatty, W. W. (2006). Verbal fluency deficits in multiple sclerosis. *Neuropsychologia, 44*(7), 1166-1174.

Henry, J. D., & Crawford, J. R. (2004a). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology, 18*(2), 284.

Henry, J. D., & Crawford, J. R. (2004b). Verbal fluency deficits in Parkinson's disease: a meta-analysis. *Journal of the International Neuropsychological Society: JINS, 10*(4), 608.

Herbert, R., Hickin, J., Howard, D., Osborne, F., & Best, W. (2008). Do picture-naming tests provide a valid assessment of lexical retrieval in conversation in aphasia? *Aphasiology, 22*(2), 184-203. doi:10.1080/02687030701262613

Herderschee, D., Stam, J., & Derix, M. M. (1987). Aphemia as a first symptom of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry, 50*(4), 499-500.

Hickok, G. (2013). The functional neuroanatomy of language. *Handbook of Clinical Neurophysiology, 10*(3), 61-70.

Hodges, J. R., Graham, N., & Patterson, K. (1995). Charting the progression in semantic dementia: Implications for the organisation of semantic memory. *Memory, 3*(3-4), 463-495. doi:10.1080/09658219508253161

Hodges, J. R., Patterson, K., Ward, R., Garrard, P., Bak, T. H., Perry, R., & Gregory, C. (1999). The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of frontotemporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology, 13*(1), 31.

Hoffman, P., Rogers, T. T., & Lambon Ralph, M. A. (2011). Semantic diversity accounts for the "missing" word frequency effect in stroke aphasia: Insights using a novel method to quantify contextual variability in meaning. *Journal of Cognitive Neuroscience, 23*(9), 2432-2446.

Homack, S., Lee, D., & Riccio, C. A. (2005). Test Review: Delis-Kaplan Executive Function System. *Journal of clinical and experimental Neuropsychology, 27*(5), 599-609. doi:10.1080/13803390490918444

Howard, D. (2000). Cognitive neuropsychology and aphasia therapy: The case of word retrieval. *Acquired neurogenic communication disorders: A clinical perspective*.

Howard, D., & Patterson, K. E. (1992). *The Pyramids and Palm Trees Test: A test of semantic access from words and pictures*: Thames Valley Test Company, Bury St. Edmunds.

Huisman, E., Papadimitropoulou, K., Jarrett, J., Bending, M., Firth, Z., Allen, F., & Adlard, N. (2017). Systematic literature review and network meta-analysis in highly active relapsing–remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. *BMJ open, 7*(3), e013430.

Hulst, H. E., & Geurts, J. J. (2011). Gray matter imaging in multiple sclerosis: what have we learned? *BMC neurology, 11*(1), 1-11.

Indefrey, P. (2011). The Spatial and Temporal Signatures of Word Production Components: A Critical Update. *Frontiers in Psychology, 2*(255). doi:10.3389/fpsyg.2011.00255

Indefrey, P., & Levelt, W. J. M. (2004). The spatial and temporal signatures of word production components. *Cognition, 92*(1), 101-144.

Janculjak, D., Mubrin, Z., Brinar, V., & Spilich, G. (2002). Changes of attention and memory in a group of patients with multiple sclerosis. *Clinical neurology and neurosurgery, 104*(3), 221-227.

Jefferies, E., Patterson, K., Jones, R., & Ralph, M. (2009). Comprehension of Concrete and Abstract Words in Semantic Dementia. *Neuropsychology, 23*, 492-499. doi:10.1037/a0015452

Jeffery, D. R., Absher, J., Pfeiffer, F. E., & Jackson, H. (2000). Cortical deficits in multiple sclerosis on the basis of subcortical lesions. *Multiple Sclerosis Journal, 6*(1), 50-55. doi:10.1177/135245850000600110

Jennekens-Schinkel, A., Lanser, J. B., van der Velde, E. A., & Sanders, E. A. (1990). Performances of multiple sclerosis patients in tasks requiring language and visuoconstruction. Assessment of outpatients in quiescent disease stages. *J Neurol Sci, 95*(1), 89-103.

Jivraj, S., & Finney, N. (2013). Local dynamics of diversity: evidence from the 2011 census. *University of Manchester: ESRC Centre on Dynamics of Ethnicity (CoDE)*.

Johansson, K., Schalling, E., & Hartelius, L. (2020). Self-Reported Changes in Cognition, Communication and Swallowing in Multiple Sclerosis: Data from the Swedish Multiple Sclerosis Registry and from a National Survey. *Folia Phoniatrica et Logopaedica, 73*, 50 - 62.

Kambanaros, M., Messinis, L., Nasios, G., Nousia, A., & Papathanasopoulos, P. (2017). Verb–noun dissociations in relapsing-remitting multiple sclerosis: verb effects of semantic complexity and phonological relatedness. *Aphasiology, 31*(1), 49-66. doi:10.1080/02687038.2016.1154498

Kamm, C. P., Uitdehaag, B. M., & Polman, C. H. (2014). Multiple sclerosis: current knowledge and future outlook. *European neurology, 72*(3-4), 132-141.

Kaplan, E., Goodglass, H., & Weintraub, S. (1978). The Boston Naming Test: Experimental edition (1978). *Boston: Kaplan & Goodglass. 2nd Ed., Philadelphia: Lea & Febiger*.

Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *Boston naming test*: Pro-ed.

Katja Laakso, K. B. L. H. E. A. (2000). Assessing high-level language in individuals with multiple sclerosis: a pilot study. *Clinical Linguistics & Phonetics, 14*(5), 329-349. doi:10.1080/02699200050051065

Katzev, M., Tüscher, O., Hennig, J., Weiller, C., & Kaller, C. P. (2013). Revisiting the functional specialization of left inferior frontal gyrus in phonological and semantic fluency: the crucial role of task demands and individual ability. *J Neurosci, 33*(18), 7837-7845. doi:10.1523/jneurosci.3147-12.2013

Kavé, G. (2005). Phonemic fluency, semantic fluency, and difference scores: Normative data for adult Hebrew speakers. *Journal of clinical and experimental Neuropsychology, 27*(6), 690-699.

Kay, J., Lesser, R., & Coltheart, M. (1996). Psycholinguistic assessments of language processing in aphasia (PALPA): An introduction. *Aphasiology, 10*(2), 159-180. doi:10.1080/02687039608248403

Kennedy, M., & Murdoch, B. (1990). Persistent Word Fluency Deficit in Patients with Dominant Hemisphere Striato-Capsular Lesions: Further Evidence for a Subcortical Role in Language? *Australian Journal of Human Communication Disorders, 18*(2), 3-20.

Kern, K. C., Gold, S. M., Lee, B., Montag, M., Horsfall, J., O'Connor, M.-F., & Sicotte, N. L. (2015). Thalamic–hippocampal–prefrontal disruption in relapsing–remitting multiple sclerosis. *NeuroImage: Clinical, 8*, 440-447.

Kertesz, A. (2007). *Western Aphasia Battery Revised: Examiner's Manual*: Pearson.

Kessels, R. P., Van Zandvoort, M. J., Postma, A., Kappelle, L. J., & De Haan, E. H. (2000). The Corsi block-tapping task: standardization and normative data. *Applied neuropsychology, 7*(4), 252-258.

Ketteler, D., Kastrau, F., Vohn, R., & Huber, W. (2008). The subcortical role of language processing. High level linguistic features such as ambiguity-resolution and the human brain; an fMRI study. *NeuroImage, 39*(4), 2002-2009.

Kiran, S., & Bassetto, G. (2008). *Evaluating the effectiveness of semantic-based treatment for naming deficits in aphasia: What works?* Paper presented at the Seminars in Speech and Language.

Klugman, T. M., & Ross, E. (2002). Perceptions of the impact of speech, language, swallowing, and hearing difficulties on quality of life of a group of South African persons with multiple sclerosis. *Folia phoniatrica et logopaedica, 54*(4), 201-221.

Kos, D., Kerckhofs, E., Nagels, G., D'hooghe, M. B., & Ilsbroukx, S. (2008). Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabilitation and Neural Repair, 22*(1), 91-100.

Kraan, C., Stolwyk, R. J., & Testa, R. (2013). The Abilities Associated with Verbal Fluency Performance in a Young, Healthy Population Are Multifactorial and Differ Across Fluency Variants. *Applied Neuropsychology: Adult, 20*(3), 159-168. doi:10.1080/09084282.2012.670157

Krämer, J., Meuth, S. G., Tenberge, J.-G., Schiffler, P., Wiendl, H., & Deppe, M. (2015). Early and degressive putamen atrophy in multiple sclerosis. *International journal of molecular sciences, 16*(10), 23195-23209.

Kristensson, J., Longoni, F., Östberg, P., Åke, S., Rödseth Smith, S., & Saldert, C. (2021). Evaluation of treatment effects of semantic feature analysis on mild anomia in multiple sclerosis. *Aphasiology*, 1-26. doi:10.1080/02687038.2021.1900535

Krupp, L. B., Alvarez, L. A., LaRocca, N. G., & Scheinberg, L. C. (1988). Fatigue in multiple sclerosis. *Archives of neurology, 45*(4), 435-437.

Laakso, K., Brunnegård, K., Hartelius, L., & Ahlsén, E. (2000). Assessing high-level language in individuals with multiple sclerosis: a pilot study. *Clinical Linguistics & Phonetics, 14*(5), 329-349.

Lacour, A., De Seze, J., Revenco, E., Lebrun, C., Masmoudi, K., Vidry, E., . . . Vermersch, P. (2004). Acute aphasia in multiple sclerosis A multicenter study of 22 patients. *Neurology, 62*(6), 974-977.

Laine, M., & Martin, N. (2013). *Anomia: Theoretical and Clinical Aspects*: Psychology Press.

Lambon Ralph, M. A., Sage, K., & Roberts, J. (2000). Classical anomia: A neuropsychological perspective on speech production. *Neuropsychologia, 38*(2), 186-202.

LaPointe, L. L. (1999). *Quality of life with aphasia.* Paper presented at the Seminars in Speech and Language.

Lassmann, H., Brück, W., & Lucchinetti, C. F. (2007). The immunopathology of multiple sclerosis: an overview. *Brain Pathol, 17*(2), 210-218.

Lebkuecher, A. L., Chiaravalloti, N. D., & Strober, L. B. (2021). The role of language ability in verbal fluency of individuals with multiple sclerosis. *Multiple sclerosis and related disorders, 50*, 102846.

Lengenfelder, J., Chiaravalloti, N. D., Ricker, J. H., & DeLuca, J. (2003). Deciphering components of impaired working memory in multiple sclerosis. *Cognitive and behavioral neurology, 16*(1), 28-39.

Lethlean, J., & Murdoch, B. (1993). Language problems in multiple sclerosis. *Journal of medical speech-language pathology, 1*(1), 47-59.

Lethlean, J., & Murdoch, B. (1994). Naming errors in multiple sclerosis: Support for a combined semantic/perceptual deficit. *Journal of Neurolinguistics, 8*(3), 207-223.

Lethlean, J., & Murdoch, B. (1997). Performance of subjects with multiple sclerosis on tests of high-level language. *Aphasiology, 11*(1), 39-57.

Levelt, W. J. (1993). *Speaking: From intention to articulation* (Vol. 1): MIT press.

Levelt, W. J., Schriefers, H., Vorberg, D., Meyer, A. S., Pechmann, T., & Havinga, J. (1991). The time course of lexical access in speech production: A study of picture naming. *Psychological review, 98*(1), 122.

Lezak, M., Howieson, D., Bigler, E., & Tranel, D. (2012). Neuropsychological assessment: OUP USA.

Longoni, G., Rocca, M. A., Pagani, E., Riccitelli, G. C., Colombo, B., Rodegher, M., . . . Filippi, M. (2015). Deficits in memory and visuospatial learning correlate with regional hippocampal atrophy in MS. *Brain Structure and Function, 220*(1), 435-444.

Lorenz, A., & Ziegler, W. (2009). Semantic vs. word-form specific techniques in anomia treatment: A multiple single-case study. *Journal of Neurolinguistics, 22*(6), 515-537. doi:https://doi.org/10.1016/j.jneuroling.2009.05.003

Lublin, Reingold, S. C., Cohen, J. A., Cutter, G. R., Sørensen, P. S., Thompson, A. J., . . . Barkhof, F. (2014). Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology, 83*(3), 278-286.

Lublin, F. D., & Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology, 46*(4), 907-911.

Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Sørensen, P., Thompson, A. J., . . . Polman, C. H. (2014). Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology, 83*(3), 278-286. doi:10.1212/WNL.0000000000000560

Mackenzie, C., & Green, J. (2009). Cognitive-linguistic deficit and speech intelligibility in chronic progressive multiple sclerosis. *Int J Lang Commun Disord, 44*(4), 401-420. doi:10.1080/13682820802697879

Marié, R. M., & Defer, G. L. (2001). Memory and executive functions in multiple sclerosis: Preliminary findings with a cognitive battery. *Revue Neurologique, 157*(4), 402-408. Retrieved from https://www.scopus.com/inward/record.uri?eid=2-s2.0-0034974061&partnerID=40&md5=4a7de0b032db5e2770e5cc391b8930af

Mark, H., Fletcher, W., & Birt, D. (1983). *Storylines: Picture sequences for language practice*: Longman.

Martin, N., Dell, G. S., Saffran, E. M., & Schwartz, M. F. (1994). Origins of paraphasias in deep dysphasia: Testing the consequences of a decay impairment to an interactive spreading activation model of lexical retrieval. *Brain and language, 47*(4), 609-660.

Martin, N., Schwartz, M. F., & Kohen, F. P. (2006). Assessment of the ability to process semantic and phonological aspects of words in aphasia: A multi-measurement approach. *Aphasiology, 20*(02-04), 154-166.

Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology, 55*(11), 1613-1620.

McAlpine, D., & Compston, A. (2005). *McAlpine's multiple sclerosis*: Elsevier Health Sciences.

McCrimmon, A. W., & Smith, A. D. (2013). Review of the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II). *Journal of Psychoeducational Assessment, 31*(3), 337-341. doi:10.1177/0734282912467756

Melrose, R. J., Campa, O. M., Harwood, D. G., Osato, S., Mandelkern, M. A., & Sultzer, D. L. (2009). The neural correlates of naming and fluency deficits in Alzheimer's disease: An FDG-PET study. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences, 24*(8), 885-893.

Messinis, L., Kosmidis, M., Vlahou, C., Malegiannaki, A., Gatzounis, G., Dimisianos, N., . . . Papathanasopoulos, P. (2013). Phonological fluency strategy of switching differentiates relapsing-remitting and secondary progressive multiple sclerosis patients. *International Scholarly Research Notices, 2013*.

Mesulam, M.-M. (2003). Primary progressive aphasia—a language-based dementia. *New England Journal of Medicine, 349*(16), 1535-1542.

Miceli, G., Caltagirone, C., Gainotti, G., Masullo, C., & Silveri, M. C. (1981). Neuropsychological correlates of localized cerebral lesions in non-aphasic brain-damaged patients. *Journal of Clinical Neuropsychology, 3*(1), 53-63. doi:10.1080/01688638108403113

Miller, D. H., Chard, D. T., & Ciccarelli, O. (2012). Clinically isolated syndromes. *The Lancet Neurology, 11*(2), 157-169. doi:http://dx.doi.org/10.1016/S1474-4422(11)70274-5

Miller, D. H., & Leary, S. M. (2007). Primary-progressive multiple sclerosis. *The Lancet Neurology, 6*(10), 903-912. doi:http://dx.doi.org/10.1016/S1474-4422(07)70243-0

Miller, D. M., Weinstock-Guttman, B., Béthoux, F., Lee, J., Beck, G., Block, V., . . . Sellebjerg, F. (2000). A meta-analysis of methylprednisolone in recovery from multiple sclerosis exacerbations. *Multiple Sclerosis Journal, 6*(4), 267-273.

Minagar, A., Barnett, M. H., Benedict, R. H., Pelletier, D., Pirko, I., Sahraian, M. A., . . . Zivadinov, R. (2013). The thalamus and multiple sclerosis: modern views on pathologic, imaging, and clinical aspects. *Neurology, 80*(2), 210-219.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *International journal of geriatric psychiatry, 21*(11), 1078-1085.

Munson, B. (2006). Nonword repetition and levels of abstraction in phonological knowledge. *Applied Psycholinguistics, 27*(4), 577.

Murdoch, B. (2000). Neuropathophysiological basis of communication disorders in multiple sclerosis.

Murdoch, B., & Lethlean, J. (2000). Language disorders in multiple sclerosis.

Murdoch, B., & Theodoros, D. (2000). *Speech and language disorders in multiple sclerosis*: Whurr.

Narayana, P. A., Govindarajan, K. A., Goel, P., Datta, S., Lincoln, J. A., Cofield, S. S., . . . at Houston, M. A. C. (2013). Regional cortical thickness in relapsing remitting multiple sclerosis: a multi-center study. *NeuroImage: Clinical, 2*, 120-131.

Nelson, H. E. (1982). *National Adult Reading Test (NART): For the assessment of premorbid intelligence in patients with dementia: Test manual*: NFER-Nelson.

Nickels, L. (2001). Words fail me: Symptoms and causes of naming breakdown in aphasia.

Nickels, L. (2002a). Improving word finding: Practice makes (closer to) perfect? *Aphasiology, 16*(10-11), 1047-1060.

Nickels, L. (2002b). Therapy for naming disorders: Revisiting, revising, and reviewing. *Aphasiology, 16*(10-11), 935-979.

Nocentini, U., Rossini, P., Carlesimo, G., Graceffa, A., Grasso, M., Lupoi, D., . . . Rizzato, B. (2001). Patterns of cognitive impairment in secondary progressive stable phase of multiple sclerosis: correlations with MRI findings. *European neurology, 45*(1), 11-18.

Noseworthy, J. H., Lucchinetti, C., Rodriguez, M., & Weinshenker, B. G. (2000). Multiple sclerosis. *N Engl J Med, 343*(13), 938-952. doi:10.1056/NEJM200009283431307

Ntoskou, K., Messinis, L., Nasios, G., Martzoukou, M., Makris, G., Panagiotopoulos, E., & Papathanasopoulos, P. (2018). Cognitive and language deficits in multiple sclerosis: comparison of relapsing remitting and secondary progressive subtypes. *The open neurology journal, 12*, 19.

Nygaard, M. K., Langeskov-Christensen, M., Dalgas, U., & Eskildsen, S. F. (2021). Cortical diffusion kurtosis imaging and thalamic volume are associated with cognitive and

walking performance in relapsing–remitting multiple sclerosis. *Journal of Neurology*, 1-10.

O'Carroll, R. E. (1995). The assessment of premorbid ability: A critical review. *Neurocase, 1*(1), 83-89.

O'Carroll, R. E., Moffoot, A., Ebmeier, K. P., & Goodwin, G. M. (1992). Estimating pre-morbid intellectual ability in the Alcoholic Korsakoff Syndrome. *Psychological Medicine, 22*(4), 903-909.

O'Gorman, C. M., Freeman, S., & Broadley, S. A. (2010). 24. Use of the addenbrooke's cognitive examination in multiple sclerosis. *Journal of Clinical Neuroscience, 17*(12), 1617. doi:https://doi.org/10.1016/j.jocn.2010.07.025

Okuda, D. T., Mowry, E. M., Cree, B. A., Crabtree, E. C., Goodin, D. S., Waubant, E., & Pelletier, D. (2011). Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. *Neurology, 76*(8), 686-692. doi:10.1212/WNL.0b013e31820d8b1d

Osterrieth, P. A. (1944). Le test de copie d'une figure complexe; contribution a l'etude de la perception et de la memoire. *Archives de psychologie*.

Papathanasiou, A., Messinis, L., Zampakis, P., Panagiotakis, G., Gourzis, P., Georgiou, V., & Papathanasopoulos, P. (2015). Thalamic atrophy predicts cognitive impairment in relapsing remitting multiple sclerosis. Effect on instrumental activities of daily living and employment status. *J Neurol Sci, 358*(1-2), 236-242.

Parmenter, B. A., Shucard, J. L., & Shucard, D. W. (2007). Information processing deficits in multiple sclerosis: A matter of complexity. *Journal of the International Neuropsychological Society: JINS, 13*(3), 417.

Parmenter, B. A., Weinstock-Guttman, B., Garg, N., Munschauer, F., & Benedict, R. H. (2007). Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Multiple Sclerosis Journal, 13*(1), 52-57. doi:10.1177/1352458506070750

Pihlajamäki, M., Tanila, H., Hänninen, T., Könönen, M., Laakso, M., Partanen, K., . . . Aronen, H. J. (2000). Verbal fluency activates the left medial temporal lobe: a functional magnetic resonance imaging study. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 47*(4), 470-476.

Poeppel, D., & Hickok, G. (2004). Towards a new functional anatomy of language. In: Elsevier.

Popescu, B. F. G., & Lucchinetti, C. F. (2012). Meningeal and cortical grey matter pathology in multiple sclerosis. *BMC neurology, 12*(1), 1-8.

Potagas, C., Kasselimis, D., Peppas, C., Alexandri, N.-M., & Dellatolas, G. (2017). Pure alexia in a patient with multiple sclerosis. *Neurological Sciences, 38*(3), 511-513.

Public Health England. (2020, 4 February). Multiple sclerosis: prevalence, incidence and smoking status - data briefing. Retrieved from https://www.gov.uk/government/publications/multiple-sclerosis-prevalence-incidence-and-smoking-status/multiple-sclerosis-prevalence-incidence-and-smoking-status-data-briefing

Rabin, L. A., Paolillo, E., & Barr, W. B. (2016). Stability in Test-Usage Practices of Clinical Neuropsychologists in the United States and Canada Over a 10-Year Period: A Follow-Up Survey of INS and NAN Members. *Archives of clinical neuropsychology, 31*(3), 206-230. doi:10.1093/arclin/acw007

Rao, S. M. (1986). Neuropsychology of multiple sclerosis: a critical review. *J Clin Exp Neuropsychol, 8*(5), 503-542. doi:10.1080/01688638608405173

Rao, S. M. (1990). The Cognitive Function Study Group of the National Multiple Sclerosis Society. *A manual for the Brief Repeatable Battery of Neuropsychological Tests in multiple sclerosis*.

Rao, S. M. (1996). White matter disease and dementia. *Brain Cogn, 31*(2), 250-268. doi:10.1006/brcg.1996.0044

Rao, S. M., Aubin-Faubert, P. S., & Leo, G. J. (1989). Information processing speed in patients with multiple sclerosis. *Journal of clinical and experimental Neuropsychology, 11*(4), 471-477. doi:10.1080/01688638908400907

Rao, S. M., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G. J., . . . Unverzagt, F. (1993). Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology, 7*(3), 364.

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology, 41*(5), 685-691.

Raymer, A. M. (2011). Anomia. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 171-172). New York, NY: Springer New York.

Raymer, A. M., & LaPointe, L. L. (2005). Naming and word-retrieval problems. *Aphasia and related neurogenic language disorders, 4*, 95-110.

Raymer, A. M., & Rothi, L. J. (2008). Cognitive neuropsychological approaches to assessment and treatment: Impairments of lexical comprehension and production. . *Language intervention strategies in adult aphasia (4th ed., pp. 524-550). Philadelphia: Lippincott, Williams, & Wilkins*.

Renauld, S., Mohamed-Saïd, L., & Macoir, J. (2016). Language disorders in multiple sclerosis: A systematic review. *Mult Scler Relat Disord, 10*, 103-111. doi:10.1016/j.msard.2016.09.005

Rey, A. (1941). L'examen psychologique dans les cas d'encéphalopathie traumatique.(Les problems.). *Archives de psychologie*.

Risser, A. H., & Spreen, O. (1985). The western aphasia battery. *Journal of clinical and experimental Neuropsychology, 7*(4), 463-470. doi:10.1080/01688638508401277

Robinson, G., Shallice, T., Bozzali, M., & Cipolotti, L. (2012). The differing roles of the frontal cortex in fluency tests. *Brain, 135*(7), 2202-2214. doi:10.1093/brain/aws142

Rocca, M. A., Mesaros, S., Pagani, E., Sormani, M. P., Comi, G., & Filippi, M. (2010). Thalamic damage and long-term progression of disability in multiple sclerosis. *Radiology, 257*(2), 463-469.

Roosendaal, S. D., Bendfeldt, K., Vrenken, H., Polman, C. H., Borgwardt, S., Radue, E. W., . . . Geurts, J. J. (2011). Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. *Multiple Sclerosis Journal, 17*(9), 1098-1106. doi:10.1177/1352458511404916

Rosser, A., & Hodges, J. R. (1994). Initial letter and semantic category fluency in Alzheimer's disease, Huntington's disease, and progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry, 57*(11), 1389-1394.

Rudick, R. A., Lee, J.-C., Nakamura, K., & Fisher, E. (2009). Gray matter atrophy correlates with MS disability progression measured with MSFC but not EDSS. *J Neurol Sci, 282*(1-2), 106-111.

Ryan, J. J., Carruthers, C. A., Miller, L. J., Souheaver, G. T., Carruthers, C. A., Gontkovsky, S. T., & Zehr, M. D. (2005). The Wasi Matrix Reasoning Subtest. *International Journal of Neuroscience, 115*(1), 129-136. doi:10.1080/00207450490512704

Sá, M. J. (2012). Physiopathology of symptoms and signs in multiple sclerosis. *Arquivos de Neuro-Psiquiatria, 70*, 733-740. Retrieved from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004282X2012000900016&nrm=iso

Sadovnick, A. D., Remick, R. A., Allen, J., Swartz, E., Yee, I. M. L., Eisen, K., . . . Kastrukoff, L. F. (1996). Depression and multiple sclerosis. *Neurology, 46*(3), 628-632.

Sage, K., Snell, C., & Lambon Ralph, M. A. (2011). How intensive does anomia therapy for people with aphasia need to be? *Neuropsychological Rehabilitation, 21*(1), 26-41. doi:10.1080/09602011.2010.528966

Sakurai, M., & Kanazawa, I. (1999). Positive symptoms in multiple sclerosis: their treatment with sodium channel blockers, lidocaine and mexiletine. *J Neurol Sci, 162*(2), 162-168.

Salthouse, T. A., Atkinson, T. M., & Berish, D. E. (2003). Executive functioning as a potential mediator of age-related cognitive decline in normal adults. *Journal of experimental psychology: General, 132*(4), 566.

Sanai, N., Mirzadeh, Z., & Berger, M. S. (2008). Functional outcome after language mapping for glioma resection. *New England Journal of Medicine, 358*(1), 18-27.

Sepulcre, J., Peraita, H., Goñi, J., Arrondo, G., Martincorena, I., Duque, B., . . . Villoslada, P. (2011). Lexical access changes in patients with multiple sclerosis: A two-year follow-up study. *Journal of clinical and experimental Neuropsychology, 33*(2), 169-175. doi:10.1080/13803395.2010.499354

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in psychology, 5*, 772.

Shewan, C. M., & Kertesz, A. (1980). Reliability and validity characteristics of the Western Aphasia Battery (WAB). *Journal of Speech and Hearing Disorders, 45*(3), 308-324.

Sicotte, N., Kern, K., Giesser, B., Arshanapalli, A., Schultz, A., Montag, M., . . . Bookheimer, S. (2008). Regional hippocampal atrophy in multiple sclerosis. *Brain, 131*(4), 1134-1141.

Siegert, R. J., & Abernethy, D. A. (2005). Depression in multiple sclerosis: a review. *Journal of Neurology, Neurosurgery & Psychiatry, 76*(4), 469-475. doi:10.1136/jnnp.2004.054635

Smith, A. (1982). Symbol digit modalities test-revised. *Los Angeles: Western Psychological Services*.

Smith, K. J., & McDonald, W. I. (1999). The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. *Philos Trans R Soc Lond B Biol Sci, 354*(1390), 1649-1673. doi:10.1098/rstb.1999.0510

Snodgrass, J. G. (1984). Concepts and their surface representations. *Journal of Verbal Learning & Verbal Behavior, 23*(1), 3-22. doi:10.1016/S0022-5371(84)90479-1

Sorensen, P., Brown, S., Logemann, J., Wilson, K., & Herndon, R. (1994). Communication disorders and dysphagia. *Journal of Neurologic Rehabilitation, 8*(3), 137-143.

Spreen, O., & Risser, A. H. (2003). *Assessment of aphasia*: Oxford University Press.

Stebbins, G. T., Gilley, D. W., Wilson, R. S., Bernard, B. A., & Fox, J. H. (1990). Effects of language disturbances on premorbid estimates of IQ in mild dementia. *Clin Neuropsychol, 4*(1), 64-68.

Štecková, T., Hluštík, P., Sládková, V., Odstrčil, F., Mareš, J., & Kaňovský, P. (2014). Thalamic atrophy and cognitive impairment in clinically isolated syndrome and multiple sclerosis. *J Neurol Sci, 342*(1-2), 62-68.

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., . . . Van Heertum, R. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex, 15*(4), 394-402.

Strong, C.-A. H., Tiesma, D., & Donders, J. (2010). Criterion validity of the Delis-Kaplan Executive Function System (D-KEFS) fluency subtests after traumatic brain injury. *Journal of the International Neuropsychological Society, 17*(2), 230-237.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of experimental psychology, 18*(6), 643.

Stuss, D. T., Alexander, M. P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., . . . Izukawa, D. (1998). The effects of focal anterior and posterior brain lesions on verbal fluency. *Journal of the International Neuropsychological Society, 4*(03), 265-278.

Suchy, Y., Kraybill, M. L., & Larson, J. C. G. (2010). Understanding design fluency: Motor and executive contributions. *Journal of the International Neuropsychological Society: JINS, 16*(1), 26.

Sumowski, J. F., Chiaravalloti, N. D., Wylie, G., & DeLuca, J. (2009). Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *Journal of the International Neuropsychological Society, 15*(04), 606-612.

Szekely, A., Jacobsen, T., D'Amico, S., Devescovi, A., Andonova, E., Herron, D., . . . Bates, E. (2004). A new on-line resource for psycholinguistic studies. *Journal of Memory and Language, 51*(2), 247-250. doi:http://dx.doi.org/10.1016/j.jml.2004.03.002

Tallberg, I. M., & Bergendal, G. (2009). Strategies of lexical substitution and retrieval in multiple sclerosis. *Aphasiology, 23*(9), 1184-1195. doi:10.1080/02687030802436884

Taylor, R. (2000). National Adult Reading Test performance in established dementia. *Archives of gerontology and geriatrics, 29*(3), 291-296.

Togher, L., McDonald, S., Coelho, C. A., & Byom, L. (2014). Cognitive communication disability following TBI. *Social and communication disorders following traumatic brain injury*, 89-118.

Tombaugh, T. N., & Hubiey, A. M. (1997). The 60-item boston naming test: Norms for cognitively intact adults aged 25 to 88 years. *Journal of clinical and experimental Neuropsychology, 19*(6), 922-932. doi:10.1080/01688639708403773

Tomoeda, C. K., & Bayles, K. A. (1993). Longitudinal effects of Alzheimer disease on discourse production. *Alzheimer Disease and Associated Disorders*.

Trapp, B. D., Peterson, J., Ransohoff, R. M., Rudick, R., Mörk, S., & Bö, L. (1998). Axonal transection in the lesions of multiple sclerosis. *New England Journal of Medicine, 338*(5), 278-285.

Troster, A. I., Fields, J. A., Testa, J. A., Paul, R. H., Blanco, C. R., Hames, K. A., . . . Beatty, W. W. (1998). Cortical and subcortical influences on clustering and switching in the performance of verbal fluency tasks. *Neuropsychologia, 36*(4), 295-304. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9665640

Valsasina, P., Benedetti, B., Rovaris, M., Sormani, M., Comi, G., & Filippi, M. (2005). Evidence for progressive gray matter loss in patients with relapsing-remitting MS. *Neurology, 65*(7), 1126-1128.

Van Casteren, M., & Davis, M. H. (2007). Match: A program to assist in matching the conditions of factorial experiments. *Behavior Research Methods, 39*(4), 973-978.

Velázquez-Cardoso, J., Marosi-Holczberger, E., Rodríguez-Agudelo, Y., Yanez-Tellez, G., & Chávez-Oliveros, M. (2014). Recall strategies for the verbal fluency test in patients with multiple sclerosis. *Neurología (English Edition), 29*(3), 139-145.

Vercellino, M., Plano, F., Votta, B., Mutani, R., Giordana, M. T., & Cavalla, P. (2005). Grey Matter Pathology in Multiple Sclerosis. *Journal of Neuropathology & Experimental Neurology, 64*(12), 1101-1107. doi:10.1097/01.jnen.0000190067.20935.42

Viterbo, R., Iaffaldano, P., & Trojano, M. (2013). Verbal fluency deficits in clinically isolated syndrome suggestive of multiple sclerosis. *J Neurol Sci, 330*(1-2), 56-60.

Vleugels, L., Lafosse, C., Van Nunen, A., Nachtergaele, S., Ketelaer, P., Charlier, M., & Vandenbussche, E. (2000). Visuoperceptual impairment in multiple sclerosis patients diagnosed with neuropsychological tasks. *Multiple Sclerosis, 6*(4), 241-254. Retrieved from https://www.scopus.com/inward/record.uri?eid=2s2.00033839186&partnerID=40&md5=20e9970984230479e0602151cfb2f15e

Waldron, H., Whitworth, A., & Howard, D. (2011). Therapy for phonological assembly difficulties: A case series. *Aphasiology, 25*, 434-455. doi:10.1080/02687038.2010.494830

Wallace, G. L., & Holmes, S. (1993). Cognitive-linguistic assessment of individuals with multiple sclerosis. *Arch Phys Med Rehabil, 74*(6), 637-643.

Wallace, S., Worrall, L., Rose, T., Le Dorze, G., Breitenstein, C., Hilari, K., . . . Webster, J. (2018). A core outcome set for aphasia treatment research: The ROMA consensus statement International Journal of Stroke, 0(0). *International Journal of Stroke, 14*. doi:10.1177/1747493018806200

Warren, C., & Morton, J. (1982). The effects of priming on picture recognition. *British Journal of Psychology, 73*(1), 117-129.

Weinshenker, B. G., Bass, B., Rice, G. P. A., Noseworthy, J. H., Carriere, W., Baskerville, J., & Ebers, G. C. (1989). The natural history of multiple sclerosis: a geographically based study. *Brain, 112*(1), 133-146.

Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal Fluency: Language or Executive Function Measure? *Applied Neuropsychology: Adult, 23*(1), 29-34. doi:10.1080/23279095.2015.1004574

Wierenga, C. E., Benjamin, M., Gopinath, K., Perlstein, W. M., Leonard, C. M., Rothi, L. J. G., . . . Crosson, B. (2008). Age-related changes in word retrieval: role of bilateral frontal and subcortical networks. *Neurobiology of aging, 29*(3), 436-451.

Winkelmann, A., Engel, C., Apel, A., & Zettl, U. K. (2007). Cognitive impairment in multiple sclerosis. *J Neurol, 254 Suppl 2*, Ii35-42. doi:10.1007/s00415-007-2010-9

Wisenburn, B., & Mahoney, K. (2009). A meta-analysis of word-finding treatments for aphasia. *Aphasiology, 23*(11), 1338-1352.

Wylezinska, M., Cifelli, A., Jezzard, P., Palace, J., Alecci, M., & Matthews, P. (2003). Thalamic neurodegeneration in relapsing-remitting multiple sclerosis. *Neurology, 60*(12), 1949-1954.

Yorkston, K. M., Baylor, C., & Amtmann, D. (2014). Communicative participation restrictions in multiple sclerosis: Associated variables and correlation with social functioning. *Journal of communication disorders, 52*, 196-206.

Yorkston, K. M., Klasner, E. R., & Swanson, K. M. (2001). Communication in context: A qualitative study of the experiences of individuals with multiple sclerosis. *American Journal of Speech-Language Pathology*.

Zakzanis, K. K. (2000). Distinct neurocognitive profiles in multiple sclerosis subtypes. *Archives of Clinical Neuropsychology, 15*(2), 115-136.

APPENDICES

Appendix 1: Tables 1, 2, 3 and 4 shows the words included in each subgroup of words of the picture naming task and information about their frequency, age of acquisition and length of phonological syllables in De Dios et al. (2020) study. The information was obtained from the IPNP (Bates et al., 2000).

Table 1. Words included in Group A (<800 ms)

Group A (<800)	Frequency	Age of acquisition	Phonological syllables
Airplane	1.95	1	2
Arrow	2.77	3	2
Baby	5.56	1	2
Balloon	1.95	1	2
Bicycle	1.79	1	3
Butterfly	2.40	1	3
Car	5.87	1	1
Clock	3.69	1	1
Eye	6.26	1	1
Fish	5.10	1	1
Foot	5.79	1	1
Giraffe	1.10	1	2
Hat	4.23	1	1
Mushroom	2.64	3	2
Scissors	1.61	1	2
MEAN	3.51	1.27	1.73
SD	1.80	0.71	0.71

Table 2. Words included in Group B (801-1000 ms)

Group B (801-1000)	Frequency	Age of acquisition	Phonological syllables
Apple	3.43	1	2
Ball	4.72	1	1
Banana	2.20	1	3
Cactus	1.39	3	2
Can	2.30	2	1
Cheese	3.47	1	1
Dolphin	1.39	3	2
Elephant	3.22	1	3
Fan	2.89	3	1
Feather	3.09	3	2
Fountain	2.56	3	2
Helmet	2.64	3	2
Horse	4.89	1	1
Igloo	0.69	3	2
King	4.60	3	1
MEAN	2.90	2.13	1.73
SD	1.24	0.99	0.71

Table 2- Words included in Group C (1001-1220 ms)

Group C (1001-1220)	Frequency	Age of acquisition	Phonological syllables
Ant	2.56	2	1
Barbecue	1.10	3	3
Canoe	1.95	3	2
Carousel	0.69	3	3
Cow	3.71	1	1
Deer	2.56	1	2
Dentist	2.30	3	2
Handcuffs	1.10	3	2
Knot	2.71	3	1
Leg	5.17	1	1
Lettuce	2.08	3	2
Panda	0.69	3	2
Peas	0.00	1	1
Pirate	1.79	3	2
Priest	3.91	3	1
MEAN	2.16	2.4	1.73
SD	1.38	0.91	0.70

Table 3- Words included in Group D (1221-1500 ms)

Table 4. Words included in Group D (1221-1500 ms)

Object (1221-1500)	Frequency	Age of acquisition	Phonological syllables
Asparagus	1.099	3	4
Balcony	2.639	3	3
Beaver	1.386	3	2
Drill	2.197	3	1
Hinge	1.609	3	1
Hoe	1.386	3	1
Lobster	1.386	3	2
Mosquito	1.792	3	3
Safety-pin	0.693	3	3
Squirrel	1.946	1	2
Stroller	0.693	1	2
Tail	3.611	3	1
Trophy	1.609	3	2
Tweezers	1.099	3	2
Wrench	1.386	3	1
MEAN	1.63	2.73	2
SD	0.75	0.70	0.93

Appendix 2: Words included in A, B, C, D groups in IPNP and psycholinguistic variables used in the replication study.

Words in Group A

Group A (<800 ms RT)	Age of acquisition	Frequency	Phonological syllables
Airplane	1	1.95	2
Arrow	3	2.77	2

Baby	1	5.56	2
Balloon	1	1.95	2
Bicycle	1	1.79	3
Butterfly	1	2.40	3
Car	1	5.87	1
Clock	1	3.69	1
Eye	1	6.26	1
Fish	1	5.10	1
Foot	1	5.79	1
Giraffe	1	1.10	2
Hat	1	4.23	1
Mushroom	3	2.64	2
Scissors	1	1.61	2
Mean	**1.27**	**3.51**	**1.73**

Words in Group B

Group B (801 - 1000 ms RT)	**Age of acquisition**	**Frequency**	**Phonological syllables**
Apple	1	3.43	2
Ball	1	4.72	1
Banana	1	2.20	3
Cactus	3	1.39	2
Can	2	2.30	1
Cheese	1	3.47	1
Dolphin	3	1.39	2
Elephant	1	3.22	3
Fan	3	2.89	1
Feather	3	3.09	2
Fountain	3	2.56	2
Helmet	3	2.64	2
Horse	1	4.89	1
Igloo	3	0.69	2
King	3	4.60	1
Mean	**2.13**	**2.90**	**1.73**

Words in Group C

Group C (1001 - 1220 ms RT)	**Age of acquisition**	**Frequency**	**Phonological syllables**
Ant	2	2.56	1
Barbecue	3	1.10	3
Carrousel	3	0.69	3
Cow	1	3.71	1
Deer	1	2.56	2
Dentist	3	2.30	2
Handcuffs	3	1.10	2
Knot	3	2.71	1
Leg	1	5.17	1
Lettuce	3	2.08	2
Panda	3	0.69	2
Peas	1	0.00	2
Pirate	3	1.79	2
Mean	**2.31**	**2.04**	**1.85**

Words in Group D

Group D (1221 - 1500 ms RT)	**Age of acquisition**	**Frequency**	**Phonological syllables**

Asparagus	3	1.099	4
Balcony	3	2.639	3
Drill	3	2.197	1
Hinge	3	1.609	1
Lobster	3	1.386	2
Safety-pin	3	0.693	3
Squirrel	3	1.946	2
Stroller/Pram	1	0.693	2
Tail	1	3.611	1
Trophy	3	1.609	2
Tweezers	3	1.099	2
Wrench	3	1.386	1
Mean	**2.67**	**1.66**	**2**